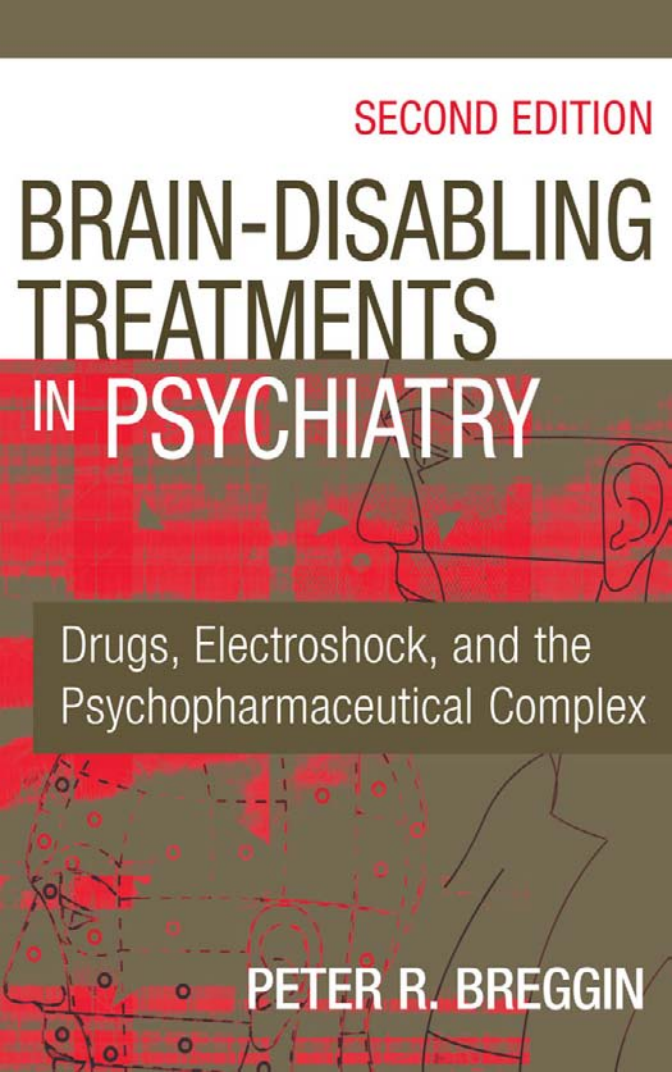
SECOND EDITION

# BRAIN-DISABLING TREATMENTS IN PSYCHIATRY

## Drugs, Electroshock, and the Psychopharmaceutical Complex



PETER R. BREGGIN

# Brain-Disabling Treatments in Psychiatry

*Second Edition*

**Peter R. Breggin, MD,** has been called "the conscience of psychiatry" for his efforts to reform the mental health field, including his promotion of caring psychotherapeutic approaches and his opposition to the escalating overuse of psychiatric medications, the oppressive diagnosing and drugging of children, electroshock, lobotomy, involuntary treatment, and false biological theories.

Dr. Breggin has been in the private practice of psychiatry since 1968, first in the Washington, D.C., area, and now in Ithaca, New York. In his therapy practice, he treats individuals, couples, and children with their families without resort to psychiatric drugs. As a clinical psychopharmacologist, he provides consultations and is active as a medical expert in criminal, malpractice, and product liability lawsuits, often involving the harmful effects of psychiatric drugs. He has been an expert in landmark cases involving the rights of patients.

Since 1964, Dr. Breggin has written dozens of scientific articles and approximately 20 books. Some of his many books include *Toxic Psychiatry, The Heart of Being Helpful, Talking Back to Ritalin, The Antidepressant Fact Book,* and, with coauthor Ginger Breggin, *Talking Back to Prozac* and *The War Against Children of Color.* His forthcoming book in early 2008 is *Medication Madness: True Stories About Mayhem, Murder and Suicide Caused by Psychiatric Drugs.*

At various stages of his career, he has been decades ahead of his time in warning about the dangers of lobotomy, electroshock, and, more recently, antidepressant-induced suicide and violence as well as many other recently acknowledged risks associated with psychiatric drugs. His views have been covered in major media throughout the world including *The New York Times* and *The Wall Street Journal* to *Time* and *Newsweek,* and from *Larry King Live* and *Oprah* to *60 Minutes* and *20/20.*

In 1972, Dr. Breggin founded the International Center for the Study of Psychiatry and Psychology (ICSPP; http://www.icspp.org). Originally organized to support his successful campaign to stop the resurgence of lobotomy, ICSPP has become a source of support and inspiration for reform-minded professionals and laypersons who wish to raise ethical and scientific standards in the field of mental health. In 1999, he and his wife, Ginger, founded ICSPP's peer-reviewed scientific journal *Ethical Human Psychology and Psychiatry.* In 2002, they selected younger professionals to take over the center and the journal, although Dr. Breggin continues to participate in ICSPP activities.

Dr. Breggin's background includes Harvard College, Case Western Reserve Medical School, a teaching fellowship at Harvard Medical School, 3 years of residency training in psychiatry, a 2-year staff assignment at the National Institute of Mental Health, and several teaching appointments, including in the Johns Hopkins University Department of Counseling and the George Mason University Institute for Conflict Analysis and Resolution.

Dr. Breggin's Web site is http://www.breggin.com.

# Brain-Disabling Treatments in Psychiatry

## *Drugs, Electroshock, and the Psychopharmaceutical Complex*

***Second Edition***

Peter R. Breggin, MD

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## *WARNING*

### *Psychiatric Drugs Are Dangerous to Take and Dangerous to Stop*

The psychiatric drugs discussed in this book are far more dangerous to take than many doctors and patients realize, but they can also become hazardous during the withdrawal process. In short, it is dangerous to start psychiatric drugs and dangerous to stop them.

Many are addictive, and most can produce withdrawal symptoms that are emotionally and physically distressing and sometimes life threatening. Tapering off psychiatric drugs should usually be done gradually with the aid of experienced clinical supervision.

A book cannot substitute for individualized medical or psychological care, and this book is not intended as a treatment guide. It provides a critical analysis of biological treatments in psychiatry written from a scientific, ethical, psychological, and social viewpoint.

Peter R. Breggin, MD

## *Professional Books by Peter R. Breggin, MD*

*College Students in a Mental Hospital: Contributions to the Social Rehabilitation of the Mentally Ill* (Jointly authored) (1962)
*Electroshock: Its Brain-Disabling Effects* (1979)
*The Psychology of Freedom: Liberty and Love as a Way of Life* (1980)
*Psychiatric Drugs: Hazards to the Brain* (1983)
*Toxic Psychiatry: Why Therapy, Empathy and Love Must Replace the Drugs, Electroshock and Biochemical Theories of the "New Psychiatry"* (1991)
*Beyond Conflict: From Self-Help and Psychotherapy to Peacemaking* (1992)
*Talking Back to Prozac* (coauthor Ginger Breggin) (1994)
*Psychosocial Approaches to Deeply Disturbed Persons* (coeditor E. Mark Stern) (1996)
*Brain-Disabling Treatments in Psychiatry: Drugs, Electroshock, and the Role of the FDA* (1997)
*The Heart of Being Helpful: Empathy and the Creation of a Healing Presence* (1997)
*The War Against Children of Color: Psychiatry Targets Inner City Children, Updated* (coauthor Ginger Breggin) (1998)
*Reclaiming Our Children: A Healing Solution to a Nation in Crisis* (2000)
*Talking Back to Ritalin, Revised Edition* (2001)
*The Antidepressant Fact Book* (2001)
*Dimensions of Empathic Therapy* (coeditors Ginger Breggin and Fred Bemak) (2002)
*The Ritalin Fact Book* (2002)
*Your Drug May Be Your Problem: How and Why to Stop Taking Psychiatric Medications, Revised and Updated Edition* (coauthor David Cohen) (2007)
*Medication Madness: True Stories of Mayhem, Murder and Suicide Caused by Psychiatric Drugs* (2008)

For Ginger Breggin

My wife, best friend, partner in life, most trusted advisor,
last human resort in all crises, and playmate

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# Contents

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# Preface

## A WORD ABOUT WORDS

Throughout this book, I use diagnostic terms such as *attention-deficit/hyperactivity disorder* (ADHD), *bipolar disorder, major depressive disorder,* and *schizophrenia*. If I were to express my scientific skepticism toward these terms each time I used them, the book would be marred by constant interruptions. Instead, I want to establish from the beginning that I am using these diagnostic terms only for the purpose of consistency with current usage in the various sources on which I am drawing, such as clinical studies, research reports, and Food and Drug Administration (FDA)-approved drug labels.

As the book will indicate, these diagnostic categories do not reflect valid diseases or illnesses comparable to Alzheimer's disease, stroke, or diabetes. Despite claims to the contrary, these psychiatric disorders have no proven genetic, chemical, or biological basis. They cannot be diagnosed with physical symptoms or laboratory studies.

Of course, no one denies that people can become highly irrational, lose touch with ordinary reality, or become suicidal or violent; but an extreme emotional response, however destructive, in itself does not demand an explanation rooted in biological dysfunction. Without any underlying medical disorder, human beings have the capacity for extreme psychological reactions, especially under stress.

Of course, genuine diseases or disorders of the brain, such as endocrine disorders or dementia, can change and disrupt human behavior. In this book and in *Medication Madness* (in press), I describe how psychiatric drugs cause brain disorders that lead to mayhem, murder, and suicide. Indeed, the FDA at long last has begun to confirm observations that I made long ago concerning antidepressant-induced mental and behavioral abnormalities. However, except for the brain dysfunction and biochemical imbalances caused by psychiatric drugs, there are no known abnormalities in the brains of people who routinely seek help from psychiatrists and

who become diagnosed with disorders like ADHD, schizophrenia, and major depressive disorder.

To label children with ADHD or to label adults with schizophrenia or major depressive disorder is to stigmatize them with damaging, discouraging labels and to encourage or coerce them to submit to biopsychiatric interventions such as drugs and electroshock. In my own psychiatric practice, I do not think in conventional diagnostic terms or tell patients that they have so-called mental disorders. Instead, I try to understand the life story of each individual—his or her personal biography—in all its subtle complexity. Often, I involve loved ones and family to help them understand each other. On this basis of genuine understanding, instead of cookie-cutter diagnoses, I am far more able to help individuals lead more satisfying, successful lives.

# Acknowledgments

Springer Publishing Company published my first medical book, *Electroshock: Its Brain-Disabling Effects,* a long time ago, in 1979. Now, almost 30 years later, this new edition of *Brain-Disabling Treatments in Psychiatry* comes at a time when the public's perception of psychiatric treatments has come closer to many of the seemingly controversial positions taken in my earlier Springer books. Even within the health care professions, there is growing recognition that the risks associated with psychiatric drugs and shock treatments are greater than originally anticipated and that their effectiveness is more limited than hoped.

None of the basic assertions in the original edition of this book or in its precursors, *Psychiatric Drugs: Hazards to the Brain* (1983) and *Electroshock* (1979), have been proven wrong. Instead, a mountain of new evidence supports the main themes that I have been developing over the last decades. In a number of areas, the Food and Drug Administration has confirmed assertions in the first edition that once seemed especially controversial, for example, that antidepressants are ineffective in children and increase the rate of suicide attempts and that they also increase suicidality in young adults. Many other conclusions made in my earlier books have been adopted by the mainstream, including recent confirmation that electroshock treatment causes permanent brain damage and dysfunction.

When Springer Publishing Company decided to bring out my first two medical books, *Electroshock* (1979) and *Psychiatric Drugs* (1983), it required courage. The president of the company, Dr. Ursula Springer, and the senior editor at the time, Carole Saltz, had to be concerned about publishing a viewpoint so critical of seemingly established concepts of treatment. The opportunity they gave me has helped to encourage a lifetime of work in the field. From then until the present, nearly all of my publications have drawn energy and direction from these first two books.

I am grateful that Dr. Springer and her company found my first two medical books of sufficient merit and importance to take the risk of

publishing them. If they had not, my career might have taken a different and ultimately less useful direction.

Nearly three decades later, and after the retirement of Dr. Springer, Springer Publishing Company and Sheri W. Sussman, Senior Vice President, Editorial, have continued to support my work with a new paperback edition of *The Heart of Being Helpful* (1997b) and now with this new edition of *Brain-Disabling Treatments in Psychiatry.*

Springer Publishing Company also worked with me and my wife, Ginger, in developing the peer-reviewed scientific journal *Ethical Human Psychology and Psychiatry,* sponsored by the International Center for the Study of Psychiatry and Psychology (ICSPP; http://www.icspp.org). The journal is now enjoying a decade of publishing under the leadership of younger professionals and provides a unique opportunity for scientists and clinicians to publish independent research in the light beyond the shadow of the psychopharmaceutical complex.

I also want to thank the many members of ICSPP who have been so supportive of my work and each other's work in the reform movement.

As in many of my books, my research assistant Ian Goddard continued to provide much-needed help obtaining original articles, sometimes under considerable time pressure, often delivering them along with a big dose of his own original ideas and remarkable insights. Beyond that, he read the entire manuscript and made many useful editorial observations. This new edition is a better book because of Ian.

And now, approaching 25 years together, my wife, Ginger, continues to provide the strength and often the inspiration behind so much of what I do. It is because of Ginger's encouragement that the book now has two concluding chapters on treatment and my 20 guidelines for therapy with disturbed patients. She insisted that I needed to write them, and then she helped to edit them.

# Introduction

## *Confirming the Science Behind the First Edition*

This book is aimed at professional audiences, but it is hoped that it is written with sufficient clarity and explanation to be read by nonprofessionals. The current edition has been very thoroughly revised, but the basic scientific thrust remains essentially the same. The past several years have confirmed the brain-disabling principle of psychiatric treatment, and many of the author's seemingly controversial conclusions have become more widely accepted.

### A THOROUGH UPDATE OF THE SCIENCE

For this edition of the book, the concept of brain-disabling treatment has been updated and expanded with the additional concept of *medication spellbinding (intoxication anosognosia)*. The neuroleptic chapters have been updated to include much more material on the newer, atypical drugs as well as new information on the neurotoxicity and cytotoxicity of all antipsychotic drugs. A massive amount of new information about antidepressant drugs and the stimulant drugs has resulted in an additional chapter on each drug.

The new edition concludes with two entirely new chapters on treatment—one on how to safely withdraw from psychiatric drugs, and the other about psychosocial and educational approaches to very disturbed people, including 20 guidelines for therapy. I am pleased to include how-to treatment information in the book for the first time.

## GROWING CONFIRMATION OF THE PREVIOUS EDITION

My observations that antidepressant drugs cause a spectrum of stimulant or activation effects—including agitation, hostility, aggression, and mania as well as crashing into depression and suicidality—have been elevated to the status of official dogma in the new Food and Drug Administration (FDA)-mandated changes in antidepressant labels. The concept that psychiatric drugs are neurotoxic is now a widely accepted principle in scientific research, especially concerning the antipsychotic drugs and mood stabilizers, and research has mounted up that demonstrates similar neurotoxic effects in all categories of psychiatric drugs. Many other medical experts have now joined in my criticism of the FDA's failure to do its duty and my concern about the corrupting influence of the drug companies on the theory and practice of psychiatry. Put simply, I am no longer quite such a lonely voice crying in the wilderness.

## CONFIRMING THE LONGER VIEW STARTING IN 1983

The lineage of this new edition began in 1983 with *Psychiatric Drugs: Hazards to the Brain,* a book that broke new ground with the first extensive review of the subject of neuroleptic-induced dementia. It also took a firm stand on the view that neuroleptics frequently cause tardive dyskinesia (TD) in young people. TD in children has become an accepted reality, and so that section has been reduced in size. Tardive psychosis is gaining increasing, if slow, recognition. Tardive dementia remains controversial—although it should not be—and an increasing amount of evidence supports my earlier observations on the cognitive deficits caused by neuroleptics. In addition, the neurotoxicity of psychiatric drugs is being studied more openly in laboratories.

In the 1970s, when I first began offering detailed critiques of psychiatric drugs, the medical model, and the psychopharmaceutical complex, I was, in many cases, breaking new ground, and initially, there were few supporters. By the time of the first edition of *Brain-Disabling Treatments in Psychiatry* in 1997, I could already cite many books that voiced strong criticism of the biological model and physical treatments from a variety of perspectives (Armstrong, 1993; Breeding, 1996; Caplan, 1995; Cohen, 1990; Colbert, 1995; Fisher et al., 1989; Grobe, 1995; Jacobs, 1995; Kirk et al., 1992; Modrow, 1992; Mosher et al., 1989; Romme et al., 1993; Sharkey, 1994).

Especially in the last few years, an escalating number of authors, many from within the medical establishment, have been offering strong

criticism of that conglomerate of powerful interest groups, and especially the dominating influence of the pharmaceutical industry (Abramson et al., 2005; Angell, 2004, 2007; Glenmullen, 2000, 2005; Healy, 2004; Jackson, 2005; Kean, 2005, 2006; Medwar et al., 2004; Moncrieff, 2006a, 2006b; O'Meara, 2006; Rost, 2006).

## THE SITUATION IN PSYCHIATRY WORSENS

Although many of my critiques and criticisms of biological psychiatry and the psychopharmaceutical complex have a broader acceptance, in many ways, the situation has deteriorated as the strength of the drug companies has grown. In the process, my predictions about the growing power of the psychopharmaceutical complex have come true.

The last two decades have seen escalating reliance on psychiatric drugs, not only within psychiatry but also throughout medicine, mental health, and even education. In private-practice psychiatry, it is common to give patients a medication on the first visit and then instruct them that they will need drugs for their lifetimes. Family practitioners, internists, and other physicians liberally dispense antidepressants and benzodiazepine tranquilizers. Nonmedical professionals, such as psychologists and social workers, feel obliged to refer their patients for drug evaluations. Managed care aggressively pushes drugs to the exclusion of psychotherapy. Adult medications are increasingly prescribed to children. Hospitals force psychiatric drugs on patients against their will.

There is a successful movement within psychiatry, implemented in many states, that makes it easy to force clinic outpatients to take long-acting injections of drugs. Under these outpatient commitment laws, if the person refuses to come to the clinic, mental health workers can come to the home to administer the injections by force. At the same time, there is a movement to screen schoolchildren, and even preschoolers, for so-called mental illness. This potentially disastrous movement is driven by drug company money and aims at increasing the market for their products.

Laypersons have joined in the enthusiasm for drugs. Because of media support for medication as well as direct advertising and promotion to the public, patients frequently arrive at the doctor's office with the name of a psychiatric drug already in mind. Teachers often recommend children for drug evaluation or treatment.

This drug revolution views psychiatric medications as far more helpful than harmful, even as an unmitigated blessing. Much as insulin or penicillin, they are vigorously promoted as specific treatments for specific illnesses. Often, they are said to correct biochemical imbalances in the brain. These beliefs have created an environment in which emphasis on

adverse drug effects is greeted without enthusiasm, and criticism of psychiatric medication in principle is uncommon heresy.

Drug companies heavily promote that unproven speculation that the problems they treat are biological in origin and result from biochemical imbalances. Advertising slogans are used to justify the prescription of medications. For example, Janssen (2005), the manufacturer of the antipsychotic drug Risperdal, offers a section "About Bipolar Disorder," downloaded from its Web site in February 2006. It declares,

> Mental illness is a medical illness, just like high blood pressure or heart disease.

The Janssen Web site goes on to say, "It is also thought that bipolar disorder may be caused by a genetic predisposition to the illness because it tends to run in families." Notice again that no claim to scientific veracity is made. But the repetition of these unscientific biochemical and genetic speculations nonetheless conditions people to believe that psychiatric drugs are specific treatments for genetic, biochemical disorders, much like antihypertensive drugs for high blood pressure or insulin for diabetes.

This book takes a decidedly different viewpoint from that of biological psychiatry. It provides theory and evidence that psychiatric drugs achieve their primary or essential effect by causing brain dysfunction and that they tend to do far more harm than good. I will show that psychiatric drugs are not specific treatments for any particular so-called mental disorder. Instead of correcting biochemical imbalances, psychiatric drugs cause them, sometimes permanently.

Health care providers and the general public have also been bamboozled by the much-advertised speculation that brain scans can demonstrate the existence of mental disorders, and even diagnose them. In reality, no psychiatric disorder is demonstrable or diagnosable by brain scan (Jackson, 2006a) or by any other medical or biological means.

This second-edition book discusses how to stop taking psychiatric drugs and presents 20 guidelines for therapy. Considerably more information on how to help disturbed and disturbing people without resort to drugs or electroshock is readily available elsewhere (Breggin, 1991a, 1992a, 1997; Breggin et al., 1994a, 1996, 2002). Chapters in *Reclaiming Our Children* (2000b), *Talking Back to Ritalin* (2001c), *The Antidepressant Fact Book* (2001a), and *The Ritalin Fact Book* (2002b) also deal with therapeutic approaches. The best overall summary of my approach to helping people can be found in *The Heart of Being Helpful* (1997b). Finally, *Medication Madness: True Stories of Mayhem, Murder and Suicide* (in press) can be viewed as a companion to this book, providing real-life cases of the devastating impact of these drugs on individual lives.

CHAPTER 1

# The Brain-Disabling, Spellbinding Effects of Psychiatric Drugs

Modern psychiatric drug treatment gains its credibility from a number of assumptions that professionals and laypersons alike too often accept as scientifically proven. These underlying assumptions qualify as myths: fictions that support a belief system and a set of practices. In contrast to these myths, this book identifies principles of psychopharmacology that are based on scientific and clinical evidence as well as on common sense.

Together, these form the *brain-disabling principles* or the *brain-disabling concept* of biopsychiatric treatment. While the book in its entirety provides the evidence for these principles, this chapter will summarize them, including the new principle of *intoxication anosognosia,* or *medication spellbinding* (Breggin, 2006d, in press).

In essence, the brain-disabling concept as a whole states that all psychiatric treatments—drugs, electroshock, and lobotomy—work by disrupting the function of the brain and mind, creating effects that are then interpreted (or misinterpreted) as improvements. Medication spellbinding is a brain-disabling effect that renders individuals unable to perceive the degree of their drug-induced impairment; causes individuals not to attribute any change in themselves to an adverse drug effect; often makes individuals believe that they are doing better than ever, when they are

doing worse; and in the extreme, drives them into compulsive activities that harm themselves and others.

## THE BASIC FOUR BRAIN-DISABLING PRINCIPLES

I. All biopsychiatric treatments share a common mode of action: the disruption of normal brain function.

Pharmacologists speak of a drug's *therapeutic index*, the dosage ratio between the beneficial effect and the toxic effect. The first brain-disabling principle of psychiatric treatment reveals that the toxic dose is the therapeutic dose—that brain disability causes the seemingly therapeutic effect. This same principle applies to electroshock and psychosurgery.

The brain-disabling principle states that as soon as toxicity is reached, the drug begins to have a psychoactive effect; that is, it begins to affect the brain and mind. Without toxicity, the drug would have no psychoactive effect.

Psychoactive drugs, including psychiatric drugs, vary in their toxicity. However, all of the major categories of psychiatric drugs—antidepressants, stimulants, tranquilizers (antianxiety drugs), mood stabilizers, and antipsychotics—are neurotoxic. They poison neurons, and sometimes destroy them.

II. All biopsychiatric interventions cause generalized brain dysfunction.

Although specific treatments do have recognizably different effects on the brain, they share the capacity to produce generalized dysfunction with some degree of impairment across the spectrum of emotional and intellectual function. Because the brain is so highly integrated, it is not possible to disable circumscribed mental functions without impairing a variety of other functions, typically causing generalized dysfunction of the brain and mind. For example, even the production of a slight emotional dullness, lethargy, or fatigue is likely to impair cognitive functions such as attention, concentration, alertness, self-concern or self-awareness, and social sensitivity. These changes can be subtle, and the spellbound individual may fail to perceive them, but the changes nonetheless adversely affect the person's quality of life.

Shock treatment and psychosurgery always produce obvious generalized dysfunction. Some medications may not obviously produce these effects in their minimal dose range, but they may also lack any substantial so-called therapeutic effect in that range.

III. Biopsychiatric treatments exert their therapeutic effect by impairing higher human functions, including emotional responsiveness, social sensitivity, self-awareness or self-insight, autonomy, and self-determination. More drastic effects include apathy, euphoria and mania,[1] and lobotomy-like indifference.

Higher mental, psychological, and spiritual functioning are impaired by biopsychiatric interventions as a result of generalized brain dysfunction as well as specific effects on the frontal lobe, limbic system, and other structures. Commonly, the result is a lobotomy-like indifference to self and to others—a syndrome that I have called *deactivation*. Recent research confirms that these effects occur with the SSRI antidepressants, such as Prozac, Zoloft, and Paxil; the stimulants, such as Ritalin, Concerta, and Adderall; and the newer antipsychotics, such as Risperdal and Zyprexa[2] (see chapters 2, 4, and 7). Chronic use of any psychoactive or psychiatric drug, including the benzodiazepines and mood stabilizers, will produce a degree of deactivation.

Spontaneous, self-generated, autonomous or voluntary activity is the vital essence of living creatures, and especially human beings. It can be viewed as the highest expression of human activity. Because it requires a fully functioning brain, impairment of spontaneous behavior occurs following any injury to the highest centers of the brain, including the frontal lobes and limbic system, as well as the deeper reticular activating system.

Because higher brain functions are fragile and dependent on overall physical well-being, a deactivating loss of spontaneous, self-generated behavior is often the first sign of any physical impairment or illness, from head injury and chronic fatigue to flulike illnesses, hormonal disorders, and brain tumors. Similarly, deactivation is one of the earliest and most essential effects of any psychoactive drug—that is, any drug that disrupts the function of the brain and mind—including all psychiatric drugs.

A variety of adverse drug reactions can be subsumed under the broader concept of deactivation. Some of these reactions include drug-induced diminished initiative, indifference, apathy, lethargy, psychomotor retardation, and loss of interest. Drug-induced depression, sedation, drowsiness, emotional dulling or blunting, malaise, and passivity often reflect a degree of deactivation. In the animal literature concerning psychiatric drug effects, deactivation is described as reductions in overall activity, spontaneous activity, social interactions, and exploration.

Biopsychiatric treatments are deemed effective when the physician and/or the patient prefers a state of diminished brain function, with its narrowed or shallower range of mental capacity or emotional expression. If the drugged individual reports feeling more effective and

powerful, it is most likely based on an unrealistic appraisal, impaired judgment, or euphoria associated with medication spellbinding. When patients on so-called maintenance doses do not experience noticeable effects, either the dose is too low to have a clinical effect, or the patient is unable to perceive the drug's impact, again characteristic of medication spellbinding.

IV. Each biopsychiatric treatment produces its essential or primary brain-disabling effect on all people, including normal volunteers and patients with varied psychiatric diagnoses.

Despite the deeply held convictions of drug proponents, there are no specific psychoactive drug treatments for specific mental disorders. There is, of course, a certain amount of biological and psychological variation in the way people respond to drugs, shock treatment, or even lobotomy or an accidental head injury. However, as a general principle, biopsychiatric interventions have a nonspecific impact that does not depend on the person's mental state or condition. For example, it will be shown that neuroleptics and lithium affect animals and normal volunteers in much the same way as they affect patients, in part by subduing their overall emotional responsiveness.

## ILLUSTRATIVE RESEARCH CONFIRMING THE BASIC FOUR BRAIN-DISABLING PRINCIPLES

The first four principles are the heart of the brain-disabling concept: basically, that all psychiatric drugs cause a generalized impairment of brain function that reduces overall mental and emotion function; that this disabling effect occurs, as well, in normal volunteers; and that the effect has no specificity for any psychiatric disorder.

On occasion, research studies directly confirm the brain-disabling principle, but without intending to do so and without acknowledging it. In some ways, this is the most objective kind of research in that the researchers are unaware of the principle that they are testing. The following three studies involve the second-generation or atypical neuroleptic risperidone (Risperdal), which is widely prescribed to children and adults.

Peter Liddle and his colleagues (2000) used positron emission tomography (PET) to study the effects of risperidone on the rate of metabolism on the ventral striatum, thalamus, and frontal cortex. Their subjects were eight neuroleptic-naïve patients diagnosed with their first episodes of schizophrenia.

First and foremost, Liddle et al. (2000) found that "a single dose of risperidone produced decreases in metabolism in ventral striatum, thalamus and frontal cortex." The authors identified this region as the cortico–striato–thalamo–cortical feedback loop. This encompasses much of the emotion-regulating centers in the limbic system and higher mental centers in the frontal lobes. Dopaminergic neurotransmission plays a significant role in this system and is profoundly blocked by risperidone. Clearly, this confirms that risperidone, like all neuroleptics, causes a chemical lobotomy, with the inevitable production of relative degrees of apathy and indifference.

Moreover, according to Liddle et al. (2000), "after six weeks' treatment with risperidone, the decreases in frontal lobe metabolism were more extensive." In other words, the risperidone produced a progressive chemical lobotomy with suppression of frontal lobe function.

In keeping with the brain-disabling principle, Liddle et al. (2000) were able to correlate a progressive suppression of symptoms with the exposure to risperidone. Although they tested for a variety of symptoms, they only reported a decreased severity of reality distortion. *Reality distortion* turns out to be a global clinical impression of the patient's delusions and hallucinations. There is certainly no question that a chemical lobotomy (or a surgical lobotomy) reduces the individual's expression of delusions and hallucinations. It does this by suppressing limbic system and frontal lobe function, causing apathy and indifference. The patients no longer care enough to express their more florid symptoms, but they also no longer care about anything. It is a global deactivation.

Liddle et al. (2000) try to correlate the reduction in reality distortion with suppression of a presumably overactive region of the hippocampus, but this is a huge stretch of the imagination. The facts are simple: The PET shows a global suppression of metabolism, and hence function, in the limbic system and frontal lobes, with increasing impact on the frontal lobes over a 6-week period, correlated with the patients no longer communicating as much about their symptoms. This is a demonstration of the brain-disabling concept of neuroleptic treatment.

Again using PET, Ngan et al. (2002) measured cerebral metabolic activity in patients before neuroleptic exposure, after an initial dose of risperidone and after 6 weeks of treatment. They found a reduction of frontal lobe function, and, in keeping with my suggestion in the 1997 edition of this book, they called it *deactivation*. They concluded that this decrease in frontal lobe metabolism is a function of the drug and not "schizophrenia" and that the mechanism of antipsychotic drug action is a "reduction in cortical metabolism," especially in the frontal and temporal regions. This is a pillar of the brain-disabling concept: that psychiatric drugs work by disabling the higher centers of the brain. The authors

pointed out that a healthy control group is needed to further demonstrate that the drug's primary effect is separate from the patient's disorder and would occur in any group of individuals, normal or abnormal.

Lane et al. (2004) conducted a related study that could have been planned for the specific purpose of testing the brain-disabling principle. Using PET, they measured changes in regional metabolism produced by a single 2-mg dose of risperidone and by placebo, administered in a randomized, double-blind study of nine *healthy* subjects. Their results confirm that risperidone has the same effect on normal people as people labeled schizophrenic and that it acts by reducing brain function in areas critical to overall mental functioning. They stated,

> **Results:** Compared with placebo, risperidone produced reductions in metabolism in the left lateral frontal cortex and right medial frontal cortex in healthy subjects. Conjunction analysis reveals that these changes occurred at locations similar to the loci of change produced risperidone with schizophrenia.

The researchers then concluded that there is a link between this reduced metabolism (a brain-disabling effect) and the reduction of clinical symptoms in patients diagnosed with schizophrenia:

> Because the reduction in metabolism in the medial frontal cortex produced by risperidone is associated with alleviation of positive symptoms in patients with schizophrenia, the observation of a reduction in metabolism at a similar site in healthy subjects supports the hypothesis that the antipsychotic effect of risperidone arises, at least in part, from a physiologic effect that occurs in both patients with schizophrenia and healthy subjects.

The positive symptoms found in patients diagnosed with schizophrenia, such as hallucinations and delusions, can be suppressed by any brain-disabling trauma, from electroshock and lobotomy to neuroleptic drugs. This is in contrast to the negative symptoms, such as apathy, which are worsened by disabling or suppressing brain function. If it had been measured, the deactivation of the frontal lobes would also have correlated with a reduction in all spontaneous mental activity and verbal expressions, which is a commonly observed clinical phenomenon during neuroleptic treatment. This suppressive effect is often identified as psychomotor retardation, parkinsonian symptoms, or an apathylike syndrome of indifference.

Studies such as these three involving risperidone completely confirm the brain-disabling principles of psychiatric treatment. There should no longer be any scientific doubt about the correctness of the brain-disabling

concept, although its general acceptance requires letting go of numerous myths surrounding psychiatric treatment.

## SIX ADDITIONAL BRAIN-DISABLING PRINCIPLES

The last series of brain-disabling principles describe clinical phenomena associated with treatment-induced brain disability.

V. Patients respond to brain-disabling treatments with their own psychological reactions such as apathy, euphoria, compliance, or resentment.

There is some variation in the way individuals respond to drugs. For example, the same antidepressant will make one person sleepy and another energized. Ritalin quiets many children but agitates others.

It can be very difficult to separate out drug-induced from psychologically induced responses. For example, all antidepressants can cause euphoria and mania.[3] At the same time, some of the people who receive these drugs have their own tendency to develop these mental states. Similarly, a variety of drugs are capable of generating agitation and hostility in patients, yet people can develop these responses without medication. The docility and compliance seen following the administration of neuroleptics can be caused by the drug-induced deactivation syndrome but can also result from the patient's realization that further resistance to psychiatric authority and control is futile or dangerous.

VI. To the extent that a physical disorder of the brain afflicts the individual, currently available biopsychiatric interventions will worsen or add to the disorder.

The currently available biopsychiatric treatments are not specific for any known disorder of the brain. One and all, they disrupt normal brain function, without correcting any brain abnormality. Therefore, if a patient is suffering from a known physical disorder of the brain, biopsychiatric treatment can only worsen or add to it. A classic example involves giving Haldol to control emotionally upset Alzheimer's patients. While subduing their behavior, the drug worsens their dementia (chapters 2–4).

After psychiatric drugs are developed and marketed by drug companies, attempts are made to justify their use on the basis of correcting presumed biochemical imbalances. For example, it is claimed that Prozac helps by improving serotonergic neurotransmission. Even electroshock

and lobotomy are justified on the grounds that they correct biochemical imbalances. There is no likelihood that these intrusions correct a biochemical imbalance. A wide variety of brain-disabling agents are used to treat the same or similar disorders—everything from Prozac to Xanax to electroshock is prescribed for depression—and each treatment ends up disrupting innumerable brain functions. In reality, all currently available biopsychiatric interventions cause direct harm to the brain and hence to the mind, without correcting any known malfunction.

The pharmaceutical industry has lobbied hard to convince the U.S. Congress, the health professions, and the public that emotional problems such as depression and anxiety are biological in origin. The supposed biological basis of psychiatric disorders is then used to justify the widespread sale of their products, psychiatric drugs. But even if one or another psychiatric disorder someday turns out to have a biological basis, that in no way would justify inflicting psychiatric drugs on these patients, thereby compounding their underlying brain disorder with drug toxicity.

VII. Individual biopsychiatric treatments are not specific for particular mental disorders.

It is often said that psychiatry has specific treatments for specific diagnostic categories of patients, for example, neuroleptics for "schizophrenia"; antidepressants for depression; benzodiazepine tranquilizers for anxiety; lithium for mania; and stimulants, such as Ritalin, for attention-deficit hyperactivity. In actual practice, many individual patients are given all of the above categories of drugs at one time or another, and, increasingly so, all at once. Often the recommended use of a drug changes over the years. While there is a general tendency for patients labeled schizophrenic to be initially treated with neuroleptics or for depressed patients to be initially prescribed antidepressants, this is, in part, a matter of convention within the profession.

When a drug seems more effective for a particular disorder, it often depends on whether it has a suppressive or an energizing effect on the central nervous system. For example, if depressed patients are already emotionally and physically slowed down, giving them a neuroleptic that causes psychomotor retardation would tend to make them look worse. These patients are more likely to seem improved when artificially energized. Conversely, if patients diagnosed with schizophrenia become agitated and difficult to control, it would not make sense to give them stimulants. They are more likely to be judged improved when taking a neuroleptic that reduces or flattens their overall emotional responsiveness. Similarly, if a child is bored and restless in the classroom, stimulants

such as Ritalin, Adderall, and Strattera will suppress spontaneous behavior and enforce obsessive–compulsive behavior, giving an illusion of improvement (chapter 10). These gross behavioral effects, however, are a far cry from having a magic bullet for a specific disease.

VIII. The brain attempts to compensate physically for the disabling effects of biopsychiatric interventions, frequently causing additional adverse reactions and withdrawal problems.

The brain does not welcome psychiatric medications as nutrients. Instead, the brain reacts against them as toxic agents and attempts to overcome their disruptive impact. For example, when Prozac induces an excess of serotonin in the synaptic cleft, the brain compensates by reducing the output of serotonin at the nerve endings, by reducing the number of receptors in the synapse that can receive the serotonin, and by increasing the capacity of the transport system to remove serotonin from the synapse. Similarly, when antipsychotic drugs such as Risperdal, Zyprexa, or Haldol reduce reactivity in the dopaminergic system, the brain compensates, producing hyperactivity in the same system by increasing the number and sensitivity of dopamine receptors. All of these compensatory reactions create new abnormalities in brain function, sometimes causing irreversible disorders, such as antipsychotic drug–induced tardive dyskinesia (chapter 4).

It is difficult, if not impossible, to determine accurately the underlying psychological condition of a person who is taking psychiatric drugs. There are too many complicating factors, including the drug's brain-disabling effect, the brain's compensatory reactions, and the patient's psychological responses to taking the drug. I have evaluated many cases in which patients have deteriorated under the onslaught of multiple psychiatric drugs without the prescribing physicians attributing the patients' decline to drug toxicity. Instead, physicians typically attribute their patients' worsening condition to "mental illness" when in reality the patient is suffering from adverse drug reactions.

Because the brain attempts to compensate for the effects of most psychoactive drugs, patients can have difficulty withdrawing from them. Physically, the brain cannot recover from the drug effect as quickly as the drug is withdrawn so that the compensatory mechanisms can require weeks or months to recover after the drug has been withdrawn. Sometimes, as in tardive dyskinesia, the brain fails to recover. In some cases, patients who have taken the newer antidepressants such as Prozac, Paxil, Zoloft, and Celexa for months or years cannot withdraw from them owing to the emotional instability and physical symptoms produced by drug-induced changes in the brain.

IX. Physicians who prescribe biopsychiatric interventions often have an unrealistic appraisal of their risks and benefits.

An entire book could be written about how little physicians appreciate the risks associated with the psychiatric drugs that they prescribe and how much they overestimate their effectiveness. The Food and Drug Administration (FDA), medical and psychiatric associations, experts with a vested interest in promoting drugs, and the pharmaceutical industry—the psychopharmaceutical complex—combine to push doctors to prescribe psychiatric drugs to children and adults.

What about the clinical judgment of individual physicians? The individual physician is not in a good position to assess the effectiveness of psychiatric drugs. In recent years, doubt has even been thrown on the objectivity of controlled clinical trials, in which drugs are compared to placebo or to alternative medications (see chapters 6–7). Too often, the investigators are influenced by their conscious or unconscious biases.

If clinical and scientific studies can be distorted by bias, it is even more likely that routine clinical practice will be affected by the hopes and expectations of the prescribing physician. Physicians in great numbers have prescribed drugs with unbounded enthusiasm for years before the agents have proven to be worthless or unacceptably dangerous. Amphetamines, for example, were freely dispensed for many years to millions of patients for both depression and weight control, without regard for their lack of efficacy, long-term hazards, and addictive potential (chapter 11). Although there has been some increased caution in recent years, benzodiazepines such as Valium and Xanax have been overly prescribed for anxiety, despite the fact that they worsen anxiety in long-term use, cause persisting memory and mental deficits, and frequently produce abuse and dependence (chapter 12). Antidepressants continue to be given freely to children and adolescents, even though the FDA itself has admitted that multiple studies have failed to prove them useful (chapter 6). Indeed, the effectiveness of antidepressants in treating depressed adults is also in doubt (chapters 6–7), while their adverse effects can be life threatening and make withdrawal impossible, yet most physicians think of them as very safe and efficacious. In even more extreme examples, both psychosurgery and electroshock continue to be utilized, despite obviously devastating effects on the mental lives of the patients and the absence of proven efficacy (chapter 9).

X. Patients subjected to biopsychiatric interventions often display poor judgment about the positive and negative effects of the treatment on their mental and emotional functioning, often causing intoxication anosognosia (medication spellbinding).[4]

Generalized brain dysfunction tends to reduce the individual's ability to perceive the existence or impact of the dysfunction. This incapacity lies at the heart of spellbinding effects of drugs and is one of the main reasons that patients continue to take psychiatric medications when the drugs are doing more harm than good.

*Anosognosia* refers to the capacity of brain damage to cause denial of lost function. Anosognosia is a hallmark of central nervous system disability from any cause (Breggin, 2006d; see subsequent sections).

Human beings are physically and psychologically complex, with varying reactions to drugs. As a result, no two cases of medication spellbinding are identical, they vary widely in intensity, and not all cases will display every characteristic. Nonetheless, spellbinding is a readily identifiable clinical phenomenon that probably characterizes all cases of drug intoxication from mild to severe and probably can be found to some degree whenever a psychoactive agent is having an impact on brain and mind.

The following four characteristics of medication spellbinding are taken from this author's book *Medication Madness* (Breggin, in press):

> First, spellbound individuals fail to perceive the degree of mental or emotional impairment that the drugs are inflicting on them.
>
> Second, spellbound individuals tend to rationalize and justify their drug-induced mental distress, typically blaming negative feelings on themselves or on something else, sometimes leading to violence against themselves or others.
>
> Third, spellbound individuals often feel as if they are doing better than ever when in reality they are doing worse.
>
> Fourth, extreme spellbinding produces medication madness in which the individual feels driven or compelled to behave in out-of-character and potentially disastrous ways—to murder her beloved mother like Emily Ashton or to drive his car into a policeman like Harry Henderson. The spellbound actions are typically carried out without the individual realizing that he or she is drug impaired and without the individual stopping to consider or grasping the disastrous consequences.

To practice applying the four principles of spellbinding, the reader can simply recall how individuals act when intoxicated with alcohol. Typically, people intoxicated with alcohols do not realize how impaired they have become; when they become emotionally distressed, they blame it on someone or something other than alcohol intoxication, often becoming depressed or belligerent; they often think that they feel better than ever when they are in reality mentally impaired and behaving badly; and finally, they can do stupid things and even perpetrate violence that is wholly out of character for them when sober.

Many individuals who chronically smoke marijuana believe that it improves their overall psychological and social functioning, but if they withdraw from the drug, it may become apparent to them that their memory, mental alertness, emotional sensitivity, and social skills have been impaired while using the drug. People intoxicated with stimulants, such as amphetamine, may feel they have superior or even superhuman capacities, when they are often seriously impaired. The same is true of all psychiatric drugs. Often the patient will have little appreciation for the degree of mental or emotional impairment until the drug has been stopped for some time and the brain has had time to recover.

In my clinical practice and in my work as a medical expert in legal cases, I often find that people are dismayed at how much better they function when they have been safely withdrawn from psychiatric medications. Many of these patients have remained for years in severe states of intoxication from one or more psychiatric drugs without realizing it. Attributing their condition to their own emotional reactions or to stresses in the environment, they have asked their doctors for more medication.

Owing to brain damage–induced spellbinding, even after a devastating series of shock treatments or psychosurgery, patients may fail to understand the iatrogenic source of their mental dysfunction and instead believe that they need repeated interventions.

## THE BIOLOGICAL BASIS OF MEDICATION SPELLBINDING

Some degree of spellbinding is characteristic of any compromise of frontal lobe function. Beer et al. (2006) noted that orbitofrontal damage is "associated with objective inappropriate social behavior." The patients "were aware of social norms of intimacy" but "they were unaware that their task performances violated these norms." The authors call this an impairment of *self-monitoring* and *self-insight*. Bach and David (2006) pointed out that self-awareness deficits are very common in patients with traumatic brain injury and key to the development of behavior disturbances: "Our research found that lack of social self-awareness predicts behavioural disturbance in acquired and traumatic brain injury independent of cognitive and executive function."

Lobotomized or electroshocked patients as well as patients chemically lobotomized by neuroleptics have greatly impaired self-awareness. They often fail to perceive their mental dysfunction and will neglect warning signs of physical illness in themselves. Consistent with spellbinding, they are likely to report that they are doing better than they are. A study of the atypical neuroleptics, including risperidone, olanzapine,

and quetiapine, found that these patients unrealistically rated themselves as improved in quality of life (Voruganti et al., 2000): "These perceived benefits, however, were not reflected in the clinician rated (objective) measure of psychosocial functioning and quality of life."

These gross disruptions of the frontal lobes, including neuroleptic toxicity, usually subdue individuals, making them docile, thereby preventing dangerous disinhibition that might otherwise occur in the absence of self-monitoring and self-insight. However, many psychoactive drugs, including antidepressants, benzodiazepine tranquilizers, and stimulants, can markedly disinhibit and/or energize and drive the individual to act in a compulsively destructive manner, sometimes leading to criminal behavior, suicide, and violence (Breggin, 2006d, in press). When neuroleptics cause akathisia, they can also drive individuals toward out-of-control behaviors.

The biological bases for the individual's failure to perceive adverse drug effects on his or her mental life include the following interrelated phenomena:

- *Drug-induced confusion.* Almost all biopsychiatric interventions can at times induce confusion, impairing the patient's awareness of the drug-induced mental dysfunction.
- *Drug-induced short-term memory loss.* Psychoactive drugs frequently impair recall and also disrupt the order of past memories, making it more difficult for individuals to recognize how a drug has been affecting them.
- *Drug-induced mental disturbances, especially various degrees of apathy and mania.* All psychiatric drugs can produce either indifference or euphoria, and many—for example, the newer antidepressants, the stimulants and the benzodiazepine Xanax—can produce both. Apathy and indifference make people less aware of and less concerned about drug-induced impairments. If the person is suffering a great deal, the apathy may be welcomed. Euphoria and mania override any sense of impairment, instead making the individual feel better, stronger, and more able than ever.
- *Drug-induced confabulation. Confabulation* is a symptom of generalized brain dysfunction with marked memory impairment. The patient uses rationalizations and various cover stories to hide the extent of mental dysfunction from himself and others. Confabulation is well understood in psychiatry and neurology but is generally ignored in regard to treatment-induced effects. Many patients confabulate good results from drug therapy, although they are obviously impaired by it.

## PSYCHOLOGICAL INFLUENCES ON MEDICATION SPELLBINDING

Psychological influences also play a role in the patient's tendency to misperceive or misjudge the effects of drugs, but they are not central to the concept of medication spellbinding, which is biologically based. Psychological influences include the following:

- *Psychological denial.* Individuals overcome by emotional suffering are likely to deny the degree of their psychological dysfunction. They do not want to admit to being severely mentally impaired. If they are hoping to feel better with the use of a drug, or if the drug initially caused euphoria or emotional anesthesia, their denial can be further reinforced.
- *Placebo effect.* Patients have faith that biopsychiatric interventions will be helpful, rather than harmful, encouraging them to disregard drug-induced dysfunction or to mistakenly attribute it to their emotional problems.
- *Compliance.* To an extraordinary extent, patients will tell doctors what the doctors want to hear. If a psychiatrist clearly wants to hear that a drug is helpful, and not harmful, many patients will comply by giving false information or by withholding contradictory evidence.
- *Psychologically induced confusion.* Emotionally upset individuals can easily lose their judgment concerning the cause of their worsening conditions. They can easily mistake a negative drug effect, such as rebound anxiety from a benzodiazepine tranquilizer like Xanax or Ativan or depression from a neuroleptic like Risperdal or Abilify, for a worsening of their emotional problems. Typically, they blame themselves rather than the medication. This confusion is abetted when the physician exaggerates the drug's benefits and fails to inform the patient of its potential adverse effects.

## IATROGENIC HELPLESSNESS AND DENIAL IN AUTHORITARIAN PSYCHIATRY

In the previous edition of *Brain-Disabling Treatments in Psychiatry,* I introduced the term *iatrogenic helplessness and denial in authoritarian psychiatry* to designate a guiding principle of biopsychiatric interventions (see also Breggin, 1983a). Although they may not recognize or admit what they are doing, biological psychiatrists use authoritarian techniques,

enforced by brain-disabling interventions, to produce increased helplessness and dependency on the part of the patient. In their journals and conferences they frequently speak of obtaining "medication compliance"—getting the patient to take drugs. In an effort to push their patients to take medications, biological psychiatrists convince them that they have biochemical imbalances, and even genetic disorders, that require treatment with drugs. This creates a submissive, dependent relationship with the prescribing physician. Physically, the psychiatrist prescribes multiple drugs or electroshock, causing brain damage and dysfunction that increases the patient's tendency to be submissive and dependent. Often these doctors encourage their patients to enter mental hospitals, and sometimes they force them into hospitals or into outpatient commitment in which they are required to submit against their will to medication.

This may seem like a harsh indictment, but it is instead a harsh reality. While most psychiatrists may not realize that they are causing dependency and helplessness, millions of patients throughout the nation are misled into believing that they have biological and genetic defects that can be corrected by medication or electroshock, in effect making them feel helpless and dependent on their doctors and on physical treatments. When many of these patients become worse as a result of treatment, they are told that their underlying "mental illness" is surfacing. When multiple drugs lead to escalating adverse emotional effects, more drugs are added to the regimen, and too often the patient is hospitalized. Rarely do these doctors admit that the drugs are the source of the patients' worsening problems and that a drug-free period of time may lead to recovery. Throughout the process, the patients remain so spellbound that they cannot perceive how badly there are doing or that the drugs are ruining their lives.

The concept of iatrogenic helplessness and denial includes the patient's and the doctor's mutual denial of the damaging impact of the treatment as well as their mutual denial of the patient's underlying psychological and situational problems. Overall, iatrogenic helplessness and denial accounts for the frequency with which psychiatry has been able to utilize brain-damaging technologies, such as electroshock and psychosurgery, as well as toxic medications. Spellbinding explains how the biological impact of the medication reinforces iatrogenic helplessness and denial.

## RELATIONSHIP BETWEEN MEDICATION SPELLBINDING AND IATROGENIC HELPLESSNESS AND DENIAL

The concept of medication spellbinding expands or elaborates on the concept of iatrogenic helplessness and denial. It specifically observes that

patients exposed to psychiatric drugs, electroshock, or lobotomy display the following indications of helplessness and denial: (a) impairment in their ability to perceive their treatment-induced mental dysfunction; (b) inability to identify that the drug, shock, or lobotomy is causing their deterioration and a tendency to attribute their distress to some other source, such as their own so-called mental illness or someone else's distressing effect on them; (c) an unrealistic belief that they are doing better than ever, when they are doing worse; and (d) in extreme cases, the development of compulsive, destructive, ego-alien actions, sometimes of a manic quality.

Most people who seek psychiatric treatment are already vulnerable to becoming helpless and dependent. Before the potential patient encounters a psychiatrist, he or she has usually been feeling helpless for some time. In my formulation, as described in *The Heart of Being Helpful* (1997b), helplessness is the common denominator of all psychological failure. Helplessness is at the core of most self-defeating approaches to life. People who feel helpless tend to give up using reason, love, and self-determination to overcome their emotional suffering, inner conflicts, and real-life stresses. They instead seek answers from outside themselves. In modern times, this often means from so-called experts.

Iatrogenic helplessness and denial, and medication spellbinding, go far beyond relatively benign *suggestion* (as used in medicine and psychiatry, e.g., to help overcome physical pain). First, in iatrogenic helplessness and denial, including medication spellbinding, the psychiatrist compromises the brain of the patient, enforcing the patient's submission to suggestion through mental and physical dysfunction. Second, in iatrogenic helplessness and denial, the psychiatrist denies to himself or herself the damaging effects of the treatment as well as the patient's continuing psychological or situational problems.

Brain damage and dysfunction from any cause, including accidents and illness, frequently produce helplessness and denial, but only in psychiatry is damage and dysfunction used as treatment to produce these disabling, spellbinding effects.

## MENTAL AND EMOTIONAL SUFFERING ROUTINELY TREATED WITH BIOPSYCHIATRIC INTERVENTIONS HAVE NO KNOWN GENETIC OR BIOLOGICAL CAUSE[5]

Keep in mind that the validity of the brain-disabling concept does not depend on the origin of psychiatric disorders but rather on the known effects of biopsychiatric treatment. Even if one or another psychiatric disorder should turn out to have a biological basis, it would not justify using current medications, all of which disable the brain. Although most

people who seek psychiatric care have nothing wrong with their brain function, some may have an underlying physical disorder (not a mythical biochemical imbalance). If, for example, a patient has a thyroid disorder or diabetes that is causing feelings of depression, the patient should be given proper medical treatment to correct the underlying physical disorder and not antidepressant drugs.

So-called schizophrenia is usually put forward as the best model for a biological and genetically based psychiatric disorder. For critiques of the genetics of schizophrenia, see Breggin (1991b) and, more recently, Joseph (1999, 2004a, 2004b, 2006). There are many detailed criticisms of the brain disease model for schizophrenia (see, e.g., Siebert, 1999) and for biochemical theories of psychiatric disorders (Breggin, in press; Colbert, 2001).

Timothy Crow's (2007) article "How and Why Genetic Linkage Has Not Solved the Problem of Psychosis: Review and Hypothesis" confirmed that even the genetic researchers admit they have not found a genetic linkage for schizophrenia. Meanwhile, the search for a biological basis, or a biological marker, for depression also continues to run aground. "What Have We Learned About the Neurobiology of Major Depression?" by Maria Oquendo and Ramin Parsey (2007) demonstrated that as of April 2007, no genetic or biological causes have as yet been discovered. As always, the editorial talks about how the search must go on. All of this, of course, will feel intellectually jarring to most health care providers, who have been taught to believe that psychiatric disorders have known biological and genetic causes.

Despite more than 200 years of intensive research, no commonly diagnosed psychiatric disorders have been proven to be either genetic or biological in origin, including the diagnostic categories of schizophrenia, major depressive disorder and bipolar disorder, the various anxiety disorders, and childhood disorders such as attention-deficit hyperactivity.

At present, there are no known biochemical imbalances in the brain of typical psychiatric patients—until they are given psychiatric drugs. It is speculative and even naïve to assert that antidepressants such as Prozac correct underactive serotonergic neurotransmission (a serotonin biochemical imbalance) or that neuroleptics such as Risperdal or Seroquel correct overactive dopaminergic neurotransmission (a dopamine imbalance). The failure to demonstrate the existence of any brain abnormality in psychiatric patients, despite decades of intensive effort, suggests that these defects do not exist.

It seems theoretically possible that some of the problems treated by psychiatrists and other health practitioners could eventually be proven to have a biological basis. As already mentioned, mental function often improves when certain physical disorders, such as hypothyroidism

or Cushing's syndrome, are adequately treated with appropriate medical interventions.

However, the vast majority of problems routinely treated as so-called mental disorders do not remotely resemble diseases of the brain or body. For example, they do not produce the cognitive deficits in short-term memory or abstract reasoning characteristic of brain disorders. They are not accompanied by fever or laboratory signs of illness. Unlike many neurological disorders, they are not degenerative. To the contrary, neurological and neuropsychological testing usually indicates normal if not superior brain function, and the body is healthy—until the brain-damaging treatments are begun. There seems little likelihood that any of the routinely treated psychiatric problems are based on brain malfunction, rather than on the life experiences of individuals with normal brains.

To claim that an irrational or emotionally distressed state, however extreme, in itself amounts to impaired brain function is simply false. An analogy to television sets and computers may illustrate why this is so. If a TV program or Internet site is offensive or irrational, it does not indicate that anything is wrong with the electronics of the television set or the hardware of the computer. It makes no sense to attribute the bad programming or the offending Internet site to bad wiring. Similarly, a person can be very disturbed psychologically, without any corresponding defect in the wiring of the brain.

However, the argument is moot since no contemporary biopsychiatric interventions can truthfully claim to correct a brain malfunction the way an expert can fix a broken TV set or computer. Instead, we blindly inflict toxic substances on a brain that is far more subtle and vulnerable to harm than the hardware of a TV or computer. We even shock or mutilate the brain in ways that would appall TV or computer repair persons or their customers, all of whom would instantly recognize that these treatments were ruining their TV sets or computers.

It is often suggested that persons suffering from extremes of emotional disorder, such as hallucinations and delusions or suicidal and murderous impulses, are sufficiently abnormal to require a biological explanation for their mental processes or behavior. However, the emotional life of human beings has always included a wide spectrum of mental and behavioral activity. Individual willingness or ability to remain rational and to control one's emotions varies enormously. That a particular mental state or action is especially irrational or destructive does not, per se, indicate a physical origin. If extremes require biological explanation, then it would be more compelling to ascribe extremely ethical, rational, and loving behaviors to genetic and biological causes since they are especially rare in human life.

The fact that a drug works—that is, influences the brain and mind in a seemingly positive fashion—does not confirm that the individual suffers from an underlying biological disorder. Throughout recorded history, individuals have medicated themselves for a variety of spiritual and psychological reasons, from the quest for a higher state of consciousness to a desire to make life more bearable. Alcoholic beverages, coffee and tea, tobacco, and marijuana are commonly consumed by people to improve their sense of wellness. Yet there is no reason to believe that the results they obtain are due to an underlying biochemical imbalance.

## CONCLUSION

As I have discussed in earlier books (Breggin, 1991a; Breggin et al. 1994a, 1994b), I believe that the concepts of mental illness and mental disorder are misleading and that none of the problems commonly treated by psychiatrists are genetic or biological in origin. The terms *attention-deficit hyperactivity disorder, schizophrenia,* and *major depressive disorder,* for example, are based on concepts whose validity can easily be challenged. However, the brain-disabling principles remain valid, even if some of the mental phenomena that are being treated turn out to have a genetic or biological basis. All of the currently available biopsychiatric treatments—drugs, electroshock, and psychosurgery—have their primary or "therapeutic" effect by impairing or disabling normal brain function, causing iatrogenic helplessness and denial and, more specifically, intoxication anosognosia (medication spellbinding).

## NOTES

1. The term *euphoria* as used in psychiatry indicates an exaggerated, irrational, or unrealistic sense of well-being. It can be psychological in origin but is commonly caused by brain damage or drug toxicity.
2. Because most laypersons and many physicians do not know the generic names for drugs, I will occasionally use trade names, such as Prozac and Risperdal, throughout the book. However, the appendix offers a list of psychiatric drugs by category, including both trade and generic names.
3. Euphoria is unusual in patients treated with the neuroleptics because of the suppressive effects on the central nervous system (see chapter 2). It is more common among patients treated with antidepressants, stimulants, and benzodiazepine tranquilizers, especially alprazolam. Drug-induced mania is an extreme of medication spellbinding.
4. The concept of medication spellbinding occurred to me when I was reviewing a lifetime of clinical and legal cases in the process of writing a new book, *Medication Madness*

(Breggin, in press), which describes approximately 70 cases that I had personally evaluated (see also Breggin, 2006e).

5. In the previous edition of this book, this subtitle was one of the brain-disabling principles, but I have removed it from the principles because, even if some future psychiatric disorder proves to have a genetic or biological basis, the current treatments in use will nonetheless remain toxic and cause brain disability.

CHAPTER 2

# Deactivation Syndrome (Chemical Lobotomy) Caused by Neuroleptics

In 2006, the so-called atypical or newer neuroleptics increased their dominance over the $11.5 billion business for antipsychotic drugs. As a group, the antipsychotics placed fourth in sales among all categories of drugs, including anticholesterol, antihypertension, and antidepressant drugs. That such specialized drugs for the treatment of psychosis and mania could garner such a huge market share is a tribute to drug company promotional skills in convincing doctors to use these medications for a wide swath of psychiatric problems, from behavior problems in children to insomnia in adults. Antipsychotic drug sales have nearly doubled since 2002.

Individual antipsychotic drugs earned the following market shares: Seroquel (26%), Risperdal (22%), Zyprexa (21%), Abilify (17%), and Geodon (6%), leaving a mere 8% for others (Vital Signs, 2007). According to IMS Health (2007), Seroquel was ninth among all drugs in sales in the United States in 2006, with total revenues of $3 billion.

In the United States, Seroquel has the growing market advantage of being approved not only to treat mania but also to treat the depression phase of bipolar disorder. It is expected to generate $1.76 billion from "global *bipolar* disorder sales" in 2008 ("New Hope," 2006). Meanwhile, the rest of the world has not quite caught on to the Seroquel promotional campaign, and Zyprexa and Risperdal led global sales for

antipsychotic drugs, with $4.7 billion and $4.6 billion in sales, respectively (IMS Health, 2007). They were seventh and eighth among all medical drugs.

Despite enormous hype to the contrary, it soon became apparent that these newer medications were no less harmful than the older ones. Studies showing a lower rate of adverse effects simply used comparatively lower doses (Smith, 2001). Given that these drugs are neither safer nor more effective than older drugs like perphenazine (Trilafon; see the subsequent sections), and given that they cost a great deal more (Rosenheck et al., 2006), this was another triumph of pharmaceutical marketing.

## THE MYTH THAT ATYPICAL ANTIPSYCHOTIC DRUGS ARE WEAKER $D_2$ BLOCKERS

More than a dozen drugs, almost all of them in use for many years, can be classified as neuroleptics. The phenothiazine derivatives were originally the most commonly used class of neuroleptic drugs. Chlorpromazine is the prototype, developed in France and introduced into North America in 1953 by Heinz Lehmann. Its brand name in Canada and England is Largactil, and in the United States, Thorazine. The antidepressant amoxapine (Asendin) is metabolized into a neuroleptic and has similar effects and, more important, adverse effects, such as tardive dyskinesia. All the classic neuroleptics block dopamine, but all of them also affect other neurotransmitter systems.

Most important, all of the newer antipsychotics—aripiprazole (Abilify), ziprasidone (Geodon), paliperidone (Invega), risperidone (Risperdal), quetiapine (Seroquel), olanzapine plus Prozac (Symbyax), and olanzapine (Zyprexa)—also block dopamine. In fact, they are pharmacologically classified as having a high affinity for $D_2$—meaning that they bind strongly to $D_2$ receptors, causing a strong blockade. The casual reader can find this information in *Drug Facts and Comparisons* (2007, p. 1280) and its table "Antipsychotic Receptor Affinity"[1] (see also Janssen, 2007, regarding Risperdal).

In addition to textbook summaries, many controlled research studies show that atypicals produce high receptor occupancy. Shortly after olanzapine was introduced, Kapur et al. (1998) used positron emission topography (PET) imaging with 12 patients diagnosed schizophrenic to determine $D_2$ receptor occupancy caused by the new atypical antipsychotic at clinical doses. The patients were medicated until steady state plasma levels were achieved. Patients taking 5–20 mg/day showed 43% to 80% occupancy, while patients taking 30–40 mg/day showed 83% to 88% occupancy. In its usual clinical dose range of 10–20 mg, occupancy

varied from 71% to 80%. The authors described this degree of receptor occupancy as similar to that of risperidone.

As a comparison, haloperidol (Haldol) is generally considered to be among the most potent neuroleptics and the most likely to cause extrapyramidal reactions. In a double-blind study of first-episode patients diagnosed with schizophrenia, the subjects were randomly assigned to take 1, 2, 3, or 5 mg/day (Kapur et al., 2000). If the patients did not respond to the lower doses, they were raised to the limit of 5 mg/day. These are relatively small doses. The recommended initial dose for moderate symptoms or geriatric or debilitated patients is 1–6 mg/day (*Drug Facts and Comparisons,* 2007). For severe or chronic patients, it is 6–15 mg/day, with higher doses for prompt control.

All patients were evaluated at 4 weeks. Patients showed a wide range of $D_2$ occupancy (38% to 87%). The likelihood of extrapyramidal reactions increased when occupancy exceeded 78%. Note that all of these occupancy figures are within the same range as those found by the same team (Kapur et al., 1998) for Zyprexa and Risperdal. This explodes the myth that atypicals have weaker occupancy of $D_2$ receptors.

Remington et al. (2006) conducted a similar PET study of the long-acting injectable form of risperidone at doses of 25, 50, or 75 mg every 2 weeks. After reaching stabilization, nine patients with a diagnosis of schizophrenia or schizoaffective disorder were scanned twice, 3 days postinjection and 5 days before the next injection. According to Remington et al. (2006), "all three doses of injectable risperidone showed peak D(2) occupancy levels above the 65% threshold associated with optimal clinical response; the 75-mg dose approximated the 80% threshold linked to increased risk of extrapyramidal reactions." Clearly, it is all in the dose; all of the atypicals are potent dopamine blockers.

Indeed, some of the older neuroleptics have less affinity or impact on $D_2$ than the newer ones. Molindone (Moban), for example, has a decidedly *weak* affinity for $D_2$ (*Drug Facts and Comparisons,* 2007), but it is rarely used.

Atypical neuroleptics are commonly given to children. Moran-Gates et al. (2007) from the Massachusetts General Hospital and Harvard Medical School examined the brain tissue of juvenile and adult rats treated with risperidone. They found that risperidone "has high affinity for $D_2$ receptors in both age groups, which is in agreement with other published reports" (p. 451). However, they found that long-term dosing (3 weeks) had a much more profound impact on the $D_2$ receptors of the juvenile animals, causing an increase in the number of these receptors. There was a 90% increase in $D_2$ receptor binding in juvenile rats, compared to 30% in adults, "which further reflects the greater sensitivity of developing animals" (p. 453) to longer-term exposure to risperidone. This

up-regulation (increased dopamine receptors in response to dopamine blockade) is considered the likely mechanism of extrapyramidal reactions and tardive dyskinesia. Unfortunately, the prescription of antipsychotic or neuroleptic drugs to children and youth continues to rise.

Much is also made of the observation that the newer atypical neuroleptics impact on a greater variety of neurotransmitter systems than the older ones (e.g., Lieberman et al., 2005b). However, there is no reason to suspect that impacting on multiple neurotransmitter systems would improve either safety or efficacy. To the contrary, it would seem bound to increase the spectrum of adverse effects. But even in regard to their impact on multiple neurotransmitter systems, the atypicals are not unique. All of the older neuroleptics affect at least three neurotransmitter systems, such as serotonin and histamine, and several affect four or five of them. For example, old-fashioned thioridazine (Mellaril) impacts at least five neurotransmitter systems.

Despite these facts, establishment psychiatry—including Lieberman et al. (2005a), the most cited neuroleptic study in years (see subsequent paragraphs)—continues to describe the atypicals as possessing a significantly and clinically important lower affinity for $D_2$ receptors. Why would so many experts buy into drug company propaganda that the atypicals have a relatively low affinity for $D_2$ and that their greater impact on numerous receptors is somehow an advantage? Because the experts are closely allied professionally and economically with the drug companies and their interests. As in the giant National Institute of Mental Health (NIMH)-sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study by Lieberman et al. (2005a), virtually all the experts have a high affinity for drug company "receptors," finding ways of making considerable money as consultants, researchers, and speakers' bureau members. Jeffrey Lieberman, first author in the CATIE study, reports having received research funding from AstraZeneca Pharmaceuticals, Bristol-Myers Squib, GlaxoSmithKline, Janssen Pharmaceutica, and Pfizer and consulting and educational fees from AstraZeneca, Bristol-Myers Squid, Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Novartis, Pfizer, and Solvay. The first seven CATIE authors report extensive ties to drug companies, and the eighth, Sonia Davis, is an employee of Quintiles, a giant support firm for the drug industry, specializing in helping speed drugs to the market. The ninth author also has ties to drug companies, and the last three worked for the government. It is astonishing that NIMH would conduct its most important study of antipsychotic drugs by relying entirely and exclusively on experts with drug company ties.

Although this fact seems to have been lost on most medication prescription writers, the dopamine-blocking capacity of all the newer antipsychotic

drugs means that their adverse effects will include the worst effects of the older neuroleptics, including the production of tardive dyskinesia and neuroleptic malignant syndrome (chapter 4; see the individual drug labels in the *Physicians' Desk Reference*, 1973, 1978, 1995–2007). It also helps to account for their primary effect of deactivation. In addition, the newer antipsychotic drugs pose even greater risks of causing potentially life-threatening disorders, including marked obesity, elevated cholesterol, and potentially lethal diabetes, cardiovascular disease, and pancreatitis.

Overall, the concept of atypical is a marketing ploy with little clinical reality. These drugs combine the risks associated with the older neuroleptics with very serious new risks. Nonetheless, health care providers, including sophisticated physicians, seem taken in by the claims. Adamou and Hale (2004), for example, expressed surprise when three of their patients developed extrapyramidal reactions, including one severe case with "oculo-gyric crisis, dysarthria, torticollis, dysphagia, tremor, and rigidity." (One wonders if he had an elevated temperature and a missed case of neuroleptic malignant syndrome.) Different neuroleptics require different doses for similar effects and may exaggerate one or another toxic effect. They also vary in the length of time they remain active in the body. Nonetheless, with some exceptions, most of these drugs can be described as a single group sharing the same characteristics and side effects. There is no evidence that any of these drugs has a substantially different impact on mental functioning, other than the tendency for some to produce more sedation. In my clinical experience, Zyprexa, Seroquel, Abilify, and Risperdal, for example, are at least as potent in suppressing the will and motivation as any of the older antipsychotic drugs.

Various neuroleptics are also used for nonpsychiatric purposes, usually in smaller doses for shorter durations. However, severe effects can sometimes develop from these limited uses. Reserpine (Serpasil) is a neuroleptic that is more often used to suppress the symptoms of tardive dyskinesia (chapter 4). Prochlorperazine (Compazine) is used as an antiemetic and rarely as a neuroleptic. If given in sufficient doses to manifest psychoactive effects, these drugs produce the same emotional indifference as the other antipsychotic drugs.

Other nonpsychiatric preparations with neuroleptic effects include some antihistamines, such as methdilazine (Tacaryl) and trimeprazine (Temaril); some antinausea drugs, such as thiethylperazine (Torecan); and adjuncts to anesthesia, such as propiomazine (Largon) and promethazine (Phenergan), which is also used as an antinausea, anti-motion-sickness agent. These drugs are less potent than neuroleptics used in psychiatry, but in sufficient doses, they have similar adverse effects.

Metoclopramide (Reglan) is used in gastroesophageal reflux, diabetic gastric stasis, and as an antiemetic. Reglan is identical to older

neuroleptics in its effects. It is well established that Reglan can cause irreversible neurological effects identical to the routinely used neuroleptics. Some researchers estimate the prevalence of Reglan-induced tardive dyskinesia to be 100 times more than the 0.2% reported in the *Physicians' Desk Reference*.

I have evaluated numerous cases of infants and children who have been treated with Reglan for gastric problems, resulting in severe and varied neurological disorders, apathy, retarded growth, and developmental delay. In cases familiar to me, the doctors recognized that the condition of the children was declining but failed to identify Reglan as the offending agent. While continuing the Reglan, they submitted the children to costly, dangerous, and intrusive medical tests in search of the elusive cause. In some of my forensic cases, doctors ended up blaming the mothers for "poisoning" their children when, in reality, the doctors themselves were dispensing the poison.

## EXAMPLES OF DIFFERENCES AMONG ATYPICAL NEUROLEPTICS

Although in many ways they can be treated as a single group of drugs, especially in regard to producing lobotomy-like activation, there are significant differences among the antipsychotic or neuroleptic drugs. Risperidone and clozapine provide examples.

### Clozapine (Clozaril)

The only atypical antipsychotic drug that lacks a high affinity for $D_2$ is clozapine. It has a relatively weak tendency to block $D_2$, and therefore it is the only one that is less likely to produce common adverse neurological effects like tardive dyskinesia. However, clozapine so often produces a dangerous and potentially lethal drop in the white blood cell count (agranulocytosis) that it requires continuous monitoring with blood tests and is infrequently prescribed. Ironically, while classified as an atypical neuroleptic, clozapine is a very old drug that was originally taken off the market in some European countries because of its toxicity, before it was later reintroduced into the U.S. market in 1989 with much fanfare, as if it were a brand new drug with great promise.

Clozapine causes a particularly high rate of grand mal seizures, estimated at 4% to 5% in the first year. This is a very serious hazard. The drug frequently produces severe low blood pressure and increased heart rate, potentially resulting in cardiovascular collapse. It can also cause hypertension. It can cause fever and a flulike syndrome. Respiratory arrest

has been reported (Westlin, 1991). It can be particularly hazardous for the elderly, who may risk falls, cardiovascular problems, or delirium (Pitner et al., 1995).

Although not a potent $D_2$ blocker, clozapine seems to be more potent in this regard in the limbic (emotion-regulating) system than in the striatal region (which controls both emotion and voluntary movement; Chiodo et al., 1983). Because of the drug's greater impact on the frontal lobes and limbic system, it was thought that it would produce more "therapeutic" effect with fewer extrapyramidal side effects. The drug probably does produce a more profound deactivation or lobotomy-like syndrome in some patients, accounting for its reputation for sometimes working better than other neuroleptics. As a result, it probably has a greater risk of producing permanent frontal lobe damage and tardive dementia or tardive psychosis.

Concern about clozapine's especially damaging effect on higher brain function was voiced as early as 1977 by Ungerstedt and Ljungberg, based on the European experience. Chouinard and Jones (1982) pointed to observations on reactive psychoses following withdrawal from clozapine and commented, "This convincing evidence of clozapine's ability to induce supersensitivity psychosis might be related to both the short half-life of the drug and its greater affinity for mesolimbic dopamine receptors." Observations have also indicated that withdrawal psychoses may be more frequent and severe than with the older neuroleptics (see chapter 5). There is a report of a clozapine withdrawal syndrome that includes new symptoms of agitation, restlessness, shakiness, dyskinesia, confusion, sweating, aggression, and suicidal behavior ("Clozapine Withdrawal Syndrome," 1994; Richardson et al., 1993). Supersensitive or withdrawal psychoses occur when the antipsychotic drug dose is reduced or stopped. It can be viewed as the mental equivalent of tardive dyskinesia, since both probably result from a reactive hyperactivity of the previously blocked dopamine functions (chapter 5).

Clozapine's anticholinergic effects can cause confusion and delirium as well as sedation and lethargy. The severity of withdrawal psychosis may be due to cholinergic rebound. Clozapine can aggravate or cause hypersalivation, glaucoma, constipation and ileus, and urinary retention (Baldessarini et al., 1991). Weight gain is also a potentially very serious problem.

While reportedly producing fewer extrapyramidal reactions, clozapine can produce every one of the neurological reactions associated with neuroleptic use, including neuroleptic malignant syndrome (Anderson et al., 1991; Dasgupta et al., 1991) and tardive dyskinesia (Weller et al., 1993).

Clozapine's efficacy has been highly touted to the public but in reality is questionable, even by conventional standards (see comments of

psychiatrist Herbert Meltzer in Winslow, 1990). Furthermore, in the arena of neuroleptics, consistent with the brain-disabling principles, a better or stronger drug is in reality a more suppressive and potentially more destructive drug.

A basic tenet of the brain-disabling principles is that all psychiatric drugs affect human beings and animals in a like fashion, without specificity for any disorder. Sorge et al. (2004) found that clozapine affects human and rat physiology in similar ways, including disrupting the sleep–wake cycle and producing abnormal brain temperatures.

## Risperidone (Risperdal)

Chapter 1 examined three risperidone studies that confirm the brain-disabling principles of psychiatric treatment by demonstrating that the drug causes a metabolic suppression in the frontal and temporal lobes (deactivation) that occurs in both normal persons and patients diagnosed with schizophrenia, and that this disabling effect correlates with a reduction in the expression of symptoms, such as hallucinations and delusions, that require a fully functioning brain. As previously noted, if measured, the effect would also correlate with an overall reduction in spontaneous mental activity and verbal expressions, which are common clinical phenomena in patients who experience psychomotor retardation in response to neuroleptics.

Risperdal was first marketed in 1994 as an atypical neuroleptic. The clinical trials, most of which lasted a few weeks, were too short to determine the rate of tardive dyskinesia and many other adverse effects. Indeed, the brief controlled clinical trials used for the approval of both clozapine and risperidone do not provide sufficient information to determine either efficacy or safety since the drugs would be used for months and years in individual patients, rather than for a few weeks (see chapter 13). Patients taking the medications over the coming years will provide the experimental data. However, since Risperdal is a potent dopamine blocker, it should have been anticipated that it would cause similar adverse reactions as the older neuroleptics. In my own experience, I have evaluated many cases of tardive dyskinesia caused by Risperdal, Zyprexa, and Geodon. Meanwhile, the Food and Drug Administration (FDA) has required the same tardive dyskinesia and neuroleptic malignant syndrome warnings on the labels of clozapine and risperidone as on the labels of the older neuroleptics.

Risperdal has a particular tendency to produce adverse stimulant effects, including insomnia, agitation, and anxiety. Probably because of these stimulant effects, it may have an increased risk of causing mania (Dwight et al., 1994). Stimulation may also account for risperidone-induced

rage attacks and the urge to resume substance abuse, although the author of the report believes that these reactions are due to despair from increased psychological insight (Post, 1994). In addition to stimulation, the drug frequently causes fatigue, sleepiness, or insomnia.

Risperdal causes all the extrapyramidal reactions found with other neuroleptics, including tardive dyskinesia (Addington et al., 1995) and neuroleptic malignant syndrome (Mahendra, 1995; Singer et al., 1995; see chapter 4). It is too early to tell if the rate of tardive dyskinesia will differ from that of other neuroleptics.

A report found that even small doses of Risperdal (average dose of 1.7 mg/day) produced or worsened acute extrapyramidal reactions in one-third of an elderly population suffering from dementia (Baker, 1996). Among 41 patients, 6 developed new parkinsonism, 5 had a worsening of previous parkinsonism, one developed cervical dystonia, and one developed neuroleptic malignant syndrome while also taking Tegretol and Mellaril.

Like most neuroleptics, Risperdal can cause mammary cancer in rats and mice, but this finding has not been taken seriously enough by the FDA, the profession. or the drug companies.

## CLINICAL ANTIPSYCHOTIC TRIALS OF INTERVENTION EFFECTIVENESS (CATIE)

In 2005, an NIMH multisite study called CATIE compared the older neuroleptic perphenazine (Trilafon) and atypical neuroleptics olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), and ziprasidone (Geodon; Lieberman et al., 2005a; see also Nasrallah, 2007; Rosenheck et al., 2006; Weiden, 2007a). Phase I involved 1,460 patients diagnosed with schizophrenia initially randomly assigned in a double-blind study to one of the five neuroleptics. The study lasted 18 months, with safety and tolerability outcomes evaluated at 1, 3, 6, 9, 12, 15, and 18 months.

In a shock to clinicians and the pharmaceutical industry alike, there was little difference among the various medications, including old-fashioned, inexpensive perphenazine, in regard to the primary criterion for efficacy, the length of period that the patients remained on their randomly assigned initial medication. Overall, a whopping 74% discontinued the study medication before 18 months: 64% for olanzapine, 74% for risperidone, 75% for perphenazine, 79% for ziprasidone, and 82% for quetiapine. According to Lieberman (2005a), "the majority of patients in each group discontinued their assigned treatment owing to inefficacy or intolerable side effects or other reasons."

Note that perphenazine (Trilafon) is in the middle of the pack; there was no statistical difference between it and the leader, olanzapine (Zyprexa). But Zyprexa had the worst adverse effect profile (see subsequent sections).

In addition, over the length of the study, treatment effects equalized among all the medications as measured on the Positive and Negative Syndrome Scale and the Clinical Global Impressions Scale. Again, there was no advantage to the newer antipsychotic drugs. These two scales are among the most commonly used to rate treatment effectiveness of these medications.

The most poorly tolerated drug, quetiapine (Seroquel), is the most commonly used in the United States and brings in the greatest revenues. Its success is a marketing triumph, not a clinical one.

Clozapine (Clozaril) was also studied, but because of the requirements for blood testing for agranulocytosis, it was not double blind. Once again demonstrating the power of clinical bias, as the only drug that was not blinded, clozapine demonstrated some greater efficacy than the others.

CATIE once again confirmed that patients do not like to take these drugs, largely due to their adverse effects, but also because of their lack of helpfulness. As noted, at the completion of the 18-month study, 74% of patients discontinued their original drug. Nasrallah (2007) viewed this as confirmation that "both patients and clinicians are often dissatisfied with the outcome achieved." There were many alternative methods for evaluating this study (e.g., Weiden, 2007a), but none gave a particularly favorable picture of any of the drugs, and none gave a significant advantage to any of the several atypicals over the older drug, perphenazine.

There has been much hype about the newer antipsychotics posing less risk of causing extrapyramidal side effects and tardive dyskinesia. However, as already discussed, with the exception of clozapine, they are all potent dopamine blockers (subtype $D_2$), and all $D_2$ blockers cause extrapyramidal effects and tardive dyskinesia. Nasrallah (2007) summed up, "There were no statistically significant differences between the rates of extrapyramidal side effects, movement disorders, or akathisia" (p. 9). However, more patients treated with perphenazine discontinued treatment because of extrapyramidal effects (Lieberman et al., 2005a), suggesting that they were more distressing. Lieberman et al. (2005a) stated in their discussion that "the proportion of patients with extrapyramidal symptoms did not differ significantly among those who received first-generation and second-generation drugs in our study. Despite this finding, more patients discontinued perphenazine than other medications owing to extrapyramidal effects." Compared to the other drugs, 8% of perphenazine patients discontinued because of extrapyramidal effects, versus 2% to 4% for the newer drugs.

Anticholinergic drugs are typically given to patients with extrapyramidal symptoms in order to provide relief. According to Lieberman et al. (2005a), "fewer patients receiving quetiapine were prescribed anticholinergic drugs (3% vs. 8 to 10%)." The real news is that patients taking the older drug, perphenazine, received roughly the same amount of anticholinergic drugs as patients taking all the newer drugs (except for quetiapine), indicating again that there was little or no difference between the older drug and the newer one in regard to causing extrapyramidal symptoms.

A point that seems to missed is that since the older drug, perphenazine, was in the middle of the pack in terms of how long patients remained on it, the extrapyramidal effects did not make perphenazine overall less tolerable than the newer antipsychotics. According to Lieberman et al. (2005a), "there were no significant differences between groups in time until discontinuation due to intolerable side effects." CATIE confirmed the high risk of developing metabolic syndrome, an array of adverse effects related to weight gain, elevated blood sugar, and elevated cholesterol, while exposed to atypical neuroleptics such as Zyprexa, Risperdal, and Seroquel. CATIE measured weight change, proportion of patients gaining weight, average weight change per month, blood glucose increased, hemoglobin $A_{1c}$ change (a diabetes test), cholesterol change, and triglyceride change. They did not measure another variable, blood pressure. The metabolic syndrome puts patients at risk for diabetes and cardiovascular disease. In a subtest of 689 patients, where the best data were available, the prevalence of metabolic syndrome was a shocking 40.9% to 42.7%, depending on the criteria, for the atypical antipsychotic drugs. Shockingly, more than 50% of the females developed metabolic syndrome.

Consistent with the huge numbers of lawsuits being settled by Eli Lilly for Zyprexa-induced diabetes (chapter 14), Zyprexa was the worst offender in regard to causing the metabolic syndrome. Zyprexa patients gained an average of 2 pounds/month. That would add up to 36 pounds in 18 months. Zyprexa patients also had greater problems with elevated glycosylated hemoglobin, total cholesterol, and triglycerides. As a medical expert in product liability cases against Eli Lilly, I have evaluated cases in which Zyprexa caused the sudden onset of lethal diabetes in relatively young adult patients who were previously free of the disorder.

If these drugs were not being prescribed to so-called mental patients, and especially to those labeled as schizophrenic, the findings on metabolic syndrome would probably lead the FDA to withdraw them from the market.

We will examine recent studies, some involving atypical neuroleptics, confirming that antipsychotic drugs shorten the life span. The production of a metabolic syndrome undoubtedly contributes to this increased risk of dying. However, this risk was also detected in regard to

the older neuroleptics. It is due, at least in part, to the indifference to oneself, including lack of self-care, caused by all lobotomizing agents, including the neuroleptics.

## DEACTIVATION SYNDROME

One of the great myths within psychiatry is the specificity of neuroleptics such as Thorazine, Haldol, Prolixin, Zyprexa, Risperdal, Seroquel, or Geodon for the treatment of patients diagnosed with schizophrenia.[2] Despite a lack of confirmatory studies (reviewed in Breggin, 1983b, 1991c; Jackson, 2005), many clinicians and researchers postulate a specific antipsychotic, and even an antischizophrenic, effect for these drugs. The concept is used to justify neuroleptic treatment as a legitimate medical approach. Instead, the neuroleptics produce what can be called a deactivation syndrome or effect, a central aspect of the lobotomy syndrome.

To help organize the clinical material that follows, it may be helpful to begin with a closer look at the concept of deactivation (Breggin, 1993):

> The term deactivation will be used to designate a continuum of phenomena variously described as disinterest, indifference, diminished concern, blunting, lack of spontaneity, reduced emotional reactivity, reduced motivation or will, apathy, and, in the extreme, a rousable stupor.

The deactivation effect is the essence of what is euphemistically called the *antipsychotic effect*. Consistent with the brain-disabling principles of psychiatric treatment, this lobotomy-like impact is the sought after, primary, and supposedly therapeutic effect. Any specific antipsychotic effect is very speculative compared to the obvious and almost unvarying lobotomy-like deactivation effect.

We will find that nearly all psychiatric drugs can produce some degree of deactivation. Even stimulants, such as Ritalin, can cause sufficient apathy or indifference in a child to enable adults to more easily control or direct the child (see chapter 11). The SSRIs, such as Prozac and Paxil, can also produce an apathy syndrome (chapter 7). However, deactivation appears in its purest form in neuroleptic treatment.

Deactivation is closely related to the frontal lobe syndrome; it describes the affective or emotional component. Adams and Victor (1989) divide the manifestations of frontal lobe syndrome into (a) cognitive and intellectual changes such as loss of abstract reasoning and planning, (b) personality deterioration, and (c) "impairment or lack of initiative and spontaneity" (p. 333). Deactivation refers to the impairment of initiative and spontaneity, which Adams and Victor call the most common effect of frontal lobe disease.

Similarly, Stuss and Benson (1987) ascribed two basic functions to the anterior portion of the frontal lobes: "sequence, set, and integration" and "drive, motivation, and will" (p. 241). The "most common alteration is apathy" (p. 242). Neuroleptic-induced impairment of the frontal lobes acts primarily by causing apathy, along with a profound degree of spellbinding.

Much of what we know about the frontal lobe syndrome comes from studying the effects of psychosurgery, whose primary clinical effect is the production of deactivation, or what Kalinowsky (1973) called "diminished concern" (p. 20). My clinical experience and reviews of the literature (Breggin, 1975, 1980, 1981b) as well as neuropsychological research (Hansen et al., 1982) indicate that the newer stereotactic procedures, such as cingulotomy, amydalotomy, and thalamotomy, continue to produce a frontal lobe syndrome, especially deactivation. Hansen et al. (1982) described the impact of modern psychosurgery in a way that is indistinguishable from neuroleptic deactivation effects:

> The patient's options for action are reduced by a weakening of initiative and ability to structure his situation; emotionality fades, is organized more shallowly and is more dependent upon the immediate situation. Contact with other people becomes more flattened and the immediate bearing more mechanical. (p. 115)

Lobotomy patients literally do not know what hit them. They are so profoundly spellbound by the injury that they often have no awareness that anything has been done to them. Some live on a euphoric (superficially silly) level, most lapse into deep apathy; none are left with the ability to understand what has happened to them.

As we shall see, pioneers in the use of antipsychotic drugs almost uniformly cited deactivation as the main clinical effect of neuroleptics. Because of this, clinicians often referred to the neuroleptic effect as a chemical lobotomy (Haase, 1959). Bleuler (1978) observed that long-term neuroleptic use "also often dampens the vitality and the initiative of the person" (p. 301). He concluded, "So we see that long-term maintenance with neuroleptics is fraught with some of the same disadvantages that are ascribed to lobotomies" (p. 301). Chapter 5 will discuss permanent cognitive impairment and dementia from these drugs.

## DEACTIVATION AND MEDICATION SPELLBINDING

Since the hallmark of medication spellbinding is a lack of appreciation or concern about adverse mental effects, any substance that produces indifference or apathy is highly spellbinding. Patients taking neuroleptics can

become so spellbound that they appear robotic or zombielike, with little awareness of or interest in themselves or their environment. They commonly think that they are doing somewhat better on the drugs, despite the fact that they are grossly impaired by a parkinsonian emotional flatness and psychomotor retardation (chapter 4).

## The Anatomy of Deactivation

Deactivation can result from dysfunction in either the frontal lobes and limbic system (as an aspect of frontal lobe syndrome) or the basal ganglia (as an aspect of subcortical dementia). It can also occur through dampening down the reticular activating system, a network in the lower portion of the brain that energizes all of its processes. All neuroleptics, including the newer atypicals, impair the dopaminergic pathways to all of these regions.

Dopamine is one of the most studied neurotransmitter systems in the brain. It has numerous receptor subtypes, including $D_2$, which provides nerve trunks from the region of their origin in the basal ganglia to the limbic system, frontal lobes, and reticular activating system. Blockade of $D_2$ is key to neuroleptic effects, including deactivation and some of the more serious adverse effects, including tardive dyskinesia and neuroleptic malignant syndrome. All drugs that block $D_2$ can cause these potentially disastrous effects.

The neuroleptic deactivation effect so closely resembles psychosurgery in its clinical impact because it disrupts the same regions of the brain. Classical lobotomy, for example, cuts the descending fibers from the frontal lobes to deeper brain structures, while the neuroleptics tend to impair the ascending dopaminergic fibers.

## Lobotomy-Like Neuroleptic Effects

Any drug that blocks $D_2$, including every newer antipsychotic medication, will, in sufficient doses, produce a lobotomy-like effect.

The very first report on the psychiatric use of chlorpromazine was published in France by Delay and Deniker (1952; translated in Jarvik, 1970). Their article described the actual state of the patient for a medical world that as yet had no familiarity with the drug:

> Sitting or lying, the patient is motionless in his bed, often pale and with eyelids lowered. He remains silent most of the time. If he is questioned, he answers slowly and deliberately in a monotonous, indifferent voice; he expresses himself in a few words and becomes silent. (Jarvik, 1970)

They also described the patient as "fairly appropriate and adaptable.... But he rarely initiates a question and he does not express his anxieties, desires or preferences" (Jarvik, 1970).

Notice the nonspecific nature of these effects. Not only symptoms such as anxiety, but also desires and preferences, are aborted or buried beneath indifference or apathy. As Delay and Deniker put it, there is an "apparent indifference or the slowing of responses to external stimuli" and "the diminution of initiative and anxiety" (Jarvik, 1970). Once again, this is iatrogenic helplessness and denial with spellbinding effects.

Heinz Lehmann introduced chlorpromazine into North America via Montreal in May 1953. Lehmann and Hanrahan (1954) published the first article in English promoting its psychiatric use. They stated,

> The aim is to produce a state of motor retardation, emotional indifference, and somnolence, and the dose must be increased accordingly as tolerance develops.

The doses required for achieving "retardation," "emotional indifference," and "lethargy" rarely exceeded 800 mg/day, and sometimes did not exceed 100 mg/day. Much larger doses—sometimes thousands of milligrams—were often used in the past and are sometimes used in contemporary treatment by psychiatrists.

Writing with that burst of honesty so characteristic of pioneers, Lehmann and Hanrahan (1954) go on to say,

> The patients under treatment display a lack of spontaneous interest in the environment... they tend to remain silent and immobile when left alone and to reply to questions in a slow monotone.... Some patients dislike the treatment and complain of their drowsiness and weakness. Some state they feel "washed out," as after an exhausting illness, a complaint which is indeed in keeping with their appearance.

Lehmann and Hanrahan (1954) recognized that they were suppressing their patients without specifically affecting or improving symptoms such as hallucinations and delusions: "We have not observed a direct influence of the drug on delusional symptoms or hallucinatory phenomena."

The following year, Lehmann (1955) published his second article on chlorpromazine. With relatively small doses, he found the primary brain-disabling effect: "Many patients dislike the 'empty feeling' resulting from the reduction of drive and spontaneity which is apparently one of the most characteristic effects of this substance." He also spoke of "lassitude" and compared the effects to lobotomy: "In the management

of pain in terminal cancer cases, chlorpromazine may prove to be a pharmacological substitute for lobotomy."

The first British report concerning chlorpromazine as a psychiatric treatment (Anton-Stephens, 1954) confirmed the impact of the drug using small doses (200 mg/day). Anton-Stephens called it *psychic indifference* and again compared it to lobotomy.

Throughout the 1950s, some psychiatric texts continued to accurately describe the impact of the neuroleptics on the mind. Here, for example, is the lobotomy-like clinical picture of *maximum benefit* described by Noyes and Kolb in the 1958 edition of *Modern Clinical Psychiatry:*

> If the patient responds well to the drug, he develops an attitude of *indifference* both to his surroundings and to his symptoms. He shows *decreased interest* in and response to his hallucinatory experiences and a *less assertive* expression of his delusional ideas. (p. 654, italics added)

It has become fashionable in contemporary psychiatry to deny the primary lobotomizing effects of the neuroleptics, but occasionally, recognition can be found in the literature. In a 1991 editorial in *Biological Psychiatry* titled "Neuroleptic Dysphoria," Emerich and Sanberg described various adverse emotional reactions to Haldol and other neuroleptics, including "cognitive blunting." The editorial describes the self-administration of Haldol by Belmaker and Wald (1977), in which each of these "normal experimental subjects" "complained of a paralysis of volition, lack of physical and psychic energy. The subjects felt unable to read, telephone or perform household tasks of their will, but could perform these tasks if demanded to do so." The editorial also mentioned reports of other mind-subduing effects, including "chemical straightjacketing," "lack of motivation," and a feeling "like a shade coming down." The editorial failed to make the obvious comparison to lobotomy, but its observations are entirely consistent with and confirm the brain-disabling principles of psychiatric treatment described in chapter 1.

Given so many acknowledgments by researchers that neuroleptics work by subduing the brain and mind, and sometimes the body itself, it is remarkable that psychiatric drug advocates continue to promote these drugs as if they have a specifically ameliorating effect on psychosis, mania, or schizophrenia.

In clinical discussions, the lobotomy effect is now sometimes subsumed under *neuroleptic-induced deficit syndrome* (NIDS). Malcolm Lader (1993), chairperson of an international symposium on the subject, wrote,

> The benefits of treatment with classical neuroleptics are, however, obtained at the expense of a number of side effects, and many patients

> frequently complain of feeling "drugged" or drowsy and of being unable to concentrate; they lack motivation and are emotionally unresponsive: they also appear slow-moving and physically rigid. Some patients have complained of "feeling like a zombie." (p. 493)

The zombie effect is the ultimate manifestation of medication spellbinding as a central aspect of the brain-disabling effects of psychiatric drugs.

At the symposium, Wolfgang Straus (as cited in Lader, 1993) described a related neuroleptic-induced *dyscognitive syndrome* characterized by "aphasia, thought disturbances, emotional withdrawal, difficulties in directing thought by will, ambivalence, thought deprivation, and reduced creativity" (pp. 495–496). Noting that early studies tried to demonstrate improved cognitive functioning on neuroleptics, Straus observed that more rigorous studies confirmed a detrimental effect.

### Atypical Neuroleptics

Chapter 1 provided examples of research studies confirming the brain-disabling principles in regard to risperidone, one of the most commonly used atypical antipsychotics.

Regardless of the mechanism, all neuroleptics produce lobotomy-like indifference or deactivation. This is the primary effect of all drugs thus far developed for the control of patients labeled schizophrenic or acutely manic. If the medications failed to produce a deactivation effect, they would not be useful for the control of very difficult or disturbed individuals. We shall find that these drugs are potent dopamine blockers, producing all of the more severe central nervous system impairments caused by other neuroleptics.

## SOCIAL CONTROL WITH ANTIPSYCHOTIC DRUGS

If a drug is sufficiently deactivating and spellbinding, it can be used on humans and animals alike under any circumstances where an authority desires to impose control. Thus the antipsychotic drugs are used in every kind of authoritarian or totalitarian institution.

### Suppression of Nursing Home Inmates

Neuroleptics are routinely used in every institution in which social control and behavioral suppression are a top priority and in which drugs can replace human services (see Breggin, 1983b, for details). Although Haldol and Mellaril have been largely displaced by newer drugs such

as Zyprexa and Risperdal, the intent remains the same—behavioral control. For decades, the suppression of elderly nursing home inmates with neuroleptics has been a national scandal (Hughes et al., 1979; Rogers, 1971). A study of nursing home residents in Tennessee found that 44% were being given the drugs (studies summarized in Bishop, 1989). A 1989 Massachusetts study (Avorn et al., 1989) found that 39% of patients were receiving neuroleptics. According to the report, "in most cases, the prescriptions had been written in the remote past and were refilled automatically."

When public scandal did not substantially improve nursing homes over the years (Kolata, 1991), Congress passed regulations limiting the use of restraints and medications in nursing homes. These statutes went into effect in 1991, too often with spotty enforcement and therefore incomplete success (Spiegel, 1991). However, when actually applied, the new regulations have reduced the use of neuroleptics in nursing home settings (Semla et al., 1994).

Two decades ago, there was a growing awareness of the inappropriateness and harmfulness of prescribing neuroleptics to elderly patients ("Antipsychotic Drug Therapy," 1988; Gomez et al., 1990; Sherman, 1987). The use of neuroleptics for the behavioral control of the elderly produces toxicity even more readily than in younger patients, and it cannot substitute for needed human services. Sherman (1987) called into question the pharmaceutical company practice of placing advertisements for neuroleptics like Haldol and Navane in journals with a geriatric-practice orientation.

Unfortunately, the drug companies have now succeeded in convincing health care providers that the newer neuroleptics are safer for the elderly than the older drugs, even though the FDA requires the labels for these drugs to display a black box warning at the top with the bold heading, "Increased Mortality in Elderly Patients with Dementia-Related Psychoses." The atypicals such as Risperdal, Zyprexa, and Geodon cause an increased death rate in elderly patients with dementia as a result of unexplained sudden death, stroke, heart attack, and pneumonia. These drugs also more frequently cause cardiac arrhythmias as well as the metabolic syndrome described earlier in the chapter, all of which especially threaten the lives of the elderly.

## Deactivating People and Animals in Varied Settings

In 1983, in *Psychiatric Drugs: Hazards to the Brain,* I devoted considerable time to confirming the brain-disabling principle of neuroleptic treatment by pointing to its effects on a variety of diverse populations. I also discussed other confirmatory sources in the literature. The material in

this section that draws on older citations is presented at greater length in my earlier book.

The deactivation syndrome produced by neuroleptics is confirmed by their use in state mental hospitals for the control of patients regardless of their diagnoses and in psychoprisons in the former U.S.S.R. for the control of political dissidents (Block et al., 1977; "Excerpts From Statement," 1976; Fireside, 1979; " 'Madhouse' Brainwashing," 1976; Podrabinek, 1979). They have been used in prisons for the suppression of difficult inmates (Booth, 1993; Coleman, 1974; Greenhouse, 1979; Kaufman, 1980; McDonald, 1979; Mitford, 1973; Oregon State Prisoner, 1971; Prison Drug Bill, 1977). Convicted prisoners have reported that the brain-numbing effects rendered them unable to make a proper defense in court (Espinosa, 1993; Ogilvie, 1992; Pund, 1993).

Neuroleptics have been commonly used in institutions for the developmentally disabled to suppress the behavior of children and adults (Kuehnel et al., 1984; Plotkin et al., 1979). Kuehnel and Slama (1984) warned that neuroleptics can further compromise the learning abilities of the developmentally disabled and cause "the sedative 'snowed' effect, which can reduce a client's positive response to learning cues" (p. 94).

Many critical books have decried the use of neuroleptics and other drugs in the suppression of children in hospitals and other settings (Armstrong, 1993; Hughes et al., 1979; Sharkey, 1994; Wooden, 1976). The control of children with neuroleptics will also be discussed in chapter 11 of this book.

The use of neuroleptics in veterinary medicine to control wild and domestic animals provides another illustration of the deactivation effect and its independence from any presumed mental illness in the individual being treated (Booth, 1977; Hall, 1971; Rossoff, 1974). Hartlage (1965) found that Thorazine dampened the emotional responses of animals, "thereby perhaps providing some clue to the widespread acceptance of the drug as effective in psychiatric settings" (see also Mirsky, 1970; Slikker et al., 1976). Jarvik (1970) pointed out that the neuroleptics produce diminished spontaneous activity and emotional indifference in all animal species, including man, but he nonetheless argued for a specific antipsychotic effect.

Not surprisingly, a variety of studies on human beings, including normals, has also shown impairment of mental functioning, including memory and learning (DiMascio et al., 1970; Fischman et al., 1976; Gillis, 1975; Seppala et al., 1976; Tecce et al., 1975).

Many former psychiatric patients and inmates have described the brain- and mind-numbing effects of the neuroleptics (Burstow et al., 1988; Chamberlin, 1978; Frank, 1980; Grobe, 1995; Hudson, 1980; Millett, 1990; Modrow, 1992).

I am not the first to suggest that neuroleptic medications are highly toxic. In fact, it was considered common knowledge in the first decades of their use (Hunter et al., 1964; Hunter et al., 1968). In support of the use of lithium, a number of investigators have criticized the neuroleptics for their stupefying effects. Fieve (cited in Shah, 1973), for example, said that neuroleptics "zonk a person out" and put them in a "mental straight jacket." Fieve (1989) also referred to the "zombielike appearance" (p. 4) produced by neuroleptics. A NIMH (1970) brochure compared the drugs unfavorably to lithium because of their effect of "wrapping the patient's entire mind in a cocoon of stupefaction." Similarly, Prien et al. (1972) found that "most patients receiving chlorpromazine were sluggish or fatigued." Wittrig and Coopwood (1970) confirmed the lobotomy-like effect of impaired "initiative and planning" (p. 488), which they called the *chemical straightjacket*. Robitscher (1980) noted that patients frequently feel "dead or 'like a zombie'" (p. 90).

Perhaps in response to growing professional and public criticism, psychiatrists have become much more reluctant to publish criticism of any treatments or to mention their brain-disabling effects. Nowadays the neuroleptic drugs are always described as having a specific antipsychotic effect, rather than a numbing, lobotomy-like deactivation effect. In the words of my research assistant, Ian Goddard, "This remarkable difference between historic and contemporary commentary on the effects of neuroleptics clearly reveals the existence of an all-pervasive denial that has consumed the profession in modern times" (2007, unpublished).

## THE UNIQUE FUNCTION OF THE BRAIN

Some proponents of brain disability as therapy assume that a little toxicity is helpful and that only excessive toxicity is harmful. They bring up precedents in medicine for drugs that reduce function of one organ or another to improve its effectiveness. Thus some cardiac medications actually weaken heart muscle function in the interest of preventing arrhythmias. But the analogy falls short when dealing with the brain. When the strength of the heart muscle is reduced, nothing substantial is done to the mind or personality of the person—unless, of course, the patient goes into heart failure. But when brain function is reduced, the individual's capacities as a sentient being are directly and proportionally reduced. He or she becomes less able to think, feel, choose, and initiate activities—and ultimately spellbound.

Beyond this, one must also look at the purposes of medical and psychiatric interventions. The medical intervention that disrupts one kind of heart function is intended to improve overall heart function. The

psychiatric intervention that disables the brain is aimed at suppressing certain thoughts, emotions, or behaviors at the cost of reducing overall mental function. In doing so, it renders the individual less self-aware and less self-determining, more helpless, and more manageable. The individual may appear to be less emotionally disturbed when he or she is, in reality, less emotionally aware or vital.

In summary, consistent with the brain-disabling principles of biopsychiatric treatment presented in chapter 1, the neuroleptic or antipsychotic drugs produce a lobotomy-like deactivation syndrome characterized by emotional indifference or apathy, reduced spontaneity, and docility. This is the primary or "therapeutic" impact of all neuroleptic drugs including Haldol, Risperdal, Zyprexa, Geodon, and Seroquel.

This clinical result is obvious in the great majority of patients, some of whom are reduced to a zombielike state. It is documented by recent research studies involving the atypical antipsychotic Risperdal and other neuroleptics. It is also confirmed by studies of animals, normal human beings, political dissenters, and rebellious children as well as by studies of the inmates of mental hospitals, institutions for the developmentally disabled, nursing homes, and prisons. Given an effective "therapeutic" dose, all human beings and animals alike are emotionally stifled and subdued by antipsychotic drugs.

Pioneers in the field recognized and wrote about the lobotomy-like effects of the neuroleptic drugs when they first came into use, but in recent years drug advocates have promoted the false impression that these medications have a specific antipsychotic or antischizophrenic effect. In reality, the overriding clinical effect of these highly toxic chemical agents is to render patients and inmates more emotionally flat and indifferent, more apathetic and docile, and less autonomous and self-directed.

As a result, these patients and inmates sometimes seem less obviously in emotional pain, and they are almost always much more manageable. But the effect has nothing to do with treating a psychiatric disorder. Instead, the patients have been rendered emotionally and neurologically disabled by the drugs.

## NOTES

1. In an apparent oversight, the table fails to note that the original antipsychotic, chlorpromazine (Thorazine), is a potent $D_2$ blocker.
2. A list of antipsychotic or neuroleptic drugs can be found in the appendix.

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CHAPTER 3

# Neuroleptic-Induced Anguish, Including Agitation, Despair, and Depression

Not all drug effects on the central nervous system can be categorized as spellbinding, but all produce disability. Often the result is a worsening of the patient's overall condition, and sometimes the result is an extremely distressing or disabling psychiatric reaction. Ironically, psychiatric drugs do not cure or ameliorate central nervous system disorders; they cause them.

Despite the lobotomy-like indifference to suffering produced by neuroleptic-induced deactivation, many patients experience varying degrees of physical and mental pain and torment in response to these drugs. The deactivation itself is often experienced as dreadful, a kind of living death or an imprisonment within one's own brain.

This chapter will describe some of the most common, reversible, drug-induced neurological reactions: acute dystonia; acute akathisia; parkinsonism; and a broad, ill-defined category called dysphoria. All of them tend to begin early in treatment but can start later on as well. Chapters 4 and 5 will review the sometimes delayed and often persistent adverse reactions, including irreversible forms of akathisia and dystonia.

Most of the neurological disorders associated with the neuroleptics fall into the category of *extrapyramidal reactions* or *extrapyramidal symptoms*, and are often designated EPS. The extrapyramidal system of the brain is an extensive, complex network that moderates and adjusts motor

control. Abnormalities in the system cause a variety of dysfunctions, including tremors, muscular rigidity and spasms, and various involuntary movements.

Casey (1993) reported that acute extrapyramidal syndromes occur in up to 90% of patients receiving neuroleptics, often causing physical and mental impairment. Unfortunately, physicians too often continue or increase the patient's medication, despite discomfort and suffering, because they have mistaken the toxic drug reaction for a psychiatric disorder. A young male patient, for several months after termination of neuroleptic treatment, suffered from a dystonia that caused one arm to rise above his shoulders. In family sessions, his parents persisted in viewing the disorder as a willful and defiant act. These acute symptoms may linger a considerable time after drug termination, even in regard to newer neuroleptics thought to produce them less frequently or intensively (Kane et al., 1994). Often, they become permanent.

It has been known for some time that the neurotoxic effects described in this and the following chapters become even more frequent and disabling in the elderly (Gomez et al., 1990; Simpson, 1977; see chapter 4).

## RESISTANCE TO TREATMENT

Van Putten (1974) evaluated the attitudes of 85 patients toward a variety of neuroleptics. *Dysphoric responders* were defined as individuals who "habitually complained about the drug effect" and who felt "miserable" and "continually pleaded to have the drug stopped or the dosage reduced." A remarkable 38% of the patients fell into this extreme category of drug resistance. When the criteria for drug resistance were broadened to include anyone who had "to be pressured" into taking medication, 46% were found to display "drug reluctance."

The study most likely underestimated the actual percentage of drug reluctance among the total population of patients on the ward. Some, and perhaps many, patients disguised their reluctance to avoid angering the staff, while quietly throwing away their pills.

How easy is it to feign taking medication in a typical psychiatric hospital? Consider the Rosenhan (1973) study, in which normal individuals had themselves admitted to various mental hospitals by faking symptoms. "All told, the pseudopatients were administered nearly 2,100 pills, including Elavil, Stelazine, Compazine, and Thorazine, to name but a few.... Only two were swallowed. The rest were either pocketed or deposited in the toilet." This is a remarkable figure indeed: Less than 1 out of 1,000 doses were taken, and none of the hospital staff were aware of it. The Rosenhan study also disclosed that regular patients were routinely disposing of their

medications in the same manner. Rosenhan believed that the failure of the staff to detect what was happening reflected their tendency to ignore everything done by the patients, unless it caused obvious trouble.

## ACUTE DYSTONIC REACTIONS

Very little has been written about the suffering associated with acute dystonia, a drug-induced neurological disorder that causes painful muscle spasms, most commonly, but not exclusively, in the neck (torticollis), and sometimes bending the entire back in a rigid arc (opisthotonus). Similarly, insufficient attention has been paid to the anguish of undergoing an oculogyric crisis, in which the eyes roll up in their sockets and become locked in place.

The spasms can affect any voluntary muscles, including those involved with speech, swallowing, and breathing, as well as gait. Simpson (1977) observed, "The masseter muscles may be tightly contracted so that the mouth cannot be opened and, on rare occasions, this can lead to damage to the teeth, tongue, or even the mandible. The possibility that such reactions can be fatal does exist, particularly if they occur during eating."

Patients who have suffered these experiences may remember them with pain, fear, and resentment for the rest of their lives. Needless to say, if their doctors originally blamed the reactions on the patient's psychiatric problems, the patient can feel enormously betrayed. Often the attacks can be aborted with proper medical intervention, but they can go on endlessly if untreated or if they develop into an irreversible tardive dystonia (chapter 4).

Silver et al. (1994) underscored the devastating impact of these disorders:

> The most common feature of this syndrome includes uncontrollable tightening of the face and neck, and spasm and distortions of the patient's head and/or back (i.e., opisthotonos). If the extraocular muscles are involved, an oculogyric crisis may occur, wherein the eyes are elevated and "locked" in this position. Laryngeal involvement [spasm] may lead to respiratory and ventilatory difficulties. These reactions are often terrifying to the patient who has no prior experience with these problems or knowledge of this side effect. When a patient with psychosis experiences a dystonic reaction, the fragile trust developed between psychiatrist and patient may be irrevocably damaged. (pp. 909–910)

Too often, these reactions are mistakenly diagnosed as mental illness. Simpson (1977) observed, "Acute dystonic reactions are of sudden onset and consist of bizarre muscular spasms that have been misdiagnosed as

tetany or hysteria (particularly because emotional reactions can contribute to their precipitation and because patients can occasionally be talked out of them)." Actually, I have never seen a psychological reaction contribute to the "precipitation" or start of a dystonic reaction; but psychological stress commonly brings out or worsens a preexisting, medication-induced dystonia. Stress will worsen almost any neurological disorder.

Consistent with psychiatric denial of adverse drug effects, psychiatrists often fail to diagnose dystonia. In a survey of 1,114 dystonia patients, only 1% of the 279 who saw a psychiatrist were correctly diagnosed ("Survey Shows," 1992). Neurologists did considerably better, correctly diagnosing 44% of the patients who came to them.

## DESPAIR IN NEUROLEPTIC-INDUCED PARKINSONISM

Parkinson's disease tends to develop spontaneously in the middle and later years of life. Its symptoms include a masklike or rigid face; a tremor of the extremities at rest; intermittent rigidity or spasms of the limbs, and a cog-wheeling, ratcheting of the arms when passively moved; a shuffling, stooped gait; and overall retardation of muscular or motor activities. In its initial or more subtle forms, the disease may be manifested by a slowness of motion, or motor retardation, called *bradykinesia*. In its extreme form, *akinesia,* it grossly impairs all activity. Feelings of depression, lobotomy-like disinterest, and some degree of dementia frequently accompany it.

All drugs that block dopamine—including nearly all of the older and newer neuroleptics—commonly produce a reversible parkinsonism syndrome. They can also cause separate aspects of the syndrome, such as bradykinesia. Van Putten (1974) described the following reaction:

> After seven days she complained of unbearable "fatigue"…"I have slowed down. I talk slower and move slower (objectively this was apparent only after she called our attention to it). I feel like an old lady. I get tired from walking around the block. I feel discouraged about the future. I have no enthusiasm. I can't type nearly as fast at my job (clerk typist)…I want my own personality back." (ellipses original)

Drug-induced parkinsonism is sometimes confused with a mental disorder like depression or schizophrenia. Davis et al. (1975) warned that psychiatrists should "be aware that patients who appear apathetic, lacking in spontaneity, relatively unable to participate in social activities, lifeless, zombielike, or drowsy may have subtle extrapyramidal side effects." As Lavin et al. (1992) confirmed, when clinicians mistakenly attribute

these symptoms to the patient's mental disorder, they either increase the dose of neuroleptic or add an antidepressant or stimulant to the regimen, further impairing the patient's overall condition.

Similarly, *The American Psychiatric Publishing Textbook of Clinical Psychiatry* (Marangell et al., 2003) pointed out:

> *Akinesia* is defined as a behavioral state of diminished spontaneity characterized by decreased gestures, unspontaneous speech, apathy and difficulty with initiating usual activities. Akinesia may appear after several weeks of therapy and often is an element of the Parkinsonism syndrome. This drug-induced syndrome may be mistaken for depression or for negative symptoms of schizophrenia.

Obviously, the overriding effect of these drugs is a lobotomy-like crushing of will and spirit, resulting in profound spellbinding. When previously excited, vocal, or disorderly patients become subdued by akinesia, it is almost always considered a positive "therapeutic" effect. The adverse effects are so spellbinding that many patients are reduced to a zombie-like condition without complaining and without seeming to perceive the severity of their loss of function and will. Mental hospitals are literally filled with patients in one degree or another of this deplorable condition.

Typically, the parkinsonism remains for the duration of the drug therapy and takes days, weeks, or even months to clear after discontinuation of the drug. Klawans (as cited in Goetz et al., 1980) attributed the delayed clearing to the persistence of the drug in the patient's body. Although some medications can ameliorate the intensity of the symptoms, the effect is usually partial, the underlying abnormal neurological condition remains, and additional adverse drug effects frequently occur.

Van Putten and May (1978) found bradykinesia (slow movements) and akinesia, aspects of parkinsonism, in 47% of their patients treated with relatively moderate doses of neuroleptic or antipsychotic drugs. Including relatively mild cases, Korcyzn and Goldberg (1976) found parkinsonism in 61% of 66 patients receiving a variety of neuroleptics. Klawans (as cited in Goetz et al., 1980) noted that rates of affliction vary in the literature from 5% to 60% of all patients treated and offered his own figure of 10% to 15% for "clear parkinsonian features." Klawans also noted that some drugs produce parkinsonism more readily than others and that one of the most frequently used, haloperidol (Haldol), may produce parkinsonism in more than 90% of patients when sensitive detection methods are used.

I have communicated with neurologists who find that neuroleptic-induced parkinsonism does sometimes become permanent. This is consis-

tent with the lessons of lethargic encephalitis, a viral epidemic from the early twentieth century in which patients developed irreversible parkinsonism from damage to the same regions of the brain that are damaged by the neuroleptics (see chapters 4 and 5). While some concern about permanent drug-induced parkinsonism was voiced in the first few decades of neuroleptic use (Crane, 1977; Hall et al., 1956; Hornykiewicz, 1967; Klawans, as cited in Goetz et al., 1980; Korczyn et al., 1976; Merritt, 1979; Simpson, 1977), little has been expressed in recent times.

### Parkinsonism as an Aspect of Brain-Disabling Therapy

Before the profession became so conscious of improving its public and professional image, many psychiatrists connected the parkinsonism syndrome to the therapeutic effect of neuroleptics (described in Davis et al., 1975; Paulson, 1959). Cole (1960) said that in some cases, the use of drug-induced parkinsonism to control the patient was the equivalent of using toxicity as therapy. Cole went so far as to use the phrase *pharmacologic straitjacket* to describe the drug effect.

## ANGUISH IN AKATHISIA

*Akathisia* is a drug-induced reaction characterized by compelling feelings of restlessness, tension, or anxiety that drive a person to move his or her body (Jeste et al., 1986; Weiner et al., 1983). People with akathisia find it difficult to sit or to keep their feet still. Some will walk in place, pace frantically, or search out activities that keep them on the move. I have evaluated patients with permanent akathisia (tardive akathisia; see chapter 4) who, for their entire lives, are trapped in perpetual suffering. The neurological distress produced by this drug-induced condition can become so extreme that even the most spellbound, relatively indifferent patient will feel tortured.

Patients suffering from akathisia often use electrical metaphors or descriptions such as "electricity going through my veins" or "shocks in my head." Words like *excruciating, torture,* and *indescribable* are commonly used. Patients often say that they would rather die than live with akathisia, and the disorder can cause suicidality. Unlike patients suffering from anxiety, these individuals seem to be describing physical phenomena as if they are being tortured from the inside out.

Doctors are frequently reluctant to acknowledge the disorder as akathisia if the patient is not frantically moving about. A report titled "Using Antipsychotics" (1989) summarized the clinical observations of several experts and concluded,

> While it is commonly believed that akathisia is characterized by obvious signs of motor restlessness, it should be noted that behavioral symptoms may be limited to expressions of anxiety, impatience, and hostility. Too often, this manifestation is misdiagnosed as recurrence of psychotic symptomatology. (p. 2)

That akathisia can occur in the absence of external bodily movements is clinically and legally important. Clinically, if medicated patients report a sense of inner pain or agitation that feels different to them than anxiety, and if the descriptions have bizarre qualities often associated with akathisia, alert physicians should consider a diagnose of akathisia. This can lead to a reduction or termination of the medication and/or the prescription of drugs to ameliorate the symptoms.

In the legal arena, patients who commit violence may be able to use akathisia as an exculpatory or mitigating factor. In cases of suicide and violence, product liability suits may be brought against drug manufacturers who fail to warn that their products cause akathisia and that akathisia is associated with potentially disastrous consequences. The existence of akathisia in the absence of external movements can be a critical diagnostic issue.

The American Psychiatric Association's (2000) *Diagnostic and Statistical Manual of Mental Disorders (DSM–IV–TR)*, as well as the earlier 1994 edition, describe akathisia as a movement disorder caused by both the antipsychotic drugs and the SSRI antidepressants. Although a document written by prodrug experts, the *DSM–IV–TR* cites very high rates for akathisia: "The reported prevalence of akathisia among individuals receiving neuroleptic medication has varied widely (20%–70%)." Sachdev and Kruk (1994) evaluated 100 patients admitted to two inpatient psychiatric units in teaching hospitals affiliated with the University of New South Wales in Australia. Mild akathisia developed in 41% of patients and moderate-to-severe akathisia in 21%. They cited studies indicating rates as high as 90% with high-potency neuroleptics such as Haldol and Prolixin.

Although estimates vary widely for the rates of neuroleptic-induced akathisia, even the lower estimates pose an astronomical risk to patients. Psychiatry and medicine have paid far too little attention to the suffering inflicted on patients by neuroleptic-induced, and also antidepressant-induced, akathisia.

The *DSM–IV–TR* observes that atypical antipsychotic drugs are less likely to cause akathisia than the new atypical drugs but that it does occur. In my experience, so-called atypicals like Risperdal and Zyprexa are equally likely to cause akathisia when given in doses equivalent to those used for the older drugs.

A single case report (Byerly et al., 1995) indicated that risperidone can produce severe akathisia, described as behavioral stimulation with anxiety and agitation. In a study of clozapine, 2 of 29 patients developed akathisia, one mild and the other moderate in intensity (Chengappa et al., 1994).

The consequences of akathisia can be devastating in terms of individual suffering and the potential for violence and suicide. Under "Associated Features and Disorders," the *DSM–IV–TR* warns that "the subjective distress result from akathisia is significant.... Akathisia may be associated with dysphoria, irritability, aggression, or suicide attempts. Worsening of psychotic symptoms or behavioral dyscontrol may lead to an increase in neuroleptic medication." It is worth reemphasizing that akathisia can cause dysphoria, irritability, aggression, or suicide attempts as well as psychotic symptoms and behavioral dyscontrol—a prescription for suicide, violence, and mental deterioration. The same important observations were made in the 1994 edition of the *DSM–IV*.

Akathisia can cause extreme iatrogenic helplessness and denial and, ultimately, a dangerous degree of medication spellbinding.

Van Putten et al. (1974) found that 35% of their patients decompensated after one injection of intramuscular fluphenazine, usually as a result of akathisia. In a striking illustration of medication spellbinding, often even the patient wanted to blame the problem on his or her mental condition:

> The drug-induced regressions resemble the original psychoses so precisely, that at the beginning of the study the treatment team (including the ward director) always explained the decompensation in plausible dynamic terms. Often, the patient himself agreed with the dynamic formulation.... Thought processes again became fragmented, and several complained of abject terror, the likes of which they had never experienced.... Statements such as "It's a horrible feeling," "I can't describe it" or "If this feeling continues, I'd rather be dead" were not unusual.

These anguished responses were rapid in onset. Van Putten et al. (1980) also described frequent severe dysphoric reactions to single doses of chlorpromazine and thiothixene.

Van Putten (1975b) found an extraordinarily high rate of akathisia, 45%, on close examination of a ward population. He described the distress in graphic terms, while demonstrating concern for the patients' suffering. He concluded,

> Since many of life's activities require sitting, a sustained akathisia is a severe hardship. The subtler akathisias often go unrecognized by the

> physician—but not by the patient! Even a mild akathisia can preclude sitting through the dinner hour, a movie, a therapy session, or a sedentary job.

Akathisia can literally drive a person crazy. Barnes (1992) pointed to studies indicating that akathisia can induce psychosis. He cited literature confirming that it can cause aggression and violence or suicide (see also Breggin et al., 1994a, for discussion of akathisia and suicide). Van Putten and Marder (1987) reviewed the literature and concluded that akathisia "in the extreme case, can drive people to suicide or to homicide." Too often, doctors are likely to mistake the akathisia for the patient's mental disorder and increase the medication, creating a vicious cycle.

Mayerhoff and Lieberman (1992) observed,

> One of the more troublesome side effects of the neuroleptics cited by many authors is a syndrome involving restlessness, excitement and aggressive behavior that may or may not be due to akathisia.... There is some evidence to suggest that violent behavior may be more frequent on moderately high-dose haloperidol than on moderate doses of low potency neuroleptics.

Haloperidol (Haldol) is among the most frequently used drugs in emergency attempts to control aggressive and violent behavior. Once again, we confront the tragic irony of treating patients with drugs that can worsen their condition. Haldol is also used to control behavior in intensive care units when postsurgery patients become delirious, exposing these vulnerable individuals to considerable additional risk and often exacerbating their disruptive behavior.

As already noted in regard to dystonia, drug-induced neurological abnormalities are often subject to some degree of self-control. They can sometimes be partially relieved by sedatives and may worsen in reaction to emotional stress. Sachdev and Kruk (1994) found that the movements in most patients would lessen when they were distracted by something.

## NEUROLEPTIC-INDUCED DEPRESSION AND SUICIDALITY

In *Psychiatric Drugs: Hazards to the Brain* (Breggin, 1983b), I reviewed and evaluated earlier studies at some length to document the frequency with which neuroleptics can cause dysphoric and psychotic responses, including schizophrenic-like reactions and depression, with or without accompanying akathisia (e.g., DiMascio, 1970; Marsden et al., 1977; Rifkin et al., 1975; Singh, 1976; Van Putten et al., 1978). The studies typically

involved drugs that are still commonly in use, including Haldol. Clozapine has been reported to cause toxic delirium, especially in the elderly (Pitner et al., 1995).

Van Putten and May (1978) found that 47% of their patients developed akinesia and that most of these became depressed. Confirming the brain-disabling principle, as these patients became depressed, they were rated as improved in their schizophrenia, probably because they became relatively inactive, retarded, withdrawn, and even mute.

Depression is an especially serious reaction to neuroleptic treatment (Aubree et al., 1980; Quitkin et al., 1975; Van Putten et al., 1978). Simonson (1964) described how his mother became despairing and hopeless after one small dose of Compazine for nausea. Ayd (1975) disclosed, "There is now general agreement that mild to severe depressions that may lead to suicide may happen during treatment with any depot [long-acting intramuscular] neuroleptic, just as they may occur during treatment with any oral neuroleptic."

Small and Kellams (1974) noted reports of patients becoming suicidal as a result of treatment with the long-acting injectable form of Prolixin. Others have confirmed that suicide can result from neuroleptic-induced depression (Alarcon et al., 1969; Hogan et al., 1983).

Neuroleptic-induced depression was recognized as a problem by Mayerhoff and Lieberman (1992), who pointed out that reported incidence rates of neuroleptic-induced so-called akinetic depression reach as high as 50%, with an average of 25%. Frequency probably increases with the long-acting intramuscular neuroleptics.

Emerich and Sanberg (1991) wrote an editorial in *Biological Psychiatry* that examined dysphoric reactions to neuroleptics. They described an array of anguished reactions, including dysphoria, anxiety, agitation, and panic. Two volunteer normals experienced severe anxiety as well as loss of willpower. They described a study in which relatively small doses of Haldol, 2.5 mg/day, produced "mood swings, crying, sadness, depression and despondence" as well as "lack of motivation." Further lowering of the dose reduced the reactions. They summarized, "Agitation, anxiety attacks, panic attacks, work avoidance, school phobia, separation anxiety and delusions are all antipsychotic side effects that have been reported following neuroleptic treatment."

## RISKS ASSOCIATED WITH ATYPICAL ANTIPSYCHOTIC DRUGS

As previously noted in chapter 2, the NIMH CATIE study summed up, "There were no statistically significant differences between the rates of

extrapyramidal side effects, movement disorders, or akathisia" (Nasrallah, 2007, p. 9). Similarly, it is worth repeating that Lieberman et al. (2005a) stated, "The proportion of patients with extrapyramidal symptoms did not differ significantly among those who received first-generation and second-generation drugs in our study."

Although relatively little has thus far been written about it, the newer neuroleptics can also cause akinesia, depression, psychosis, and suicidality. Aripiprazole (Abilify) has already been reported to cause or worsen psychosis (Grover et al., 2006; Raja, 2007). I have seen several cases in which olanzapine (Zyprexa) has caused zombielike behavior and profound depression. As chapter 2 also documented, all of the newer neuroleptics, including Risperdal, Geodon, and Seroquel, suppress dopaminergic function (dopamine $D_2$), the most probable neurochemical cause of these clinical states (Wu et al., 2007).

Any difference between the older and the newer antipsychotic drugs in regard to blocking dopamine and causing adverse neurological effects is at best a matter of degree. Seeman (2002), for example, argued that "the newer, atypical antipsychotics…all bind more loosely" to dopamine than the older neuroleptics. According to this theory, they occupy their blockading position for a briefer period of time, thereby producing fewer adverse effects, such as EPS. Weiden (2007b) noted that "in theory" it might be possible to treat patients with the newer atypicals without causing as many EPS effects. But he concluded, "In practice, however, EPS remain a significant problem even in the era of atypical or second generation antipsychotics.… Because all of the post-clozapine SGAs [second-generation antipsychotics] still affect the dopamine $D_2$ receptor, it may be more accurate to say these medications have lower EPS liabilities" than the earlier antipsychotics (p. 13). However, this therapeutic hope assumes that the newer drugs are not being given in larger doses to achieve the same effect as the older drugs, thereby producing the same adverse effects. Chapter 4 will examine evidence indicating that neuroleptic-induced psychoses can become permanent in the form of tardive psychosis and tardive dementia, leading to a tragic situation in which worsening symptoms require greater doses of the offending medication.

## THE ISSUE OF COERCION

None of the studies reviewed in this chapter considered whether the patients wanted to be in treatment or whether they were being coerced. None mentioned whether the patients were legally voluntary or involuntary, let alone whether ostensibly voluntary patients were undergoing treatment under duress, as frequently happens. The absence of such considerations

is particularly startling in studies in which drug resistance and painful adverse drug reactions are the issues under investigation. Psychiatrists too often seem to believe that resistance is wholly a matter of mental illness so that it does not matter if the patient resents being forcibly subjected to hospitalization, medication, or even electroshock. Nor do these studies take into account the reality that patients warn each other against complaining about treatment on the grounds that complaints lead to increased doses of drugs or other punishing results.

Publishing more than four decades ago, my 1964 study "Coercion of Voluntary Patients in an Open Hospital" remains the only peer-reviewed scientific article that systematically investigated the various threats and outright forms of coercion used to control mental patients, including drugs, electroshock, and commitment.

In conclusion, the neuroleptics cause an enormous amount of physical and emotional suffering, including anguish and psychosis. Frequently, the drugs produce a feeling of deadness and depression, and they can cause suicide. Often the suffering is associated with extrapyramidal reactions such as parkinsonism, dystonia, and akathisia. The result in most cases is a profound state of iatrogenic helplessness and denial. The patient is emotionally devastated without realizing what has happened. Many times, the patients become spellbound, failing to recognize their degree of impairment, failing to attribute their mental collapse to the drug, sometimes believing that they are doing better when they are in fact worse, and, on occasion, especially when driven by akathisia, committing compulsive suicide or violence.

Unfortunately, some of these painful and mentally disabling neurological reactions, including dystonia and akathisia, can also be caused by the newer antidepressants such as Paxil, Prozac, Zoloft, and Celexa. These distressing adverse drug reactions sometimes contribute to or cause violent and suicidal behavior (chapters 6 and 7).

CHAPTER 4

# Severe and Potentially Irreversible Neurological Syndromes (Tardive Dyskinesia and Neuroleptic Malignant Syndrome) Caused by Neuroleptics

This chapter focuses on two well-known neurological disorders caused by the neuroleptics—tardive dyskinesia (TD) and neuroleptic malignant syndrome (NMS)—with emphasis on their frequency and their destructive impact on the physical and emotional life of the individual. It also discusses neuroleptic withdrawal syndrome. The next chapter will explore irreversible damage to the brain that primarily affects mental functioning, including tardive psychosis and tardive dementia. However, as products of neuroleptic neurotoxicity, all these drug-induced abnormalities are clinically and neurologically interrelated. Chapter 5 will examine the neurotoxic effects of these medications that cause or contribute to these adverse drug effects.

The so-called clinical effect of neuroleptics, their chemical lobotomizing impact, is primarily caused by the blockade of dopaminergic nerves, especially the $D_2$ receptors, in the ventral striatum, with their connections to the limbic system and frontal lobes (chapters 1 and 2). However, blockade of the same $D_2$ receptors in the dorsal striatum is the probable cause of extrapyramidal reactions, including TD (Ethier et al., 2004; Seeman, 1995). Hence, as described in chapter 1, the so-called therapeutic effect is inextricably entwined with some of the worst adverse effects.

## TARDIVE DYSKINESIA (TD)

### Clinical Manifestations of TD

TD often begins with uncontrolled movements of the face, including the eyes (blinking or blepharospasm), tongue, lips, mouth, and cheeks, but it can start with almost any group of muscles. The most common early sign is a quivering or curling of the tongue. Tongue protrusions and chewing movements are also common and can become serious enough to harm teeth and impair chewing and swallowing. The hands and feet, arms and legs, neck, back, and torso can be involved.

The movements displayed are highly variable and include rapid jerking movements (*chorea*) or slower twisting movements (*athetosis*), tics, spasms, and tremors. The person's gait can be badly impaired. More subtle functions can be affected and are easily overlooked: respiration (involving the diaphragm), swallowing (involving the pharyngeal and esophageal musculature as well as the tongue), the gag reflex, and speech (Yassa et al., 1985).

The movements usually disappear during sleep, although I have seen exceptions. They sometimes can be partially suppressed by willpower, frequently are made worse by anxiety or tiredness, and can vary from time to time (see subsequent discussions).

Many cases of TD appear to be relatively mild, often limited to movements of the tongue, mouth, jaw, face, or eyelids. Nonetheless, they are frequently disfiguring and often embarrassing. Patients have been known to commit suicide (Yassa et al., 1985).

The abnormal movements can sometimes become totally disabling. Turner (1971) described patients who cannot eat and must have their teeth removed to facilitate the entry of food into their mouths. He also described patients who cannot keep shoes on their feet because they wear them out while sitting with the constant foot-shuffling activity. I have evaluated a number of cases in which the TD was wholly disabling, including massive distortions of the position of the neck or body, rocking and swaying, shoulder shrugging, and rotary or thrusting movements of the pelvis as well as disturbances of respiration, such as periodic rapid breathing, irregular breathing, and grunting.

Ironically, the disease makes the patient look very crazy because of the seemingly bizarre facial and bodily movements. Tragically, this has often led to patients being treated more vigorously with neuroleptics, ultimately worsening their TD.

As in other neurological disorders, the patient may attempt to hide the disorder by adding voluntary movements to the involuntary ones to disguise them. For example, to cover up a tendency to move the arms continually, the patient may make grooming movements around the face

and hair. This can make it seem as if the individual suffers from a psychological compulsion instead of a neurological disorder. Or the patient may clasp his or her arms together to control the movements, making it seem as if he or she is trying to psychologically hold onto himself.

## TD Rates

As the following section will document, rates for TD among patients treated with antipsychotic drugs are astronomical. Otherwise healthy adults develop TD at the cumulative rate of 3% to 8% per year of exposure to neuroleptics. The elderly (over age 55) develop TD at a cumulative rate that can exceed 20% per year of drug exposure. Children are at high risk as well.

In 1980 the APA produced a detailed analysis of the iatrogenic disease in its *Task Force Report: Tardive Dyskinesia*. The task force made it clear that TD is a serious, usually irreversible, largely untreatable, and highly prevalent disease resulting from therapy with neuroleptics. The task force estimated the prevalence rate for TD in routine treatment (several months to 2 years) as *at least* 10% to 20% for *more than minimal* disease. For long-term exposure to neuroleptics, the rate was at least 40% for more than minimal disease.

Even after the publication of the 1980 task force report and a mountain of confirmatory evidence, some biologically oriented psychiatrists, such as Nancy Andreasen (1984), in *The Broken Brain: The Biological Revolution in Psychiatry,* continued to misinform the public that TD is "infrequent" (p. 210) and occurs in "a few patients" (p. 211).

A more recent APA (1992) task force report cited a rate of 5% per year, cumulative over the first several years of treatment. Jeste and Caligiuri (1993) estimated the annual incidence rate among young adults at 4% to 5%. According to these two estimates, 12% to 15% of patients will develop TD within the first 3 years of exposure to antipsychotic drugs. In reality, the rates are probably even higher.

In a prospective project emanating from Yale, Glazer et al. (1993) reported a long-term evaluation of 362 outpatient psychiatric patients who were free of TD at baseline and who were being maintained on neuroleptics. For patients who are starting neuroleptics, according to projections from their data, the risk of TD will be 31.8% after 5 years of exposure—a rate of slightly over 6% per year. The risk is 49.4% after 10 years, 56.7% after 15 years, 64.7% after 20 years, and 68.4% after 25 years.

Chouinard et al. (1986) followed a group of 136 persons who had already been receiving neuroleptics but had not yet manifested TD. Over 5 years, 35%—a rate of 7% per year—developed the disorder.

The American Psychiatric Association is a conservative organization that tends to be self-protective of psychiatric treatments. Nonetheless, the two most recent editions of the APA's *Diagnostic and Statistical Manual of Mental Disorders* (1994, 2000) find a prevalence of 20% to 30% for TD in long-term patients (meaning a few years or more). The estimated rate for "younger individuals" is 3% to 5% per year.

Overall, in relatively young and healthy patients, the cumulative risk of contracting TD when exposed to neuroleptics ranges from 4% to 7% per year during the first several years of treatment. Approximately one-third of the patients will develop this largely irreversible disorder within the first 5 years of treatment. This represents an astronomical risk for patients and should become part of the awareness of all mental health professionals, their patients, and their patients' families. Furthermore, we shall find that TD brings with it the additional risk of irreversible cognitive dysfunction and dementia (chapter 5).

There is evidence that rates for TD increased in the 1990s. It may have been caused by the tendency to use drugs with seemingly more toxic effects on the extrapyramidal system such as Haldol and Prolixin (see Jeste et al., 1981). These drugs also come in long-acting intramuscular preparations that do not permit patients to independently lower their own dosages by taking fewer pills than prescribed. The development of long-acting forms of newer neuroleptics, such as Zyprexa, is likely to continue this trend.

It is unusual for TD to develop in less than 3–6 months of treatment. However, as Tepper and Haas (1979) and others (e.g., Hollister, 1976) noted, TD can develop even in low-dose, short-term treatment. DeVeaugh-Geiss (1979) saw cases develop in a matter of weeks. I have evaluated several cases of TD that developed at around 3 months of treatment. One patient developed TD after 1 month of recent exposure, with a history of 2 months' prior exposure several years earlier. I have also seen cases develop after a few doses of Compazine or Reglan for the control of nausea, for example, 3–5 doses given over a several month period. In the elderly, many cases may develop within a few weeks (see subsequent discussions).

## Atypical Neuroleptics Cause TD in Adults

All the neuroleptics (see the appendix) can cause TD, including the atypical neuroleptics such as clozapine (Weller et al., 1993), olanzapine (Herran, 1999), and risperidone (Addington et al., 1995; Buzan, 1996; Kumar et al., 2000; Kwon, 2004). Aripiprazole (Abilify) has been considered one of the safer atypicals, but there are already reports of tardive dyskinesia (Maytal et al., 2006; Oommen et al., 2006). Given that the atypicals,

with the exception of clozapine, are all potent dopamine ($D_2$) blockers (chapters 2 and 3), it is irrational to anticipate that they will produce a significantly lesser amount of TD when given at equivalent doses to the older neuroleptics.

As already noted, in the clinical antipsychotic trials of intervention effectiveness among adults exposed to older neuroleptics and several atypicals (Nasrallah, 2007), no difference was found between the older antipsychotic drugs and the newer ones in regard to producing extrapyramidal effects, movement disorders, or akathisia.

One variant of TD called *rabbit syndrome* is characterized by fine, rapid, rhythmic movements along the vertical axis of the mouth. A recent review found 11 cases associated with atypicals, mostly risperidone (Dell'Osso et al., 2007). All of the FDA-approved atypical neuroleptic labels carry the same class warning as the older neuroleptics.

A key study in misleading the medical profession was published by the *American Journal of Psychiatry* in 1997, comparing TD rates on olanzapine and on haloperidol. It seemed lost on psychiatrists that the first two authors, Gary Tollefson and Charles Beasley, were longtime employees of Eli Lilly, the manufacturer of olanzapine, and well known for stepping into the fray in defense of the company's products, going all the way back to early days of the Prozac controversies (Breggin et al., 1994a). The study purported to show that olanzazpine had a lower rate of TD over a several-month period. But three factors were noteworthy. At the last visit, 2.3% of the olanzapine patients displayed treatment-emergent TD. But the average exposure time was less than a year. If the actual annual rate of TD on olanzapine were calculated, it would be approximately 3%, which is within the range of rates for classic neuroleptics (3% to 8%).

Furthermore, at the times they were being evaluated, the patients continued to take the olanzapine, which, like all neuroleptics, suppresses the appearance of TD symptoms while at the same time causing or worsening the underlying disorder (see subsequent section). Therefore, the only way to determine an accurate rate of TD is to withdraw the patients from the offending drug before the final evaluation. In this study, the actual rate of TD would have been much higher than 3% per year if the patients had been withdrawn from the olanzapine before the final TD evaluation.

Finally, the dose of olanzapine was relatively low compared to haloperidol, an old trick for making one drug look safer than another. The recommended starting dose of olanzapine is 5–10 mg with the aim of achieving 10 mg within several days. The recommended starting dose of haloperidol is 1–6 mg/day (*Drug Facts and Comparisons,* 2007). The patients were given up to 20 mg of either drug as if they were of comparable strength milligram for milligram.

The average physician does not have the time or inclination to analyze a study in the depth with which I have evaluated the Tollefson et al. report. Often physicians will not notice or grasp that the main authors are drug company employees flogging their product under the guise of publishing a scientific study. Physicians are not likely to know that these particular authors specialize in fixing potential promotional problems as they surface among professionals or with the public. As a result, this study convinced many physicians that Zyprexa is safer than it is.

As of May 2006, two of the more knowledgeable TD experts, Daniel Tarsy and Ross Baldessarini, concluded that the risk of TD with atypicals had *not* been clearly established to be less than that with the classic neuroleptics and that patients should be treated with atypicals with the usual caution concerning neuroleptic treatment.

## Atypical Neuroleptics Cause TD in Children

In 1983, while writing the earliest edition of this book, I became one of the first to conclude and to emphasize that TD is a major risk in children. While too many psychiatrists have continued to minimize the risk to children, awareness has grown. In the 2003 edition of *The American Psychiatric Publishing Textbook of Clinical Psychiatry,* now in the era of the atypical antipsychotics, Cozza et al. explained,

> Tardive or withdrawal dyskinesias, some transient but others irreversible, seen in 8%–51% of antipsychotic-treated children and adolescents, mandate caution regarding casual use of these drugs. Tardive dyskinesia has been documented in children and adolescents after as brief a period of treatment as 5 months and may appear even during periods of constant medication dose. Cases of tardive dyskinesia have been reported in youths treated with risperidone, indicating that atypical antipsychotics may also cause this serious adverse reaction. (p. 1422)

To further examine the risk of atypical neuroleptics causing TD in children, Wonodi and a team from the Maryland Psychiatric Research Center (2007) followed up 118 children who had been taking neuroleptics, mostly atypicals, for at least 6 months. As a sign of the irrational overprescription of these drugs, only 19% of the children on antipsychotic drugs had ever displayed psychotic symptoms.

Eleven (9%) of the children developed TD, compared to 0% in a matched control group ($p = .003$). The TD rate was particularly high among African American children (15%). Given the relatively short period of exposure, these rates are astronomically high and should discourage any attempts to give neuroleptics, atypical or not, to children.

## History of TD

Within a few years after the development of the first neuroleptic, it became obvious that many patients were not recovering from their drug-induced neurological disorders, even after termination of the drug treatment. Reports were made in the late 1950s, and Delay and Deniker (1968) date their awareness of irreversible neurological syndromes to 1959. By 1968, they were able to provide a vivid review of several varieties, including buccolingual, truncal, and variable choreic movements. In 1964, Faurbye et al. (1964) named the disorder *tardive dyskinesia*.

As if governed by one mind, psychiatry as a profession for two decades refused to give any official recognition to this potential tragedy. Then, nearly two decades after chlorpromazine initially flooded the state mental hospitals of North America, Crane (1973) made it a personal crusade to gain the profession's recognition of the problem. In the same year, the American College of Neuropsychopharmacology/Food and Drug Administration Task Force (1973) described the syndrome in a special report. Following 1973, everyone in the profession should have been alerted to the dangers of neuroleptic-induced TD, but too many psychiatrists have continued to act as if the risk is too inconsequential to affect their treatment decisions.

In 1980, the American Psychiatric Association (APA, 1980b) published a task force report on TD. In 1985, the FDA took the unusual step of setting specifically worded requirements for a class warning in association with all neuroleptic labeling and advertising ("Neuroleptics," 1985). The FDA's decision to reexamine the labeling for neuroleptics was driven in large part by the 1983 publication of the first edition of this book, *Psychiatric Drugs: Hazards to the Brain,* and the national campaign I conducted to alert the nation and the profession to the dangers of TD, including a special Dan Rather report that highlighted my book and my concerns. In a wholly unprecedented move, in the same year, the APA sent out a warning letter about the dangers of TD to its entire membership (see chapter 13 for further discussion of the FDA's role).

## Masking the Symptoms of TD With Continued Neuroleptic Treatment

The symptoms of TD are paradoxically masked or suppressed by the drugs that cause them so that the disease symptoms do not fully appear until the patient has been removed from the treatment. For this reason, in addition to using the smallest possible dose for the shortest possible time, whenever possible, patients should periodically be removed from their neuroleptics, if only for a short period, to determine if they are developing TD. Permanent removal from the neuroleptics is a more difficult matter,

often requiring many months of gradual withdrawal for the brain to adjust to the drug-free environment. The best approach to neuroleptics, in this author's opinion, is never to use them (chapter 16).

Because the neuroleptics suppress TD symptoms, some physicians have advocated their use for the treatment of TD. Harold Klawans has discussed the danger of trying to control or treat TD with the causative agent. He asserts (in the discussion following Goetz et al., 1980), "Treatment of tardive dyskinesia with neuroleptics themselves is clearly treatment with the presumed offending agent and should be avoided." He calls it short-sighted to use the neuroleptics in the treatment of tardive dyskinesia and concludes that the therapy "serves to aggravate its pathogenesis." Unhappily, Klawans himself, in the same article, too readily recommends reserpine as a helpful agent in the treatment of TD, because it also has neuroleptic effects and can cause the disorder.

Despite my serious reservations, I have seen cases of TD that were so disabling that the only recourse was treatment with a neuroleptic. But two points must be borne in mind about these cases. First, in each instance, the case became so severe because physicians failed to detect the TD when it first appeared and continued neuroleptic treatment long after it should have been terminated. This has been true in nearly all the most disabling cases I have examined. Second, the individuals in question were overcome with suffering and rendered wholly unable to function by the TD. They and their families were warned about the danger of worsening the TD and then made informed decisions to continue the offending agent because the TD was making life unbearable for the patient. By contrast, most patients who develop severe cases of TD have not been warned about the risk.

The anticholinergic drugs typically used to ameliorate the symptoms of drug-induced parkinsonism also may aggravate the symptoms of TD (Yassa et al., 1992). They include benztropine (Cogentin), biperiden (Akineton), and trihexyphenidyl (Artane, Tremin). These agents are known to worsen similar symptoms in Huntington's chorea (Hunter et al., 1968; Klawans, 1973). At present, the role of these drugs in the development or exacerbation of TD is controversial and undetermined, but caution is required in giving them to patients on neuroleptics. These agents are often used to treat acute extrapyramidal symptoms and may be mistakenly prescribed for TD.

## Extrapyramidal Symptoms As Predictors of Future TD

The neuroleptics produce a variety of acute, temporary neurological disorders referred to as extrapyramidal symptoms (EPS) in the great majority of patients. As described in chapter 3, drug-induced parkinsonism is one

of the most common, probably occurring to some degree in the vast majority of patients exposed to effective doses of neuroleptics; akathisia is also very common. Dystonia, often characterized by cramping of the muscles of the neck and shoulders, is less common but can be extremely painful and disabling.

These acute EPS reactions often resemble TD, and indeed, the dystonias and akathisia can become tardive (persistent) disorders. All of them, including parkinsonism, result from neuroleptic effects on the dopaminergic neurotransmitter system in the basal ganglia.

I have already noted that the atypical neuroleptics can cause EPS and that studies indicating lower rates have sometimes used lower equivalent doses. A Taiwanese research team tried to determine the comparative frequency of EPS by examining the rates at which patients taking one or more of 14 different neuroleptics were coprescribed anti-Parkinson drugs (Yang et al., 2007). They found a tendency for the anti-Parkinson drugs to be prescribed less frequently to patients taking atypicals, but there was considerable overlap. Quetiapine had the lowest coprescribing rate (27%), but risperidone had one of the highest (66.5%). Mellaril was lower (61%) than risperidone, and loxapine was the highest (96%). A confounding factor, however, is the tendency for doctors to prescribe anti-Parkinson drugs as a prophylaxis and to prescribe them more readily if they consider the drug likely to cause EPS.

The question naturally arises, Do acute EPS increase the risk of TD? If acute EPS do predict an increase in future TD, then the emergence of EPS indicates an increased need to terminate the medication. These questions have been debated over the years, but recent research gives the best-informed answer to date. In 2006 a prospective follow-up study of 9,298 patients by the European Schizophrenia Outpatient Health Outcomes (SOHO) Study found a statistically significant correlation between baseline EPS and later TD. According to Tenback et al. (2006), "about half of the patients who developed tardive dyskinesia had earlier extrapyramidal symptoms." They concluded that "drug regimens . . . that increase extrapyramidal symptoms are likely to result in increased risk of tardive dyskinesia."

## The Elderly and Other Vulnerable Populations

Medication adverse effects in general are more likely to develop in the elderly (Nolan et al., 1988). People who are elderly and people suffering from dementia are at extreme risk for many different adverse effects when exposed to neuroleptics. A recent study of administrative data from a health care insurer in the United States examined 959 cases of patients at least 45 years old who had been diagnosed with dementia,

who had made a claim for at least one prescription drug, and who had been enrolled for 3 years (Kolanowski et al., 2006). They found that 29% of this community-dwelling population had been dispensed antipsychotic treatment, with a disproportionate number being female. The atypicals were the most commonly prescribed. Even when controlled for polypharmacy, age, and sex, the group treated with neuroleptics, either classic or atypical, had an increased risk of adverse events, including delirium, depression, hip fracture, falls, and syncope. Combined with research showing increased rates of cardiovascular problems and death as well as the metabolic syndrome, neuroleptics should be contraindicated in the elderly.

The vulnerability of the elderly is nowhere more apparent than in regard to TD. The two most recent editions of the *Diagnostic and Statistical Manual of Mental Disorders* (APA, 1994, 2000) provide a consensus statement that sums up the degree of risk in the elderly, noting "prevalence figures reported up to 50% and an incidence of 25%–30% after an average of 1 year's cumulative exposure to neuroleptic medication." This is so hard to believe that it is worth paraphrasing: More than one-quarter of the elderly will develop TD within the first year of exposure!

In addition to age, prior brain damage probably increases the risk of TD (Breggin, 1983b; Chouinard et al., 1979; McKeith et al., 1992). Cohen and Cohen (1993) found a correlation between TD and prior organic brain disorder.

Yassa et al. (1988) found that 41% of elderly patients developed TD over a period of only 24 months and that none fully recovered. None of the non-drug-treated controls made up of elderly patients developed spontaneous dyskinesias during the 2 years. Yassa et al. (1988) found TD in 45% of an outpatient clinic population with a mean age of 60. Yassa et al. (1992) found that 35.4% of patients developed TD after a mean exposure of 20.7 months. Saltz et al. (1991) found that the incidence of TD was 31% following 43 weeks of cumulative neuroleptic treatment in the elderly. The incidence was higher among patients who had previous electroshock treatment. Patients with early signs of parkinsonism developed TD at a faster rate. Of great importance, in this older population, the mean cumulative time while taking neuroleptics was very brief, a mere 22.7 weeks. One patient developed TD at 2 weeks.

Jeste et al. (1993), in an ongoing prospective study, found that 26% of middle-aged and elderly patients developed TD after 12 months. Reviewing the literature on neuroleptic withdrawal, the authors found "that almost 60 percent of the patients withdrawn from neuroleptics did not relapse over a mean period of 6 months." They concluded, "It seems

feasible to discontinue neuroleptic medication from a select population of older schizophrenic patients, if it is done carefully with adequate monitoring and follow up." They also experimented with brief 2-week placebo-substituted withdrawal in their own group of patients, both younger and older patients, and found it relatively benign: None relapsed or required resumption of neuroleptics. They concluded, "Given the heightened risk of TD in older patients, it seems that a trial of neuroleptic withdrawal is warranted in this population." I would add that the same is true for all ages: Take as many as possible off these drugs.

Jeste et al. (1993) emphasized, "The potential seriousness of neuroleptic-induced TD warrants obtaining competent, informed consent to treatment from patients or guardians." They recommended that consent be periodically renewed and cited other sources to confirm their position.

Woerner et al. (1998) studied a group of neuroleptic-naïve patients aged 55 and above, evaluated them at baseline before the start of neuroleptics, and followed up at 3-month intervals. Relatively low doses of conventional neuroleptics were used: "The rates of TD were 25%, 34%, and 53% after 1, 2, and 3 years of cumulative antipsychotic treatment." Once again, the rates were astronomically high: "A greater risk of TD was associated with history of [electroconvulsive therapy] treatment, higher mean daily and cumulative antipsychotic doses, and presence of extrapyramidal signs early in treatment."

Jeste et al. (1999) concluded, "The risk of tardive dyskinesia in older outpatients is high, even with relatively short treatment with low doses of conventional neuroleptics."

Although there appear to be few, if any, studies of the rates of TD induced by atypical drugs in the elderly, they, too, will undoubtedly be high. In the meanwhile, the other risks associated with atypical drugs in the elderly—including cognitive impairment, neuroleptic malignant syndrome, EPS, stroke, sudden death, hypertension, diabetes, pancreatitis, obesity, and elevated cholesterol—provide ample reason never to give these drugs to older people. Again, in rational and ethical medicine, the neuroleptics would be contraindicated—forbidden—in the treatment of the elderly.

## Relapse, Exacerbation, and Delayed Onset After Termination

TD typically waxes and wanes, both in the course of a day and in the course of weeks or months. Especially in the elderly, both partial remissions and relapses are common (Lacro et al., 1994).

As in many neurological disorders, the manifestations of TD can worsen during stress and can be somewhat calmed with sedation (Jeste

et al., 1993). In my clinical experience, and as confirmed by the literature, anxiety, exhaustion, and other general stresses to the mind and body can temporarily exacerbate the symptoms, while relaxation, when possible, can temporarily reduce them.

With great effort, patients can sometimes suppress some of their symptoms for a short time. As mentioned earlier in the book, they can also integrate their movements into more natural-looking actions, such as grooming or smiling, to disguise them. One patient with whom I consulted would hide her involuntary facial grimaces by trying to smile. Unfortunately, the effect was to make her look even stranger to the casual observer. Neither the fact that TD waxes and wanes, sometimes in response to stress, nor the patient's ability to partially suppress it with an exertion of will should mislead observers into believing that it is psychological or emotional in origin. Too often, the early signs of TD are overlooked, denied, or dismissed by physicians on these mistaken grounds.

I have, on occasion, seen cases that did not become apparent until several months or more after termination of treatment. Christensen et al. (1970) have documented that a significant percentage of TD cases may not show up at all until many months or even several years after discontinuation of the treatment. They believe that the symptoms are brought on by the interaction between the damage caused by the drugs and by the aging process. If this is true, then a tragic reality may develop as we observe the evolution of TD in aging populations.

## Reversibility Is Rare

In the vast majority of cases, TD is irreversible, and there is no effective treatment. One report indicated that among patients with persistent TD, followed for a period of 5 years, 82% showed no overall significant change, 11% improved, and 7% became worse (Bergen et al., 1989).

Another study followed 49 outpatient TD cases for a mean of 40 weeks (range 1–59 months) after discontinuation of medication (Glazer et al., 1990). Many patients showed noticeable improvement in their movements within the first year after stopping neuroleptics, but only 2% showed complete and persistent recovery. The authors concluded, "A major finding of this study is that complete reversal of TD following neuroleptic discontinuation in chronically treated patients was rare."

With the increasing number of children receiving neuroleptics, in the last few years, I have evaluated several dozen cases of TD in youngsters. Atypicals like Risperdal and Zyprexa commonly cause TD in children. However, the rate of recovery in my experience seems better than in regard to adults, and I have seen a few cases completely resolve. Nonetheless, TD remains a catastrophic disorder in children in terms of its frequency,

its incapacitating and disfiguring effects, its associated cognitive deficits, and the sheer number of children afflicted.

## Physician and Patient Denial of TD

Physicians understandably find it painful to face the damaging effects of their treatments. Too often, it is difficult for them to confront the damage done to patients by other physicians as well. In addition, physicians may consciously seek to protect themselves or their colleagues from criticism or malpractice lawsuits by failing to acknowledge or to record obvious symptoms of TD. I have seen many hospital and outpatient records in which obvious, severe cases of TD have gone either unrecognized or undocumented, sometimes by several physicians in succession. For example, the nurse's notes may make clear that the patient is in constant motion, yet the doctor's physical examination or progress notes will give no indication of the disorder. Even official discharge summaries may fail to record TD in patients who have been demonstrating the disorder throughout the period of hospital or clinic treatment. Even when the TD diagnosis has been made during the hospitalization and can be found buried inside the chart, the diagnosis may not be put in the discharge summary, even though it is critical for future physicians to be warned about the patient's condition in order to avoid further exposure to neuroleptics. This denial of the obvious is mirrored within the profession itself, which has been very remiss in recognizing or emphasizing the seriousness of the problem (for an analysis of this history of denial, see Breggin, 1983b; Brown et al., 1986; Cohen et al., 1990; Wolf et al., 1987).

Psychiatrists sometimes accuse patients of exaggerating their TD. In reality, most patients tend to deny the existence or severity of their TD. As discussed in detail in chapter 5, patient denial is caused in part by neuroleptic-induced lobotomy effects and in part by denial associated with TD brain damage. Patient nonrecognition of TD symptoms is a reflection of the spellbinding effects of the drug when being taken and the continued spellbinding effect of the biological disorder itself.

The mutual denial of TD by physician and patient is an aspect of iatrogenic helplessness and denial—the use of brain-disabling treatments in psychiatry to enforce the patient's denial of both his or her original personal problems as well as the iatrogenic brain dysfunction and damage (chapter 1).

## The Size of the Epidemic

It is difficult to determine the total number of TD cases. Van Putten (as cited in Lund, 1989) estimated 400,000–1,000,000 in the United States.

My own earlier estimate is higher, ranging in the several millions (Breggin, 1983b). It is no exaggeration to call TD a widespread epidemic and possibly the worst medically induced catastrophe in history.

## TARDIVE DYSTONIA

There are at least two relatively common variants of TD: tardive dystonia and tardive akathisia. According to Burke et al. (1982), tardive dystonia involves "sustained involuntary twisting movements, generally slow, which may affect the limbs, trunk, neck, or face" (p. 1335). The face and neck are by far the most frequently affected areas of the body. Severe deformities of the neck (*torticollis*) can cause extreme pain and disability. I have seen several cases affecting the orbital muscles of the eyes (*blepharospasm*) to the degree that the individual's vision was impaired, requiring botulinum (Botox) injections to paralyze the muscles. I have also seen respiratory and abdominal muscles affected in a painful and debilitating manner.

Tardive dystonia can produce cramplike, painful spasms that temporarily prevent the individual from carrying out normal activities. Sometimes the spasms are so continuous that the individual is largely disabled. Damage to the joint and skeleton system, including fractures, can occur (Burke et al., 1988). The pain and muscle tension as well as the effort to compensate for the spasms can be exhausting and demoralizing.

The torsions (twisting movements, often involving the neck) can be worsened by activity such as attempts to write or walk. Sometimes they can be relieved by particular movements such as touching the chin to relieve torticollis or touching the brow to relieve blepharospasm.

As Burke and Kang (1988) pointed out, tardive dystonia can be mistakenly dismissed as a manifestation of hysteria or some other psychological problem: "In this regard it is important to realize that dystonia, like many other neurological disorders, can be influenced transiently by suggestion, placebo, or sedation (e.g., during an amobarbital interview) and such maneuvers cannot exclude a true dystonia." Also, like many other neurological disorders, it can sometimes be partially controlled by extreme exertions of will.

Tardive dystonia can make an individual appear unsympathetic or bizarre, especially to the uninformed observer, who equates the facial grimaces or neck distortions with being crazy. As in all the drug-induced dyskinesias, the individual may try to cover up the disorder with additional movements that make the disorder seem voluntary and therefore not a product of mental illness. The result can be very confusing and even distressing to the observer. I have read several medical records in which

nurses recorded their complaints about supposedly rude patients who seemingly stuck out their tongues or made faces at them. The patients had undiagnosed TD. The nurses' errors in clinical judgment delayed recognition of the disorder and speedy termination of the causative drugs.

In a 1988 review of tardive dystonia, Burke and Kang found 21 reports describing 131 patients (for reviews, see also Greenberg et al., 1985; Kane et al., 1992). As already emphasized, because all the atypical neuroleptics are potent dopamine blockers (except clozapine), it should have been assumed that all of them could cause TD and tardive dystonia. Case reports confirm that risperidone (Vercueil et al., 1999; Narendran et al., 2000) and olanzapine (Gunal et al., 2001; Dunayevich et al., 1999) can cause tardive dystonia.

Tardive dystonia is a particularly painful, disabling, and intractable disease often requiring injections of Botox or even surgical excision of muscle to relieve the spasms. In a review of 107 patients by Kiriakakis et al. (1998), only 14% had a remission over a mean of 5.2 years from onset and 2.6 years after discontinuation of neuroleptics (range 1 month to 9 years). According to Kiriakakis et al. (1988), "discontinuation of neuroleptics increased the chances of remission fourfold." Patients with 10 years or less exposure to neuroleptics had a 5 times greater chance of remission. Therefore, as in regard to TD in general, it is imperative to limit long-term exposure to neuroleptics and to stop them at the earliest sign of tardive dystonia.

Kiriakakis et al. (1988) confirmed my experience that neck pain can be a precursor to cervical dystonia. Some patients also experience "odd somatic sensations heralding their tardive dystonia." The most common presentations were blepharospasm (with or without oromandibular dystonia) or torticollis. Less common initial symptoms included pharyngeal dystonia, causing dysphagia, and oromandibular dystonia, causing severe disturbance. Other patients experienced dystonia of the limbs or trunk. Five had "very bizarre" disturbances of gait. The dystonia often progressed stepwise, involving additional parts of the body. Thirty percent of the patients also had TD, 22% had akathisia, 27% had parkinsonism, and 9% had a prior acute dystonic reaction.

Kiriakakis et al. (1988) concluded, "Tardive dystonia can develop at any time between 4 days and 23 years after exposure to [neuroleptics] and there is no 'safe' period." It can afflict anyone independently of their psychiatric diagnosis, and patients with schizophrenia have accounted for only half of reported TD cases. From assorted studies, they estimate the prevalence at 2.8% among neuroleptic-treated patients.

In my clinical and forensic practice, I have consulted with and evaluated many cases of tardive dystonia, mostly involving the face, neck, and shoulders, but sometimes the torso. I see a disproportionate number of

dystonia cases, probably because they suffer from considerable pain and disability and are therefore more likely to seek a clinical consultation or to hire me as a medical expert in a malpractice or product liability case.

In my clinical experience, patients who develop permanent dystonias during neuroleptic therapy are sometimes misdiagnosed with idiopathic (of unknown origin) dystonia. The argument is made that neuroleptic-induced dystonia is rare compared to dystonia of unknown origin in the general population. However, the reverse is true. Friedman et al. (1987) found a prevalence rate of tardive dystonia of 1.5% among chronically hospitalized patients, but as they pointed out, the rate in the U.S. population as a whole is a mere 0.000003% (0.3 per 100,000). When a persistent dystonia appears in association with neuroleptic exposure, by 500,000 to 1, the odds are overwhelming in favor of a diagnosis of tardive dystonia, rather than idiopathic dystonia.

## TARDIVE AKATHISIA

Tardive akathisia involves a feeling of inner tension or anxiety that drives the individual into restless activity, such as pacing (see chapter 3 for details), although on occasion, it can occur with little or no display of hyperactivity. The first report of tardive akathisia that I was able to locate in the literature was published by Walter Kruse in 1960. He described three cases of muscular restlessness that persisted at least 3 months after discontinuation of treatment with the classic neuroleptics fluphenazine and triflupromazine. The "akathisic syndrome…consisted of inability to sit still, pacing the floor all day, jerky movements of arms and shoulders." Once again, Delay and Deniker (1968) were also among the first clinicians to notice the disorder. In discussing "syndromes persisting after cessation of medication," they mentioned "hyperkinetic" ones. As early as 1977, Simpson more definitively made an association between TD and irreversible akathisia. Gualtieri and Sovner (1989) reviewed the subject of tardive akathisia, cited studies with prevalence rates of 13% to 18% among neuroleptic-treated patients, and called it "a significant public health issue."

The anguish associated with both acute and persistent akathisia should not be minimized. Consider Van Putten's (1974) description of a mild, temporary akathisia or hyperkinesia: "Patient feels 'all nerved up,' 'squirmy inside,' 'uptight,' 'nervous,' 'tense,' 'uncomfortable,' 'impatient.'…Subjective feeling of ill-being may be accompanied by restless changes in posture."

One reason that so little attention has been given to the mental disruption associated with the dyskinesias is the tendency to blame the mental component on preexisting emotional problems attributed to the

patient. Indeed, it has been commonplace to blame the obvious motor disturbances on the so-called mental illness, often resulting in increased treatment, and a worsening of the symptoms, until neuroleptic-induced immobility sets in, masking the entire process.

It takes no great imagination to grasp the suffering of a patient condemned to even a relatively mild tardive akathisia for a lifetime. I have seen cases of this kind that were previously mistaken for severe anxiety or agitated depression. Chapter 3 reviewed research indicating that acute akathisia can drive a patient into psychosis and to violence and/or suicide. Considering the millions of patients subjected to this torment, the problem takes on epidemic proportions.

Tardive akathisia can be subtle. A woman in her mid-60s consulted me because of seemingly bizarre feelings that other doctors attributed to her depression and to delusions or hallucinations. She had a feeling of "electricity" going in periodic bursts throughout her body. Although she sat quietly in the office, she spoke of feeling fidgety and driven to move about.

Her hospital and clinic charts disclosed that 2 years earlier, she had been treated for approximately 6 months with neuroleptics. The sensation she was describing had first been noted while she was taking the medication. I concluded that she probably had tardive akathisia, a subtle case that did not force her to move about. However, because she did not show external signs of the disorder, other physicians were reluctant to make the diagnosis. The patient felt "driven to distraction" and even to suicide, but after my diagnosis, she felt somewhat relieved. At last, a physician was taking her seriously and talking honestly to her.

In 1993, Gualtieri wrote,

> In terms of clinical treatment and the public health, however, TDAK [tardive akathisia] is a fact, not a question. It is one more serious side effect of neuroleptic treatment, like TD and the Neuroleptic Malignant Syndrome. Taken together, they define neuroleptic treatment as a necessary evil, a treatment that should be administered with care and caution, and reserved for patients who have no other recourse.

I agree with Gualtieri about everything, except for the "necessity" of this evil. It is entirely possible and even preferable to treat children and adults without resort to these highly toxic agents (chapter 16).

## COMPLICATIONS OF TARDIVE DISORDERS

TD is a complex disorder with mental and emotional effects that are often overlooked by health care providers. In my professional capacity

as a doctor of last resort for patients with iatrogenic disorders, and as a medical expert on behalf of injured patients, I often am confronted with the task of evaluating the overall damage to patients and their families by the various tardive disorders, including classic TD, tardive dystonia, and tardive akathisia.

## Physical Exhaustion

Fatigue to the point of exhaustion almost always accompanies tardive disorders of any severity. Patients often become exhausted by the movements, by the effort to hide them, and by increased difficulty associated with carrying out daily activities. The primary impact on the brain itself may also produce fatigue. Although the disorders tend to disappear in sleep, they can make it difficult to fall asleep, adding to the exhaustion. Having to contend with the physical pain associated with tardive akathisia (inner torment) and with tardive dystonia (muscle spasms) can also wear a person down.

Because of the fatigue, as well as any motor disabilities, patients are often unable to continue working. Many give up recreational activities such as bike riding, walking, and swimming. As a result, they gain weight and feel sluggish.

## Psychological Suffering

Because TD often makes the sufferers look odd or even bizarre, they experience shame and humiliation, typically leading to lowered self-esteem and social withdrawal. Even a seemingly mild dyskinesia that affects facial expression can be sufficiently humiliating to cause a person to want to stay at home and away from people. Similarly, a speech abnormality that makes a person "talk funny" can lead to the avoidance of communicating.

The experience of constant pain from dystonia or inner torture from akathisia can drive a person to suicidal despair. The physical disabilities associated with disorders can also become very depressing to patients.

In a clinical report from the Mayo Clinic by Rosenbaum (1979), depression was found to be closely linked to TD. Rosenbaum stated, "Almost all patients in our series had depressive symptoms accompanying the onset of tardive dyskinesia," and he cited other studies confirming his observation.

TD patients often feel very betrayed by the doctors who prescribed the medication or who failed to detect the disorder or to tell the patients about it. Too frequently, perhaps in a self-protective stance toward their colleagues, several psychiatrists or neurologists in a row will fail to

inform the patient or family about the obvious iatrogenic disorder. This neglect of the truth can leave patients feeling that they cannot trust psychiatrists.

Chapter 5 will look at impairments to mental functioning that are almost always found in patients with drug-induced tardive disorders. Overall, even a slight or minimal degree of tardive disorder can end up seriously impairing an individual's quality of life.

## NEUROLEPTIC WITHDRAWAL SYMPTOMS

Withdrawal frequently causes a worsening mental state, including tension and anxiety. Drugs that produce potent anticholinergic effects, such as Thorazine and Mellaril, can cause cholinergic rebound that mimics the flu, including emotional upset, insomnia, nausea and vomiting, diarrhea, anorexia and weight loss, and muscle aches.

Withdrawal symptoms often include a temporary worsening of dyskinetic effects, both painful and frightening. As documented in chapter 5, withdrawal from neuroleptics commonly produces a level of emotional suffering and disturbance more severe than anything the individual experienced prior to starting the medication. In adults, this frequently manifests as psychotic symptoms worse than anything experienced prior to starting on the medication. In children, it can result in very disturbed behavior.

The atypical or newer neuroleptics are not free of withdrawal symptoms. In one of my cases, a young woman became extremely fatigued, depressed, and suicidal when withdrawing from Zyprexa. I have seen severe dyskinetic symptoms during withdrawal from Zyprexa, Risperdal, and Abilify. While on the drug, she was zombielike. Withdrawal took careful supervision over several months. Clozapine may have an especially marked withdrawal syndrome characterized by a worsening psychosis, angry or abusive language, hyperactivity, agitation and restlessness, dyskinesia, confusion, and aggressive or suicidal behavior ("Clozapine," 1994). Chapter 5 will discuss a variety of neuroleptic withdrawal symptoms, including tardive psychosis.

How to withdraw from psychiatric drugs is discussed in chapter 15.

### Are Neuroleptics Addictive?

While classic addiction to these substances has not been demonstrated, the antipsychotic drugs can cause severe withdrawal symptoms, making it impossible for patients to stop taking them. For this reason, I long ago suggested viewing these drugs as *addictive* (Breggin, 1989a, 1989b). I believe

that my earlier observations need modification. It is more accurate to say that neuroleptics create *dependence* in the form of withdrawal reactions that prevent patients from stopping them, but they do not cause the compulsive drug-seeking behavior commonly associated with dependence and with the older term *addiction*. Instead, individuals often find neuroleptics unpleasant, painful, or debilitating but cannot endure the withdrawal process.

For clarification, it is necessary to discuss the terms *dependence* and *addiction*. For generations, the term *addiction* had been used to describe the effects of drugs, such as alcohol, stimulants, and benzodiazepines, that cause physiological tolerance, physical withdrawal symptoms, and, in the extreme, compulsive drug taking that results in harmful physical, psychological, social, and economic consequences. *Addiction* is a term that continues to be used in the professional community that treats addicts as well as in the lay community. However, by one vote, a *DSM* committee voted to replace the term *addiction* with the term *dependence* in the *DSM–III* (APA, 1980a), in part to remove some of the stigma. The result has been enormous confusion (O'Brien et al., 2006).

Many people exposed for months or years to psychiatric drugs such as the SSRI antidepressants and the neuroleptics find that they cannot easily withdraw from them, but they do not, like the classic addict, compulsively pursue drug seeking. Similarly, people treated for pain often become dependent on the opiates without necessarily seeking ever-increasing doses. For clarity, I propose using the term *dependence* to describe primary drug effects, such as tolerance and withdrawal symptoms, while reserving the term *addiction* for cases that involve compulsive, escalating, drug-seeking behavior. In short, antidepressants, neuroleptics, and some mood stabilizers cause dependence without causing addiction; stimulants, benzodiazepine tranquilizers, and related sleeping medications can cause both dependence and addiction.

Because of the withdrawal symptoms, it is often necessary to reduce neuroleptic drugs at a very slow rate. Sometimes withdrawal seems to become impossible. I describe the principles of safely withdrawing from psychiatric drugs in chapter 15.

## OTHER ADVERSE REACTIONS

The neuroleptics can produce a variety of other symptoms of central nervous system dysfunction, including abnormal electroencephalogram (EEG) findings, an increased frequency of seizures, respiratory depression, and disturbances of body temperature control (Davis, 1980; Davis et al., 1975). Endocrine disorders, especially in females, may also be of central

nervous system origin (Davis, 1980). There is some evidence that autonomic dysfunction can become irreversible (*tardive autonomic disorders*).

## NEUROLEPTIC MALIGNANT SYNDROME

This devastating disorder was seemingly so bizarre, unexpected, and inexplicable that physicians for years literally refused to believe their eyes. Seven years after the introduction of the drugs into North America, Leo Hollister (1961) reviewed their side effects in the *New England Journal of Medicine*. In two separate places, he referred to syndromes that probably were NMS. He described a "bizarre" dystonic syndrome that can be "confused with hysteria, tetanus, encephalitis or other acute nervous-system disorders; a rare fatality may occur." Later, he mentioned, "Other clinical syndromes attributed to central nervous-system effects of these drugs have resembled acute encephalitis, myasthenia gravis, bulbar palsy or pseudotabes."

Although NMS was identified in an English-language publication by Delay and Deniker as early as 1968, physicians continued to be reluctant to recognize the syndrome. Delay and Deniker declared that it was caused by the neuroleptics, specifically including haloperidol (Haldol) and fluphenazine (Prolixin), although we now know that any neuroleptic can cause NMS, including the newer ones such as Zyprexa and Risperdal. Clinicians have also found an increased danger with long-acting injectable neuroleptics, probably because patients are unable to secretly cut back on the amount they are taking.

Delay and Deniker (1968) were already able to identify many of the components of NMS, including pallor, hyperthermia, a severe psychomotor syndrome with akinesia and stupor, or hypertonicity with varying dyskinesias. They warn that at the first suspicion, "one must stop medication *immediately and completely.*" They were already aware of fatalities. That the syndrome was named and definitively identified in English in 1968 is most remarkable in light of the failure of drug companies to give it formal recognition until compelled to do so by the FDA almost 20 years later (see chapter 13 for further discussion).

NMS is characterized by "such symptoms as severe dyskinesia or akinesia, temperature elevation, tachycardia, blood pressure fluctuations, diaphoresis, dyspnea, dysphagia, and urinary incontinence" (Coons et al., 1982). The *DSM–IV–TR* establishes criteria of severe muscle rigidity and elevated temperature plus 2 more of 10 associated features, including sweating, swallowing problems, tremor, incontinence, changes in level of consciousness from confusion to coma, mutism, elevated heart rate, unstable blood pressure, elevated white count, or laboratory evidence of

muscle injury (e.g., elevated serum level of creatine phosphokinase, or CPK).

In my clinical and forensic experience, rigidity is too narrow a criterion for establishing NMS. Instead, the clinician should look for any acute, severe increase in abnormal movements, including any one or several of the movements associated with TD and tardive dystonia. Consistent with my experience, after reviewing episodes of NMS in 20 patients, Rosebush and Stewart (1989) found that most cases fit the following cluster of symptoms: delirium; a high fever with diaphoresis; unstable cardiovascular signs; an elevated respiratory rate; and an array of dyskinesias, including tremors, rigidity, dystonia, and chorea. Patients spoke little during the acute illness and later reported that they had found themselves unable to express their anxiety and feelings of doom.

Almost all patients were agitated shortly before developing NMS, suggesting to Rosebush and Stewart (1989) that they were undergoing akathisia. White blood cell counts were elevated in all cases, dehydration was common, and lab tests showed a broad spectrum of enzymatic abnormalities, including indications of muscle breakdown such as an elevated CPK.

If unrecognized, as too often happens, NMS can be fatal in more than 20% of cases. The syndrome frequently leaves the surviving patient with permanent dyskinesias and dementia (see chapter 5).

Most cases develop within the first few weeks of treatment (even within 45 minutes), but some develop after months or years or after increased dosage (Gratz et al., 1992).

Estimates for rates of NMS vary widely, but studies indicate that they are very high. Pope et al. (1986) surveyed 500 patients admitted during a 1-year period to a large psychiatric hospital and found a rate of 1.4%. The cumulative rate for patients would be much higher. The authors remarked, "Neuroleptic malignant syndrome may be more common than previously thought and may be underdiagnosed."

Addonizio et al. (1986) carried out a retrospective review of 82 charts of male inpatients and found an even higher prevalence of 2.4% for diagnosed NMS. Again, the cumulative rate over repeated hospitalizations or years of treatment would be much higher. Although it is sometimes called "rare," NMS should be described as common or frequent (1/100 is common by FDA standards).

The rates for NMS, as well as its potential severity and lethality, make it an extreme risk for patients receiving antipsychotic drugs. A risk of this size would probably result in most drugs in general medicine being removed from the market.

As a medical expert, I have reviewed cases in which several physicians at a time missed making the correct diagnosis in what seemed, from

my retrospective analysis, like an obvious case of NMS. The failure to stop the neuroleptic and to institute proper treatment resulted in severe, permanent impairments, or death. The mistaken idea that NMS is rare may contribute to these errors in judgment. In several of my forensic cases, the tendency to attribute anything strange to the patient's mental illness played an obvious role in physician failure to make the proper diagnosis.

There is little or nothing about acute NMS to distinguish it from an acute, severe episode of encephalitis, especially lethargic encephalitis (also called von Economo's disease), except for the fact of recent exposure to neuroleptic therapy. I have previously compared neuroleptic toxicity and lethargic encephalitis in detail (Breggin, 1983b, 1993; see also chapter 5).

Although Rosebush and Stewart (1989) provided insufficient data to draw exact parallels, their NMS patients also suffered chronic impairments similar to those reported in lethargic encephalitis patients. Of the 20 patients, 14 continued to have "extrapyramidal symptoms or mild abnormalities of vitals signs and muscle enzymes at the time of discharge" (p. 721), but we are not told how many of the 14 specifically had persistent extrapyramidal signs. In a striking parallel with lethargic encephalitis, three patients displayed persistent parkinsonism symptoms until they were lost to follow-up. One patient, who had mild cognitive impairment prior to NMS, developed a persistent worsening of her dementia.

The *DSM–IV–TR* indicated,

> The essential feature of Neuroleptic Malignant Syndrome is the development of severe muscle rigidity and elevated temperature in an individual using neuroleptic medication. This is accompanied by two (or more) of the following symptoms: diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness ranging from confusion to coma, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, and laboratory evidence of muscle injury (e.g., elevated creatine phosphokinase [CPK].[1]

In my clinical and forensic experience, the emphasis on muscle rigidity is much too narrow. NMS can be accompanied by any kind of severe extrapyramidal reaction. Especially early in NMS, patients can display any of the wide array of neuroleptic-induced abnormal movements, including choreoathetoid movements, dystonia, and akinesia. Some cases look very much like severe TD, and often, the patients are left with persistent symptoms of TD.

NMS has been reported with the atypical neuroleptics clozapine (Anderson et al., 1991; Dasgupta et al., 1991) and risperidone (Dave, 1995; Mahendra, 1995; Raitasuo et al., 1994; Singer et al., 1995).

In 2007 Zarrouf and Bhanot published the most extensive recent review and identified 88 reports of NMS associated with six atypical neuroleptics: olanzapine, clozapine, risperidone, ziprasidone, quetiapine, and aripiprazole. As a warning to those doctors who cavalierly resume neuroleptics once the NMS has gone into remission, 20 cases showed a "clear history" of prior NMS, indicating that a patient's first case of NMS predisposes toward another when reexposed to neuroleptics. Olanzapine (Zyprexa) has been touted as being relatively free of the risk of NMS, but the authors located 36 cases.

Zarrouf and Bhanot (2007) confirmed that NMS often leads to irreversible brain damage in the form of various manifestations of tardive dyskinesia; ataxia and balance problems; abnormal movements of the trunk and limbs; speech abnormalities; and violent, unilateral outbursts of movement (hemiballismus). NMS also left patients suffering from multiple cognitive disabilities including difficulties comprehending commands, attention problems, and persistent amnesia. Postmortem studies revealed "cerebellar degeneration, reduction of the Purkinje and granule cells, and gliosis in the dentate nucleus" (p. 93).

Zarrouf and Bhanot correctly find that "no conclusive evidence indicates which antipsychotic might lower a patient's risk of recurrent NMS" (p. 94). NMS is one more devastating risk associated with all neuroleptics, including the newer atypicals!

Research indicates that typical and atypical neuroleptic drugs increase the vulnerability of neurons to cell death and even kill brain cells and that the risk increases in patients already suffering from brain disorders such as Alzheimer's (chapter 5). Consistent with this, Sechi et al. (2000) reported on a case of NMS following exposure of a patient with familial dementia with Lewy bodies to low doses of risperidone.

## BIOLOGICAL BASIS OF NEUROLEPTIC-INDUCED NEUROLOGICAL SYNDROMES

Drug-induced parkinsonism apparently develops in part, but not wholly, from blockade of dopamine receptors in the basal ganglia, specifically the striatal region or striatum (the caudate and putamen), producing motor retardation, rigidity, and other symptoms. Damage and degeneration in the pigmented neurons of the substantia nigra play a key role. These neurons terminate in the striatum, where, when functioning normally, they release dopamine to act on striatal dopamine receptors.

TD is a more delayed reaction, probably based in part on the development of reactive supersensitivity or hyperactivity in these same striatal dopamine receptors following continuous blockade (see APA, 1980b;

Fann et al., 1980; Klawans, 1973; and chapter 5 in this volume). This supersensitivity of the dopamine receptors becomes most obvious when the drug is reduced or eliminated, terminating the blockade. The overactive, unblocked receptors produce the TD symptoms. Undoubtedly, a great deal more must be learned about the neuropathology of both these drug-induced diseases, which probably involve multiple neurotransmitter system abnormalities. However, if health care providers were to stop prescribing these drugs to patients, the problem would virtually disappear.

More recent studies have indicated that TD may be the result of complex interactions between dopamine and the cholinergic system, which becomes more active when the suppressive or balancing effect of the dopaminergic system is blocked by the neuroleptics. In addition, the neuroleptics are directly toxic to neurons by means of disrupting a number of separate biochemical pathways (chapter 5).

## CHILDREN AND NEUROLEPTICS

In recent years, unscrupulous physicians have been pushing for the increased prescribing of neuroleptic drugs to children. The main justification has been the diagnosis of bipolar disorder in children, a complete sham based on nothing more than the assumption that certain common childhood behaviors, such as anger and agitation, are precursors to adult bipolar disorder. These drug advocates have largely ignored the manifold serious risks associated with giving neuroleptics to children, including tardive dyskinesia (see previous discussion), brain cell damage and brain shrinkage (chapter 5), obesity, and diabetes. Nor have these drug advocates considered the difficult-to-measure risks associated with bathing the growing brain in toxins.

In an editorial titled "Gaining: Pediatric Patients and Use of Atypical Antipsychotics," published in the *American Journal of Psychiatry* in December 2006, Tobin stated:

> Recent studies of overall pediatric use have shown a 6- to 20-fold increase in prescription of atypical antipsychotics in four state Medicaid-programs and, nationally, a sixfold increase in pediatric visits that included prescriptions of antipsychotic medication, more than 90% of which were prescriptions for atypical antipsychotics.

Tobin claims that there are some good justifications for prescribing antipsychotic drugs to children but warns about the drugs causing excessive weight gain and type II diabetes. After showing this concern, does the editorial recommend cutting back on prescribing atypical antipsychotic

drugs to children? No. Does the editorial recommend stopping the drug when children and adolescents begin to show signs of drug-induced weight gain? No. The editorial recommends continuing the neuroleptic while adding the highly experimental and potentially dangerous drug metformin (Klein et al., 2006), which is used for treating type II diabetes. As a result of its determination to prescribe neuroleptic drugs to tens of thousands of children, psychiatry has created a major public health threat to the *physical* health of America's youth.

There has also been an increase in children displaying maniclike symptoms consistent with a manic episode or bipolar disorder. Prior to the advent of Prozac in 1989, I never saw a child with genuine manic symptoms. Since then, I have seen an increasing number. Why? Every single case of childhood bipolar disorder or mania that I have seen has resulted from an adverse drug reaction, usually to the newer antidepressants such as Prozac or Paxil, and on fewer occasions, to stimulants like Ritalin and Adderall. In no case have the offending health care providers admitted that the disorder was caused by their prescribed medications. At the most, they told parents that the drug had unmasked a preexisting bipolar disorder, a claim wholly lacking in scientific foundation.

As a result of the increased prescription of drugs like Zyprexa, Risperdal, and Geodon to children, I am seeing an increasing number of TD cases in young people. I have personally evaluated well over a dozen cases involving Risperdal and an additional number caused by Zyprexa and Geodon, several of which I describe in detail in *Medication Madness* (in press).

In my experience, TD is no less frequent in children than in adults, and it can be more severe, often involving the torso and causing difficulties with gait (see Breggin, 1983b, for a review). As already mentioned, children seem more resilient than adults, and I have seen several cases that have improved dramatically and a limited few that have gone into remission after withdrawal of the drug. Sometimes the gradual improvement has required many months, subjecting the child to a lengthy disability.

The stigmatizing consequences of TD are even more devastating to children than to adults. I evaluated one 10-year-old child who largely recovered from a severe case caused by Risperdal, leaving her only with an occasional abnormality of her eye muscles that caused her eyes to briefly roll up inside her head, showing the whites. Imagine how she is going to feel when she develops an interest in boys and realizes, on her own or through humiliating experiences, that little boys will not feel comfortable watching a little girl's eyes roll up inside her head.

## Treating Childhood Tourette's With Neuroleptics

One of the most tragic situations in the treatment of children today involves the use of neuroleptics for the control of Tourette's disorder.

Tourette's involves a combination of tics and spontaneous, inappropriate vocalizations, such as curse words. While claims have been made for a biological origin, none has been demonstrated. On the other hand, it is extremely well documented that neuroleptics frequently produce TD in children with far more disabling tics, spasms, and other abnormal movements.

The devastating effects of neuroleptics in children diagnosed with Tourette's often go unrecognized. Dulcan (1994) reported that the symptoms of Tourette's can be exacerbated for several months following withdrawal from neuroleptics. Bruun (1988) reviewed 208 cases. She found that 34 suffered from drug-induced dysphoria that appeared in the form of an "organic affective syndrome," 9 from a drug-induced worsening of their Tourette's, 5 from aggression and hostility, 3 from "fog states," and 2 from "frank psychomotor seizures." A number of the children endured drug-induced akathisia, which worsened their emotional and neurological condition. The author also noted the appearance of withdrawal dyskinesias. Three of the children developed symptoms of TD, which, the author reported, resolved over a period of weeks or months.

I have evaluated several children and young adults who developed severe cases of tardive dyskinesia following neuroleptic treatment for Tourette's. One, a 20-year-old man who had been treated with Risperdal, eventually recovered from Tourette's. However, his drug-induced severe abnormal tongue movements and jaw spasms have required treatment with Botox, and he may never fully recover from them. He had been able to live a happy and largely unimpaired life with Tourette's; but the TD has severely impaired his school, occupational, and social life.

The use of neuroleptics for the treatment of Tourette's does not meet a reasonable medical standard in terms of its risk:benefit ratio.

## The Food and Drug Administration Opens the TD and NMS Floodgates for Children

On October 6, 2006, the FDA announced its approval of Risperdal for the treatment of "extreme irritability" in autistic children. The only way Risperdal can reduce this so-called extreme irritability (anger and temper tantrums) is by deactivating the frontal lobes, limbic system, and reticular activating system, causing a chemical lobotomy with emotional blunting. Since Risperdal is a potent dopamine blocker, it has this capacity.

A primary effect will be the further impairment of the autistic child's already limited ability to care about and relate to other people. Risperdal will make children more autistic. In many cases, it will also worsen the child's so-called irritability by causing agitation and akathisia. But in the process of making children more robotic, it will make some seem less troublesome.

Worst of all, the FDA's limited approval of the drug for treating extreme irritability in autistic children will further encourage the widespread, off-label use of this devastating drug in large numbers of children with behavior problems. Risperdal is already frequently prescribed off label with no scientific justification to a wide range of children, usually with the aim of suppressing unwanted behaviors. The FDA's action will greatly encourage this abusive use of the drug, ultimately causing a new wave of TD, tardive dementia, and tardive psychosis among children.

After I had written these concerns about the increasingly widespread use of Risperdal for treating children, the FDA (2007d, August 22) took an even more reckless step when it made this announcement:

> The U.S. Food and Drug Administration today approved Risperdal (risperidone) for the treatment of schizophrenia in adolescents, ages 13 to 17, and for the short-term treatment of manic or mixed episodes of bipolar I disorder in children and adolescents ages 10 to 17. This is the first FDA approval of an atypical antipsychotic drug to treat either disorder in these age groups.

Risperdal, with its potent capacity to block dopamine $D_2$ receptors, is the least "atypical" of all the so-called atypicals. Most of the cases of TD in children that I have evaluated have been caused by Risperdal. As you read in chapters 2–5 about the devastating toxicity of the "antipsychotic" drugs, keep in mind that America's drug watchdog agency has turned on its children by unleashing one of the worst iatrogenic disorders upon them.

## HURRYING DEATH

Until the advent of neuroleptic drugs, it was observed that patients diagnosed with schizophrenia lived normal life spans, unless subjected to the violent and unhealthy environments of state mental hospitals (Breggin, 1991c). Since the advent of neuroleptics, almost every patient in the Western world diagnosed with schizophrenia ends up being afflicted with a variety of neurological disorders induced by neuroleptics as well as the risk of many other serious disorders, such as stroke, heart disease, obesity, and diabetes.

In 2006 Joukamaa and colleagues, in the *British Journal of Psychiatry,* examined the mortality rates for patients diagnosed with schizophrenia in a representative population sample of 7,217 Finns age 30 and over. A comprehensive health and psychiatric examination, including

previous medical records, was utilized, and the patients were followed up for 17 years. At that time, 39 of 99 individuals had died. The relative mortality risk between those with schizophrenia and others was 2.84 (95% confidence interval [CI] 2.06–3.90). According to the authors, "the number of neuroleptics used at the time of the baseline survey showed a graded relation to mortality." Still short of willing to face the reality, the authors concluded, "There is an urgent need to ascertain whether the high mortality in schizophrenia is attributable to the disorder itself or the antipsychotic medication."

There cannot be any question whether the lethal agent is schizophrenia or the neuroleptics. There are no known physical disorders, not even any abnormal lab tests, associated with the diagnosis of schizophrenia, whereas the neuroleptic drugs are cytotoxic and cause numerous physical disorders of the brain and body from diabetes and liver disease to unexplained sudden death. They also produce apathy and indifference as their primary effect, greatly reducing the capacity of an individual to respond to the early onset signs of heart disease, stroke, and other illnesses that require immediate treatment. In April 2005, the FDA (2005b) issued a public health advisory that the use of atypical antipsychotics to treat elderly patients with dementia was associated with an increased risk of death in placebo-controlled clinical trials. In June 2005, Health Canada issued a similar warning. The trials that provided the data involved risperidone, olanzapine, quetiapine, and aripiprazole. Mortality was approximately 1.6 to 1.7 times higher when compared to placebo.

In 2007, Gill et al. examined antipsychotic use and mortality in older adults with dementia in Ontario, Canada, over a 5-year period (see also Medline Plus, 2007). A total 27,259 matched pairs were identified. Comparisons were made between atypical neuroleptic exposure and no antipsychotic drug exposure and between atypical neuroleptic drug exposure and conventional antipsychotic drug exposure. Patients were in community or in long-term care. The risk of death was assessed at 30, 60, 120, and 180 days after the initial dispensing of the antipsychotic drug. Both the older and the atypical neuroleptics were associated with an increased risk of death at all assessment times, including 180 days, by a factor of 1.31–1.55 times. Conventional antipsychotics had a greater risk than atypicals at all points in time. The authors concluded,

> Our study provides further evidence that use of atypical antipsychotics is associated with a small but significant increase in morality among older patients with dementia. In addition, the risk of death associated with antipsychotics is apparent after as little as 1 month of use and may persist for six months.

## CONCLUSION

The widespread use of neuroleptics has unleashed an epidemic of neurological disease on the world. Even if TD were the only irreversible disability produced by these drugs, this would be among the worst medically induced disasters in history. In reality, the antipsychotic drugs also reduce the quality of life, cause multiple severe and potentially lethal physical disorders, and shorten the life span.

Meltzer (1995) urged that attempts be made to remove long-term patients from neuroleptics and tried to demonstrate its feasibility. Gualtieri (1993), warning about the extreme dangers, suggested that neuroleptics be viewed as a necessary evil and a therapy of last resort. I believe that the profession should make every possible effort to avoid prescribing antipsychotic drugs. Meanwhile, the FDA-driven escalation in prescribing these drugs to children and adolescents should be stopped.

As a step toward a more ethical psychiatry, the use of any neuroleptics in the treatment of children should be prohibited. In the long run, if psychiatry entirely *gave up* the use of neuroleptics, it would find that psychosocial approaches are much less risky and much more genuinely effective. Chapter 16 will examine some of these better alternatives.

## NOTE

1. Myoglobinuria should be added to this list.

CHAPTER 5

# Neuroleptic-Induced Neurotoxicity, Brain Damage, Persistent Cognitive Deficits, Dementia, and Psychosis

Since I first voiced my concerns and reviewed the subject (Breggin, 1983b), much more evidence has been accumulating that the neuroleptics can cause persistent damage or dysfunction to the highest centers of the brain, including cerebral atrophy. My concept that neuroleptics or antipsychotics are neurotoxic and cytotoxic in general seemed radical at the time, but we will find that it is now an accepted concept by the laboratory researchers who study these toxic effects. In the last few years, laboratories around the world have focused on the mechanisms of how typical and atypical neuroleptics cause neuronal cell death, but textbooks and clinicians have largely turned a blind eye on these critical findings.

## DEMONSTRATING NEUROLEPTIC-INDUCED BRAIN DAMAGE AND CELL DEATH

A recent study involving primates has demonstrated that both the older and the atypical neuroleptics shrink brain tissue during routine clinical exposure. Dorph-Petersen et al. (2005), from the Department of Psychiatry at the University of Pittsburgh, subjected three groups of six macaque monkeys each to oral haloperidol (Haldol), olanzapine (Zyprexa),

or sham for a 17–27 month period. The doses of Haldol and Zyprexa produced plasma concentrations similar to those used in clinical practice with human beings. After exposure, the researchers found an 8% to 11% reduction in brain weight in both drug groups but not in the sham group. Shrinkage of the brain was observed "across all major brain regions (frontal, parietal, temporal, occipital, and cerebellum), but appeared most robust in frontal and parietal regions" (p. 1649). The frontal region is the most critical in producing lobotomy-like brain-disabling effects (chapter 1).

The authors concluded: "In summary, we found that chronic exposure of monkeys to haloperidol or olanzapine in a manner that mimics clinical use is associated with a significant reduction in brain volume that affects both gray and white matter" (p. 1659). A follow-up study conducted by the same research team (Konopaske et al., 2007) and based on the same protocol sought to identify the specific cellular damage associated with the brain shrinkage caused by Haldol and Zyprexa in clinical doses. An examination of the gray matter in the parietal region found that a 14.6% reduction in gray matter was associated with a 14.2% reduction in the glial cells. The numbers of neurons and endothelial cells were unchanged, resulting in their increased density in the shrunken tissue.

The authors concluded that their data raised the possibility that changes seen in the brains of patients diagnosed with schizophrenia might be due at least in part to antipsychotic medication. This was a dramatic suggestion from researchers who were sponsored by both NIH and Eli Lilly, the manufacturer of Zyprexa. As this chapter will confirm, in fact there can be no serious scientific doubt that the destructive changes seen in the brains of patients labeled schizophrenic are wholly attributable to the medications inflicted on them.

By themselves, these studies should have been sufficient to raise warning flags of concern about inflicting these drugs on human beings. NIH, the sponsoring federal agency for the research, held no press conference to warn about these ominous findings. Eli Lilly, the manufacturer of olanzapine, sent no "Dear Healthcare Provider" letter warning about widespread shrinkage of the brain resulting from the death of brain cells. Despite this research and the existence of earlier, confirmatory animal studies (see further in the chapter), the medical profession has yet to blink an eye over subjecting its patients to a class of drugs, the neuroleptics, that destroy a large percentage of brain cells and substantially shrink the brain size of its patients.

Neuroleptics can damage or destroy brain cells through a variety of mechanisms. They not only suppress the gross function of dopaminergic neurons, they disrupt a variety of metabolic functions within neurons and other cells throughout the body.

It has been known for several decades that these drugs inhibit most enzyme systems in the mitochondria (Teller et al., 1970), which are the principal sites for many of the most important metabolic processes in the cell. Research by Inuwa et al. (1994) demonstrated that neuroleptics are absorbed into human cell mitochondria, where they interfere with metabolic processes and cause structural abnormalities. The authors suggested, "It is possible that such interaction may be cytopathic leading to premature cell death" (p. 1091).

Recent research has become more sophisticated in studying the toxic effect of neuroleptics on cells of neuronal processes. Ethier et al. (2004) found that haloperidol impairs striatal neuropeptide gene expression. They correlated this in rats with the production of *catalepsy*—a slowing down of bodily movements—thereby creating a study of the brain-disabling effects of neuroleptics. These drugs damage cellular processes and simultaneously inhibit spontaneous movement. The overall reduction of spontaneity in patients is closely related to the so-called therapeutic effect.

Bonelli et al. (2005) observed that "the influence of psychotropic drug medication on acute cell death has not been studied so far in vivo, although some experiments performed in vitro suggest that antipsychotic dugs are neurotoxic." Tissue transglutaminase (tTG) is a marker for apoptosis, a stage in the death of neurons. The researchers studied the occurrence of this marker for cell death in the spinal fluid of patients exposed to classic and atypical neuroleptics. Some of the patients had Alzheimer's disease and other neurological disorders, and some did not: "A significant influence ($P < .01$) of antipsychotic drugs for both the Alzheimer's and the non-Alzheimer's group was found with respect to tTG protein levels in cerebral spinal fluid." A variety of other drugs, including tranquilizers and antidepressants, had no such effects on "cerebral cell death." The authors concluded, "The results suggest that typical and atypical antipsychotic drugs may induce cerebral cell death." The results were worse for females than for males.

Consistent with Bonelli et al.'s biochemical finding, Alzheimer patients given the newest neuroleptics have a significantly greater loss of autobiographical memories than untreated patients (Harrison & Therrien, 2007). Put simply, neuroleptics worsen Alzheimer's dementia.

In an attempt to shed light on the mechanism by which neuroleptics induce extrapyramidal reactions, Bishnoi et al. (2007) chronically administered haloperidol (1 mg/kg) and chlorpromazine (5 mg/kg) to rats, resulting in a time-dependent increase in orofacial hyperkinetic movements. They found a corresponding time-dependent decrease in extracellular levels of norepinephrine, dopamine, and serotonin in various cortical and subcortical regions of the brain.

Because of their neurotoxicity, neuroleptics probably worsen any brain disorder. A controlled experiment with rats subjected to traumatic brain injury demonstrated that chronic, high doses of risperidone or haloperidol were detrimental, causing persistent cognitive deficits (Kline et al., 2000).

Consistent with my own clinical observation that neuroleptics worsen Alzheimer's disease and other dementing disorders, Bonelli et al. (2005) warned that individuals with Alzheimer's disease are even more vulnerable to neuroleptic-induced cell death. The researchers stated, "A limit on the use of first- and second-generation antipsychotics in elderly patients is proposed." Finally, they saw a possible connection between "the observed increased cerebral cell death and tardive dyskinesia, the most threatening side effect in antipsychotic therapy."

Jarskog et al. (2007) studied the effects of haloperidol, clozapine, and quetiapine on numerous so-called apoptotic markers to study the impact of these drugs on apoptosis. Essentially, they examined the neurotoxicity of neuroleptics, specifically their capacity to induce cell deterioration typical of the process of cell death. They found that the neuroleptics, both the older ones and the atypicals, caused activation of caspase-3, a marker for apoptosis. They tried to reassure their readers that "this activity was probably non-lethal."

Jarskog et al. (2007) did not find evidence for faddish research that tries to prove that neuroleptics actually protect cells from trauma (see chapter 8 for the allegedly protective effects of neuroleptics and mood stabilizers). Indeed, the evidence for the opposite continues to grow, confirming that neuroleptics kill brain cells. Noting that haloperidol causes abnormal motor behavior, Kim et al. (2006) sought to increase knowledge about "how it triggers neuronal impairment." Citing Tseng and Lin-Shiau (2003), they pointed out that "chronic blockade of dopamine D2 receptors in the striatum results in persistently enhanced release of glutamate, which kills striatal neurons." Using hippocampal neurons from mice, Kim et al. found that haloperidol induces a calcium ion influx into the cell and that this renders neurons more susceptible to oxidative stress. Neuroleptics do not protect cells from stress, they induce toxic processes that render them more susceptible to stress, at times killing them.

Neuroleptics are toxic to cells throughout the body. The clinical observations have demonstrated that atypicals cause diabetes and weight gain (Jin et al., 2004) and recently caused the FDA to include warnings in all atypical psychotic labels (package inserts). This has led to research explorations of the underlying cytotoxic processes. Vestri et al. (2007) compared the effects of two older neuroleptics with the atypicals risperidone, clozapine, olanzapine, and quetiapine in regard to glucose metabolism in cultured cells. All of the medications interfered with some of the

intracellular processes. However, only the atypicals "were able to impair the insulin-responsive glucose transport system and to impair lipolysis in adipocytes.... These effects of SGAs [second-generation antipsychotics] on adipocytes could explain, in part, the association of SGAs with weight gain and diabetes."

Neuroleptics increase the toxicity of the sunlight to human skin, causing discolorations and other adverse dermal reactions. Researchers noted this phenomenon, called *phototoxicity,* and set out to study its effects on cells loaded with the neuroleptics fluphenazine, perphenazine, or thioridazine (Bastianon et al., 2005). They found that exposure of these cells to light caused abnormalities in both the plasma membrane and mitochondria.

Clozaril causes potentially fatal agranulocytosis of white blood cells due to bone marrow suppression. The mechanism is probably a direct toxic effect on bone marrow cells. When tested, the neuroleptics chlorpromazine, olanzapine, and quetiapine were also toxic to bone marrow cells (Pereira et al., 2006).

Neuroleptics can cause sudden death that, at times, is related to cardiac failure. Belhani et al. (2006) demonstrated that numerous classic and atypical neuroleptics produced cardiac lesions and/or hypertrophy in rabbits treated for 3 months. For example, olanzapine (0.30 mg/kg/day) produced ventricular hypertrophy. The lesions were consistent with toxic myocarditis. Again, neuroleptics are generally cytotoxic.

Dwyer et al. (2003) reviewed the literature on antipsychotic cytotoxicity and noted, "The cytotoxic properties of the older phenothiazine antipsychotic drugs are well known." They cited studies confirming that these drugs "inhibit proliferation in a variety of cell lines and alter cell morphology." They set out to compare and evaluate the cytotoxic effects of the newer atypicals by studying the effects of glucose metabolism. They confirmed that antipsychotics produce some of their toxic effect by inhibiting the utilization of glucose in cells. Although generally, the atypicals were less toxic, the results were inconsistent, but all displayed some toxicity. They described the complexity:

> Risperidone was a fairly potent inhibitor of glucose transport but was not very toxic for cells [in their tests] and olanzapine, a modest inhibitor of glucose transport, actually stimulated proliferation of neuronal cells. Haloperidol was toxic for [experimental cells], however, it did not affect glucose transport. On the other hand, this drug inhibited mitochondrial function (energy metabolism), which may explain its toxicity.

The researchers also pointed out that neuronal cells, unlike others, rely exclusively on glucose metabolism, making them especially vulnerable

to the effects of antipsychotic drug inhibition of glucose metabolism. However, since multiple toxic effects are produced by the antipsychotics, they concluded: "Taken together, the various data suggest that the cytotoxicity of the antipsychotic drugs may result from a summation of effects on numerous independent pathways that converse to compromise cell viability" (p. 37).

Although the researchers do not discuss it, reduced glucose utilization would produce the reduced metabolic rate and hypoactivity in the frontal lobes caused by neuroleptics, causing or contributing to their brain-disabling, lobotomy-like effect. And they fall prey to wishful thinking, imagining that the abnormal proliferation of neural cells stimulated by olanzapine may be therapeutic.

The reader will find little or nothing in the major psychiatric and psychopharmacological textbooks about these well-documented neuroleptic-induced neurotoxic and cytotoxic processes.

## PET Scans

In the last two decades, positron emission tomography (PET) scanning has been used to measure the metabolic rate and blood flow of various parts of the brain. This instrument can detect dysfunction that does not necessarily manifest as gross pathology. It can also measure functional changes that have no pathological origin. When an individual pays attention, frontal lobe activity will increase. When the same individual looks at pictures, visual centers of the brain will become activated. Chapter 1 analyzed three PET scan studies involving the effects of risperidone (Lane et al., 2004; Liddle et al., 2000; Ngan et al., 2002). Together these studies demonstrated the brain-disabling concept: first, that risperidone causes a generalized malfunction (suppressed metabolism) in the frontal and temporal lobes; second, that this effect takes place in normal volunteers as well as patients labeled schizophrenic and is therefore not specific for schizophrenia; and third, that this malfunction correlated with so-called improvement in the form of a reduction in communications about symptoms. The suppression of metabolism in the brain is a neurotoxic effect.

From the earliest studies, there has been a somewhat consistent finding of hypoactivity in the frontal lobes and frontal cortex of neuroleptic-treated people with schizophrenia (Buchsbaum et al., 1982; Farkas et al., 1984; Wolkin et al., 1988, as reviewed in Andreasen, 1988; Wolkin et al., 1985). In most studies, the patients had long histories of neuroleptic treatment prior to the PET scans, and the drugs were temporarily stopped at the time. However, temporarily stopping neuroleptic treatment would not have reversed its long-standing and persistent suppressive effects on the frontal lobes.

The PET scan has been used to study specific parts of the brain in which the neuroleptics are known to produce dysfunction by blockade of the dopamine neurotransmitter system, including the basal ganglia. A variety of studies show that the basal ganglia of neuroleptic-treated patients develop abnormalities (Farde et al., 1988). However, there are also many negative PET studies (see Buchsbaum et al., 1992, and a lengthy summary table in Andreasen et al., 1992; see also Andreasen, 1988).

One PET study involving unmedicated patients found no frontal hypoactivity (Sheppard et al., 1983). Another with unmedicated patients showed increased frontal metabolism (Cleghorn et al., 1989). The failure to demonstrate hypoactivity in the frontal lobes of unmedicated patients confirms that the effect, when found, is probably caused by the antipsychotic medications. As an exception to this, Buchsbaum et al. (1992) found hypofrontality in never-medicated patients diagnosed with schizophrenia. However, the results were not definitive: "The hypofrontality effect was modestly sensitive and not strongly specific."

Some PET studies have measured cerebral blood flow in patients labeled schizophrenic who had never been exposed to neuroleptics. The PET measurements were made while the subjects were asked to perform a task intended to activate the frontal lobes. Andreasen et al. (1992) found that "decreased activation occurred only in the patients with high scores for negative symptoms. These results suggest that hypofrontality is related to negative symptoms and is not a long-term effect of neuroleptic treatment or of chronicity of illness."

Andreasen et al.'s conclusion has an obvious flaw. Negative symptoms of "schizophrenia" include apathy, indifference, lack of emotion, lack of willpower or volition, lack of verbal communication, and social withdrawal. High scores for negative symptoms mean that the patients were unable or unwilling to cooperate with the demands of the project to perform the requested tests, therefore putting less energy into the task that was supposed to elicit frontal lobe activity. Notice as well that all of these symptoms can be caused by the antipsychotic drugs (chapters 1 and 2), suggesting that these patients may have been especially heavily medicated, resulting in suppression of their frontal lobe activity.

Overall, the finding of subtle differences in energy usage in the brains of any individuals, whether diagnosed schizophrenic or not, could have a psychological origin. It is well known, for example, that different states of consciousness affect the amplitude and frequency of electrical waves in different parts of the brain. For example, visual and auditory activities are reflected in heightened electrical activity in different regions of the brain. Biofeedback experiments have shown that people can consciously control some aspects of brain wave activity.

In most cases, however, the finding of hypoactivity in the frontal lobes of patients diagnosed with schizophrenia results from neuroleptic-induced

brain dysfunction and damage. PET scans showing hypoactivity in the frontal lobes of medicated and previously medicated patients confirm the brain-disabling principles of biopsychiatric treatment.

## MRI

In her review of neuroimaging studies, Jackson (2005) commented on the inconsistency of results. The common finding is that studies of patients exposed to neuroleptics reveal a wide variety of anatomical abnormalities in the brain. As Lang et al. (2004) stated, "Antipsychotic medications are known to alter the structure and metabolism of basal ganglia in humans and animals."

Meanwhile, considerable evidence has accumulated that neuroleptics cause enlargement (increased volume) of the striatum (caudate, putamen, and globus pallidus; study results and review in Lang et al., 2004). Dopaminergic nerves predominate in this area, and the enlargement may represent proliferation within the dopaminergic system in response to neuroleptic blockade. On the other hand, the neuroleptics cause shrinkage of brain tissue in the frontal regions, with a compensatory increase in the volume of the ventricular spaces. This probably results from the destruction of brain cells.

Magnetic resonance imaging (MRI) has been replacing CT scans in recent years for studying brain morphology. Lieberman et al. (2005b) assessed brain volume changes in first-episode patients diagnosed with schizophrenia and treated with haloperidol or olanzapine. The patients treated with haloperidol "exhibited significant decreases in gray matter volume, whereas olanzapine-treated patients did not." The authors suggested that the haloperidol "effects on brain morphology could be due to haloperidol-associated toxicity." They cited three studies showing that haloperidol can "induce oxidative stress and excitatory neurotoxicity." That, of course, is the only reasonable conclusion, given that neuroleptics are toxic to brain cells. In addition, they observed an increase in the size of the caudate, which they acknowledge is "known to be due to treatment effects of conventional drugs causing ultrastructural changes in striatal neurons" (p. 368).

However, Lieberman et al. (2005b) waffle, suggesting that the "greater therapeutic effects of olanzapine" threw off the results. The second author of the study, Gary Tollefson, has been a longtime consultant and then staff member of Eli Lilly, the manufacturer of olanzapine (Breggin et al., 2004 and author affiliations at the end of the article). Another author, Mauricio Tohen, is also a Lilly employee, and the project received partial funding from the Lilly Foundation.

The summary in the abstract of the article is also misleading. Olanzapine did cause some degree of reduction in the volume of the frontal lobes, but it was relatively less. In addition, the doses of olanzapine were relatively mild compared to those for haloperidol. The range of olanzapine doses (5–20 mg) was similar to that of haloperidol (2–20 mg), but milligram for milligram, haloperidol is much more potent and hence toxic. The recommended initial dose of olanzapine is 10–15 mg/day, and for haloperidol, the initial recommended dose is a fraction of that amount at 1–6 mg/day (*Drug Facts and Comparisons,* 2007). The comparative doses of haloperidol were thus much larger, indicating why it was causing more damage to the frontal lobes. This is a common trick used by drug companies when trying to show that their drug is less toxic than a competitor's drug: utilize a comparatively lower and hence less toxic dose for your drug.

Khorram et al. (2006) found that conventional antipsychotics caused a dose-dependent increase in the volume of the thalamus compared to normal volunteers. The thalamic volumes returned to normal when the patients were switched from the older antipsychotic drugs to olanzapine. However, the doses of olanzapine are not provided. The authors conclude, "Antipsychotic medication could contribute to the wide range of thalamic volumes reported in schizophrenia" (p. 2007). In other words, the drugs and not the disorder are causing the brain structure abnormalities. This, of course, confirms the brain-disabling principles of neuroleptic effects.

## CT SCANS AND NEUROPSYCHOLOGICAL CORRELATIONS

Many older studies involved computerized axial tomography (CT) scans of psychiatric patients, most but not all of whom were diagnosed schizophrenic. They have found enlarged lateral ventricles and sometimes enlarged sulci, indicating shrinkage or atrophy of the brain. Nearly all these studies involved patients heavily treated with neuroleptics.

A number of the CT scan studies have found a correlation between atrophy and persistent cognitive deficits or frank dementia in these neuroleptic-treated patients (DeMeyer et al., 1984; Famuyiwa et al., 1979; Golden et al., 1980; Johnstone et al., 1976; Lawson et al., 1988). Some of these studies used the Nebraska and Halstead–Reitan batteries, considered among the most sensitive for detecting brain damage and dysfunction.

While some of the studies claimed that drugs could not have caused the observed brain abnormalities, they did not provide evidence that confirmed this viewpoint (e.g., Johnstone et al., 1976; Johnstone et al., 1978;

Lawson et al., 1988; Shelton et al., 1988; Weinberger et al., 1980; Weinberger et al., 1979).

Two studies that evaluated relatively young and relatively untreated patients diagnosed with schizophrenia found enlarged ventricles, a marker for brain atrophy (Schulz et al., 1983; Weinberger et al., 1982; reviewed in detail in Breggin, 1990). However, very small numbers of patients were involved, and other studies have not confirmed their findings (Benes et al., 1982; Iacono et al., 1988; Jernigan et al., 1982; Tanaka et al., 1981).

### Correlating Tardive Dyskinesias (TD) With Brain Damage and Dementia

Surprisingly few studies have attempted to correlate brain scan findings with the presence of tardive dyskinesias (TD). Bartels and Themelis (1983) found abnormalities in the basal ganglia of TD patients, but overall, the results have been mixed and inconclusive (Besson et al., 1987; Goetz et al., 1986; Jeste et al., 1980; Koshino et al., 1986). However, as noted in chapter 4 in regard to neuroleptic malignant syndrome (NMS), patients with these more extreme reactions to antipsychotic drugs often show gross brain damage (Zarrouf and Bhanot, 2007).

### Summary of Brain Study Data

Mounting radiological evidence from PET, MRI, and CT scans confirms the presence of chronic brain dysfunction (PET scans) and brain atrophy (MRI and CT scans) in neuroleptic-treated patients diagnosed with schizophrenia. It also confirms the brain-disabling concept.

By 1988, Kelso et al. estimated the total number of relevant CT scan studies to be over 90, most of which show damage. Some studies implicate the total lifetime amount of neuroleptic intake (DeMeyer et al., 1984; Lyon et al., 1981). A number of researchers try to attribute the findings to schizophrenia, but there is little justification for this (see subsequent discussion).

## RATES OF TARDIVE DEMENTIA BASED ON BRAIN SCANS

Studies indicate that the percentage of drug-treated patients diagnosed with schizophrenia who demonstrate atrophy on CT scans varies from 0% to over 50%. If treatment has been lengthy and intensive, as in Suddath et al.

(1990), most patients may show brain atrophy. Reported rates are substantial, typically in a range of 10% to 40%. Coming to a similar conclusion, Andreasen (1988) reviewed the literature and found a range of 6% to 40%. Andreasen noted that higher rates were reported with increasing severity and length of illness. However, severity and length of "illness" would also correlate with intensity and duration of treatment with neuroleptics.

## CLINICAL EVIDENCE

Evidence from several different clinical sources confirms that the neuroleptics can permanently impair mental functioning.

### Early Correlations Between TD and Cognitive Dysfunction

The term *dementia* will be defined as a syndrome of organically based multiple cognitive deficits, including memory impairment as well as other brain dysfunctions, such as emotional lability, personality change, or impairments in abstract thinking, judgment, and other higher cortical or executive functions (see American Psychiatric Association, 2000). The chapter focuses on gradually evolving persistent brain damage and dysfunction associated with chronic exposure to neuroleptics.

An earlier review (Breggin, 1983b) disclosed that many patients with TD are also suffering from severe cognitive dysfunction (e.g., Edwards, 1970; Hunter et al., 1964; Ivnik, 1979; Rosenbaum, 1979). Often the data had to be culled from charts and footnotes because most of the studies relegated this correlation to obscurity within the article. Other studies concluded, without evidence, that the brain damage must have predated the TD. However, multiple subsequent studies have confirmed my initial observations, and the correlation between tardive dyskinesia and cognitive function is now well established. (See subsequent sections).

### Tardive Dysmentia and Tardive Dementia

Many clinical studies have now confirmed the existence of persistent cognitive deficits and dementia in association with neuroleptic use. However, to some extent, researchers have lost their enthusiasm for demonstrating over and over again that neuroleptics cause cognitive deficits, and textbooks of psychiatry simply do not want to mention it (e.g., Hales et al., 2003). This is reminiscent of the history of research into the brain-damaging effects of shock treatment (chapter 9). When repeated

animal studies showed that electroconvulsive therapy caused brain damage, including scattered small hemorrhages and cell death, the research stopped, and textbooks ignored or denied its existence.

A clinical study of hospitalized drug-treated patients found many suffering from mental deterioration typical of a chronic organic brain syndrome that the researchers labeled *dysmentia* (Wilson et al., 1983). Tardive dysmentia consists of "unstable mood, loud speech, and [inappropriately close] approach to the examiner." It is probably a variant of hypomanic dementia.[1] The mental abnormalities in the study by Wilson et al. (1983) correlated positively with TD symptoms measured on the Abnormal Involuntary Movement Scale. In addition, length of neuroleptic treatment correlated with three measures of dementia: unstable mood, loud speech, and euphoria. The authors stated, "It is our hypothesis that certain of the behavioral changes observed in schizophrenic patients over time represent a behavioral equivalent of tardive dyskinesia, which we will call tardive dysmentia" (p. 188). The tendency in the literature, perhaps in search of a euphemism, has been to use the term *tardive dysmentia* even when a full-blown dementing syndrome is described.

A variety of studies confirmed the existence of tardive dysmentia (dementia; Goldberg, 1985; Jones, 1985; Mukherjee, 1984; Mukherjee et al., 1985; Myslobodsky, 1986). Myslobodsky (1993) summarized the triad of features of tardive dysmentia as "occasional excessive emotional reactivity, enhanced responsiveness to environmental stimuli, and indifferent or reduced awareness of abnormal involuntary movements." He reviewed a study indicating that patients diagnosed with schizophrenia with TD score significantly higher on measures of aggression and tension than similar patients without TD. He pointed out that some of these patients suffer from typical frontal lobe signs. He also warned that routine neuropsychological testing can miss the frontal lobe syndrome associated with TD.[2]

In addition to Wilson et al. (1983), several other studies reported an association between TD symptoms and generalized mental dysfunction (Baribeau et al., 1993; DeWolfe et al., 1988; Itil et al., 1981; Spohn et al., 1993; Struve et al., 1983; Waddington et al., 1986a&b; Wolf et al., 1982; many reviewed in Breggin, 1993). After eliminating schizophrenia as a causative factor, Waddington and Youssef (1988) also found increased cognitive deficits in neuroleptic-treated bipolar patients with TD in comparison to those without the disorder.

Wade et al. (1987) pointed out that Huntington's and Parkinson's diseases provide a related model for TD, including the development of cognitive impairments (see Koshino et al., 1986; Breggin, 1993, for similar discussions). They studied 54 patients who were diagnosed with mania or schizophrenia with TD and concluded that TD is one expression of a

larger "chronic neuroleptic-induced neurotoxic process" (Wade et al., 1987, p. 395).

Paulsen et al. (1994) reviewed the literature and found that "TD was generally reported to be associated with cognitive impairment." Krabbendam et al. (2000) found a particular correlation between orofacial TD and cognitive impairment, especially delayed memory that may be caused by a "frontal subcortical disturbance" related to orofacial TD. It is apparent that TD is not merely a motor disorder but afflicts a range of cognitive and emotional functions.

Palmer et al. (1999) focused on extrapyramidal symptoms (EPS) rather than TD and found that severity of EPS correlated with the severity of neuropsychological deficits, especially in the areas of learning and motor skills. Krausz et al. (1999) found a similar correlation between EPS and cognitive deficits on a self-rating scale. They believed the deficits were sufficient to cause potential difficulty with insight and everyday life skills.

Gualtieri and Barnhill (1988) pointed out, "In virtually every clinical survey that has addressed the question, it is found that TD patients, compared to non-TD patients, have more in the way of dementia" (p. 149). They believed that the dementia results from damage to the basal ganglia caused by the TD (see subsequent discussion).[3] Gualtieri (2002), one of the most experienced researchers in the field, has continued to make the point that TD patients have more "signs of dementia" (p. 401) than similar patients who do not have TD.

Since the rates of TD are so high (see chapter 4), affecting a large proportion of neuroleptic-treated patients, its association with cognitive dysfunction and dementia is especially ominous. These data by themselves provide sufficient evidence to conclude that neuroleptics frequently and irreversibly impair mental function. Once again there is ample reason to be cautious about prescribing these toxic agents to adults and to prohibit giving them to children and youth.

## A Serendipitous Finding of Neuroleptic-Induced Generalized Cognitive Dysfunction

A multisite national research project evaluated brain dysfunction caused by polydrug abuse, including street drugs (for a more detailed analysis, see Breggin, 1983b). Using the Halstead–Reitan Neuropsychological Battery, the study unexpectedly uncovered a significant correlation between generalized brain dysfunction and total lifetime psychiatric drug consumption in patients diagnosed with schizophrenia (Grant et al., 1978a&c). More than one-fourth of the neuroleptic-treated patients had persistent brain dysfunction. The chronic brain dysfunction was related more to

lifetime neuroleptic intake than to the diagnosis of schizophrenia: "Neuropsychological abnormality was associated with greater antipsychotic drug experience" (Grant et al., 1978c, p. 1069). Indeed, patients diagnosed with schizophrenia who abused street drugs rather than taking neuroleptics showed no correlation between the diagnosis of schizophrenia and increased brain dysfunction. None of the patients had been exposed to neuroleptics for more than 5 years.

In an unpublished version of the paper presented at a professional meeting (Grant et al., 1978a), the authors underscored the connection between TD and cognitive deficits and warned in their concluding sentence, "It is also clear that the antipsychotic drugs must continue to be scrutinized for the possibility that their extensive consumption might cause general cerebral dysfunction" (p. 31). The version published in the *Archives of General Psychiatry* (Grant et al., 1978c) warned of the possibility of long-term cognitive deficits associated with neuroleptic use, but in somewhat less threatening language. The danger of neuroleptic-induced chronic brain dysfunction was expurgated from the *American Journal of Psychiatry* version (Grant et al., 1978b). The misleading correlation with schizophrenia was highlighted. Prodrug editing made the risk disappear from the supposedly scientific article.

## Neuroleptic-Induced Mental and Behavioral Deterioration in Children

Reports by Gualtieri and his colleagues (Gualtieri, 2002; Gualtieri et al., 1988; Gualtieri et al., 1984; Gualtieri et al., 1986) indicated that many institutionalized children and young adults go through a persistent period of worsening psychiatric symptoms after withdrawal from neuroleptics, typically impairing them more than their original symptoms prior to treatment. This occurred in developmentally disabled patients in whom schizophrenia had not been diagnosed. The researchers attributed the withdrawal-emergent problems to a drug-induced dementing process. Some patients stabilized or improved if kept medication-free, but others seemed permanently worsened by the medications. They required increased medication to control their drug-induced symptoms.

## Denial of Symptoms in TD Patients As a Symptom of Cognitive Dysfunction

Clinical reports of denial or anosognosia among TD patients also confirm that they are suffering cognitive dysfunction and, in more severe cases, a dementing process. Anosognosia involves denial of impaired or

lost function following neurological injury (chapter 1). My experience coincides with that of Fisher (1989), who stated that anosognosia "may qualify as one of the general rules of cerebral dysfunction" (p. 128). Thus the presence of anosognosia in TD patients tends to confirm the existence of generalized cerebral dysfunction in these patients. Anosognosia, as described in chapter 1, is an aspect of the broader concept of intoxication anosognosia or medication spellbinding. The spellbinding effect of neuroleptics is caused by their direct toxic effects and also by the irreversible damage that they inflict upon the brain.

Multiple publications confirm that most TD patients do not complain about their symptoms and will even refuse to admit their existence when confronted with them (Alexopoulos, 1979; Breggin, 1983b, 1993; Chard et al., as cited in Myslobodsky, 1993; DeVeaugh-Geiss, 1979; Smith et al., 1979; Wojcik et al., 1980).

Patients with TD not only display indifference toward their symptoms, they sometimes confabulate about them. Smith et al. (1979) cited several studies showing that TD patients typically refuse to recognize their symptoms. They observed,

> We were so convinced that many patients were aware of their symptoms but unwilling to report them that toward the end of the project we started to ask patients at the completion of the examination if they noticed any abnormal movements in other patients. Several of the patients described the symptoms of tardive dyskinesia in other patients in great detail. Although it is conceivable that these patients might have been unaware of their own tongue or mouth movements, it is difficult to see how they could not have observed their own hand, feet, or leg movements.

DeVeaugh-Geiss (1979) confirmed denial of symptoms as well as lobotomy-like indifference in TD patients. Despite repeated inquiries,

> Seven of these [fifteen TD] patients consistently and repeatedly denied that they had abnormal or involuntary movements, despite the fact that most of them had symptoms that were severe enough to cause some difficulty with speech, ambulation, or coordination of ordinary motor movements such as those used in eating or dressing.

Wojcik et al. (1980) found that 44% of patients with TD denied awareness of their abnormal movements. Joyce Kobayashi (as cited in "Patient May Not Be Cognizant," 1982) described the lack of awareness or concern about their symptoms found in more than half the TD patients selected from four wards at the Bronx Veterans Administration Medical Center.

Myslobodsky et al. (1985) found that 88% of the TD patients "showed complete lack of concern or anosognosia with regard to their involuntary movement" (p. 156). The study also found other indications for cognitive deficits in these patients. Myslobodsky (1986) reported "emotional indifference or frank anosognosia of abnormal movements" in 95% of TD patients. He theorized that the most probable cause was "some form of cognitive decline associated with dementia disorder, probably owing to some neuroleptic-induced deficiency within the dopaminergic circuitry" (p. 4). In 1993, Myslobodsky pointed out that patients suffer from denial of TD even while they remain able to voice complaints about their other medical problems and symptoms. He postulated at that time that "TD patients lose the motor part of their 'road map of consciousness.'"

These studies of denial in TD patients strongly confirm the association between TD and cognitive dysfunction. As mentioned earlier, the cause is probably twofold: the spellbinding effect of the drugs themselves, when the patients are still taking them, and the persistent effect of the brain damage caused by the drugs.

## Permanent Lobotomy or Deactivation

Chapter 2 described and documented the primary lobotomizing or deactivating effect of the neuroleptics. The anosognosia or denial exhibited by so many TD cases probably reflects a permanent deactivation phenomenon as well as a more specific intoxication anosognosia (medication spellbinding).

Bleuler (1978) suggested that long-term exposure to neuroleptics can produce an irreversible frontal lobe syndrome with apathy and indifference. The syndrome would seem an inevitable consequence of the permanent dysfunction of dopaminergic neurons that frequently results from neuroleptic treatment. Some of these neurons (originating in the ventral tegmentum) project to the limbic system and frontal lobes. Others (from the substantia nigra) project to the striatum, where they also interconnect with the limbic system as well as with the reticular activating system (Alheid et al., 1990; see also Ethier et al., 2004; Seeman, 1995). Injury in any of these regions of the brain tends to lead to deactivation of the brain and mind (chapter 1).

## Tardive Psychosis in Neuroleptic-Treated Patients

Chapter 3 documented that the neuroleptics can produce acute depression and psychosis. This chapter has documented the existence of tardive dysmentia and tardive dementia as well as tardive behavioral abnormalities in children. There is further evidence that the neuroleptics can

also produce *irreversible,* schizophrenic-like psychoses, variously called *supersensitivity psychosis, tardive psychosis,* and *rebound psychosis.*

When Chouinard and Jones first announced their discovery of tardive or supersensitivity psychosis at the annual meeting of the Canadian Psychiatric Association (see Jancin, 1979), one psychiatrist in the audience protested,

> I put my patients on neuroleptic drugs because they're psychotic. Now you're saying that the same drug that controls their schizophrenia also causes a psychosis and that on top of that the drug causes tardive dyskinesia one third of the time. It's a Hobson's choice. My patients are going to lose in the end either way.

One of the panelists, Barry D. Jones, warned, "Some patients who seem to require lifelong neuroleptics may actually do so because of this therapy."

In the published version (Chouinard et al., 1980), the authors suggested that the irreversible supersensitivity psychosis results from rebound hyperactivity of the blockaded dopamine receptors in the limbic system. They compared the mechanism of supersensitivity psychosis to that of TD. Tardive psychosis may be a mental manifestation of the same processes that cause the motor phenomena of TD.

Chouinard and Jones (1980) noted that both the TD and the supersensitivity psychosis are masked, or hidden, when the patient is taking drugs. They further stated that continuous use of the drugs tends to worsen both diseases. Neuroleptic-treated patients have often developed tardive psychoses that became more severe than their original psychiatric disorders (Chouinard et al., 1980; Chouinard et al., 1982; Chouinard et al., 1978; Csernansky et al., 1982; Hunt et al., 1988; Mayerhoff et al., 1992; see also news reports by Jancin, 1979; "Supersensitivity Psychosis," 1983). Tragically, patients can require lifetime medication for a disorder that could have had a much shorter and more benign natural history.

Although Chouinard and Jones (1980) found a prevalence of 30% to 40%, Hunt et al. (1988) reviewed the charts of 265 patients and located only12 probable and no definite cases of tardive psychosis. Kirkpatrick et al. (1992) cast a critical eye on the existence of tardive psychosis. Research commonly fails to detect even the most obvious adverse drug effects, resulting in so many drugs reaching the market without their most serious side effects being detected. That so many researchers have documented tardive psychosis should, by now, confirm its existence.

## Psychiatry Avoids Facing Tardive Psychosis

Since my lengthy review of the subject in *Psychiatric Drugs: Hazards to the Brain* (1983b), and then in the 1997 edition of this book, the literature

on tardive psychosis has become sparser. After an initial burst of research in this arena, much like in research concerning cognitive disorders and dementia, there has been a slowing down of interest. Not surprisingly, the psychopharmaceutical complex discourages research that undermines its products.

The 2003 edition of *The American Psychiatric Publishing Textbook of Clinical Psychiatry* makes no mention of tardive psychosis or supersensitivity psychosis in the discussion of adverse neuroleptic effects, including in the section "Tardive Disorders" (Hales et al., 2003). Nor is there any discussion of the many studies on cognitive deficits associated with neuroleptics and in particular with TD. The only mention of tardive psychosis occurs within a discussion of mood disorders with citations to three studies spanning 1991–1993. The 1993 study points to a possible biological mechanism in the death of striatal cholinergic neurons, caused by prolonged exposure to neuroleptics (Miller et al., 1993).

It is as if the profession has found the concept intolerable—that taking so-called antipsychotic drugs for prolonged periods of time causes a persistent psychosis worse than the original disorder—so it has chosen to ignore it. It is similar to the resistance we will find to admitting that so-called antidepressants, even in the short run, cause depression and suicidality (chapters 6 and 7).

Nonetheless, some studies continue to crop up, and concerns continue to be expressed. Llorca et al. (2001) described a case of supersensitivity psychosis following abrupt olanzapine withdrawal. Lu et al. (2002) reported two cases of older patients who developed hallucinations and delusions following withdrawal from metoclopramide (Reglan).

Stanilla et al. (1997) described three cases of delirium with psychotic symptoms due to clozapine withdrawal (see also Adams et al., 1991, for an early report of clozapine withdrawal psychosis). They believed that clozapine produces more severe withdrawal symptoms than typical antipsychotic agents. In a 3-year open label study of quetiapine, Margolese et al. (2004) switched 23 male patients from classical antipsychotics and risperidone to quetiapine: "Six of the seven patients who relapsed after being stabilized on quetiapine for at least three months met the criteria for supersensitivity psychosis." This is a very high rate, again raising questions about whether atypicals may be more prone to cause tardive psychosis.

British psychiatrist Moncrieff (2006b) reviewed the literature and found especially strong evidence that clozapine causes withdrawal psychoses. She observed that some reported cases occurred in people without a psychiatric history and concluded, "These effects require further urgent research." In another article discussing why it is so difficult for patients to stop psychiatric medication, Moncrieff (2006a) warned, "The implications of these effects include the possibility that much of the research on

maintenance treatment is flawed and that the recurrent nature of psychiatric conditions may sometimes be iatrogenic." She noted studies indicating that 20% to 40% of people with severe psychotic disorders "can stop long-term treatment without difficulty" and urged consideration for the careful management of neuroleptic withdrawal.

### Tardive Akathisia and Cognitive Deficits

Gualtieri (1993) observed that the anxiety and emotional tension suffered by tardive akathisia patients are primary emotional and cognitive components of the disease. After reviewing the functional neuroanatomy, Gualtieri concluded,

> One is entitled to surmise, therefore, that affective instability and intellectual impairment may be the consequence of neuropathology at the level of the basal ganglia.... TDAK [tardive akathisia] is one manifestation of that effect. There are probably others.

In other words, the existence of the syndrome of tardive akathisia demonstrates that the neuroleptics can produce irreversible damage to the mental life of the individual.

## HUMAN AND ANIMAL AUTOPSY STUDIES

Animal autopsy data provide strong evidence that the neuroleptics frequently cause brain damage. Human autopsy studies are too few and contradictory to lead to a definite conclusion. Once again, interest in them has declined.

### Animal Autopsy Studies of Neuroleptic-Induced Brain Damage

Earlier in the chapter I summarized the findings of Dorph-Petersen et al. (2005) that clinical doses of haloperidol and olanzapine in monkeys produced marked shrinkage of the brain tissue with cell death through the brain, but most markedly in the frontal and parietal lobes. Multiple earlier controlled animal studies indicate that long-term, and sometimes short-term, neuroleptic treatment cause brain damage. Evidence of structural damage, including cell degeneration and death in the basal ganglia, is especially consistent after chronic administration of neuroleptics (Coln, 1975; Jeste et al., 1992; Mackiewicz et al., 1964; Nielsen et al., 1978; Pakkenberg et al., 1973; Popova, 1967; Romasenko et al., 1969;

reviewed in Breggin, 1983b). Far fewer studies have been negative (Fog et al., 1976; Gerlach, 1975).

After one "comparatively low" dose of chlorpromazine, 0.5–5 mg/kg, Popova (1967) found structural changes in rat brains, including "swelling, chromatolysis and vacuolization of the nerve cell bodies" (p. 87) in many regions, including the sensory-motor cortex, midbrain, hypothalamus, thalamus, and reticular formation. In 1992, Jeste et al. reviewed the literature and published the results of exposing rats to fluphenazine decanoate (5 mg/kg, intramuscular) every 2 weeks for 4, 8, or 12 months. The density of large neurons in the striatum was measured after sacrifice by a computerized image analysis system. This team found a reduced density by 8 months of treatment.

Most animal studies report irreversible neuronal damage, including cell death, after relatively brief exposure to neuroleptics. Of great importance, animal studies with longer durations of exposure to neuroleptics—1 year (Pakkenberg et al., 1973), 8 months (Jeste et al., 1992), and 36 weeks (Nielsen et al., 1978)—show the expected neuronal deterioration in the basal ganglia.

Animal research provides definitive and apparently incontrovertible evidence that neuroleptics often cause irreversible brain damage. This is consistent with more recent studies reviewed earlier in the chapter that demonstrate how both older and newer atypical neuroleptics are highly toxic to living cells in animals.

### Human Autopsy Evidence for Neuroleptic-Induced Brain Damage

There are surprisingly few human autopsy reports examining the effects of chronic neuroleptic therapy. Older studies have been reviewed by Bracha and Kleinman (1986), Brown et al. (1986), Jeste et al. (1986), and Rupniak et al. (1983). Although somewhat inconclusive, autopsy evidence does suggest that the neuroleptics can damage the basal ganglia, an area potentially critical in the production of both TD and tardive dementia. But the literature, overall, is scant, contradictory, and not conclusive. The studies of Arai et al. (1987), Brown et al. (1986), Christensen et al. (1970), Forrest et al. (1963), Gross and Kaltenback (1968), Hunter et al. (1968), Jellinger (1977), Roizin et al. (1959), and Wildi et al. (1967) are reviewed in more detail in Breggin (1990).

## LESSONS OF LETHARGIC ENCEPHALITIS[4]

Chapter 3 mentioned the similarity between neuroleptic malignant syndrome and an acute episode of the viral disorder, lethargic encephalitis

(encephalitis lethargica, or von Economo's disease). The parallel suggests that the neuroleptics, in their primary impact, produce a controlled chemical encephalitis, which, when out of control, becomes neuroleptic malignant syndrome, indistinguishable from a fulminating viral encephalitis (Breggin, 1993).

There are many other ways in which neuroleptic drug effects closely mimic those of lethargic encephalitis, as reported during and after World War I (Breggin, 1993). Both the neuroleptics and the viral disease produce mental apathy and indifference. In a 1970 retrospective, Deniker observed,

> It was found that neuroleptics could experimentally reproduce almost all symptoms of lethargic encephalitis. In fact, it would be possible to cause true encephalitis epidemics with the new drugs.

The parallel between lethargic encephalitis and neuroleptic toxicity is remarkable in several respects. Both groups of patients initially display apathy or disinterest, followed by the onset of various dyskinesias. After a delay, the dyskinesias sometimes become permanent in both groups. Many lethargic encephalitis patients seemed to recover, only to relapse into devastating neurological disorders years later. While a Parkinson-like disorder was the most common tardive, or delayed, motor disorder associated with lethargic encephalitis, other dyskinesias more similar to drug-induced TD were also known to develop.

After an apparent recovery, many of the encephalitis victims later went on to develop severe psychoses and dementia (Abrahamson, 1935; Matheson Commission, 1939). Thus the completion of the parallel between lethargic encephalitis and neuroleptic effects awaited the discovery that in addition to TD, tardive psychosis and tardive dementia could follow the exposure to neuroleptics.

The parallel between the medication effects and the viral encephalopathic effects sounded a warning that similar mechanisms—and hence similar adverse outcomes—were possible. Only a few years after the advent of the neuroleptics, Paulson (1959) raised this concern when he wrote,

> The sequelae of encephalitis include many muscular, psychic and autonomic responses; and most of the neurologic complications from the phenothiazines are within the range of post-encephalitic Parkinsonism. (p. 800)

Other investigators also noticed comparisons between neuroleptic toxicity and lethargic encephalitis (Brill, 1959; Hunter et al., 1964). Brill (1959) documented that the hardest hit areas in lethargic encephalitis

are the cells of the basal ganglia and the substantia nigra, the areas most affected by the neuroleptic medications in the production of TD (see Breggin, 1993, for a further discussion of the anatomic pathways). There are multiple interconnections between the basal ganglia, reticular activating system, limbic system, and cerebral cortex, involving both motor and mental functions (e.g., Adams et al., 1989; Alheid et al., 1990; Brodal, 1969). As a result of the interconnections, neuroleptic-induced damage to the basal ganglia, if severe enough, would be expected to produce persistent cognitive deficits and dementia.

The association of mental deterioration with diseases of the basal ganglia and substantia nigra led to the concept of subcortical dementia (Huber et al., 1985), that is, dementia arising from damage to the basal ganglia and surrounding structures. Patients with subcortical dementia tend to be more depressed and apathetic, without as much evidence of gross impairment to higher cortical functions. Subcortical damage to the basal ganglia is one of the brain-disabling mechanisms that make neuroleptic-treated patients more docile and less troublesome to others. Because higher cortical functions are less obviously damaged, observers can reassure themselves that the patients are not being grossly harmed, when in fact their overall energy level and quality of life are impaired by damage to subcortical functions.

Marsden (1976) observed, "If long-term neuroleptic therapy can cause an apparently permanent change in striatal dopamine-receptor action, then one must assume that the same can occur in the mesolimbic cortical dopamine receptors" (p. 1079), that is, the highest centers of the brain. Marsden and Obeso (1994) pointed out the complex interconnections between the basal ganglia and the frontal lobes and their possible role in higher mental functioning.

Animal research confirmed that supersensitivity of dopamine receptors develops in the mesolimbic and cerebral cortical areas, much as it does in the striatum (Chiodo et al., 1983; White et al., 1983), and that it can become chronic after termination of neuroleptic treatment (Jenner et al., 1983; Rupniak et al., 1983). While TD is difficult to reproduce in animals, Gunne and Haggstrom (1985) were able to create both acute and irreversible dyskinesias in monkeys and rats. With persistent dyskinesias, they found evidence of irreversible biochemical changes in the basal ganglia and related areas (substantia nigra, medial globus pallidus, and nucleus subthalamicus).

Many researchers remarked on the relationship between neuroleptic-induced inhibition in the mesolimbic and cortical dopamine system and the clinical production of blunting or apathy (Lehman, 1975; White et al., 1983). Irreversible changes to these biological systems account for many findings of permanent cognitive dysfunction.

Gualtieri and Barnhill (1988) confirmed these observations:

> Persistent TD is probably the consequence of irreversible striatal damage. But the corpus striatum is responsible for more than motor control; it is a complex organ that influences a wide range of complex human behaviors. No disease that afflicts striatal tissue is known to have only motor consequences; Parkinson's disease and Huntington's disease are only two examples. (p. 150)

It is tragic that psychiatry persists in promoting the antipsychotic or neuroleptic drugs as specific treatments for "psychosis," "schizophrenia," and "mania," when in fact the drugs cause severe brain damage and dysfunction, effectively disabling the brain and mind, rendering individuals more docile as well as relatively indifferent to their own needs or suffering. The use of the neuroleptics is, to a great extent, a convenience for physicians and caretakers at the expense of the patients' well-being.

## CAN SCHIZOPHRENIA CAUSE DEMENTIA?

There is a very cogent reason to believe that the atrophy found on CT scans cannot be the product of schizophrenia. Brain atrophy is far more accurately and definitively evaluated by a direct postmortem pathological examination than on a CT or MRI brain scan. The actual pathology, if it exists, can more easily be identified and accurately measured by direct observation and microscopic analyses.

The CT scan and the MRI scan capture images in the range of the human eye. The MRI scan, for example, examines a slice of brain approximately 1–3 mm thick (Innis et al., 1995). That is the width of one to three pencil leads. Furthermore, the images are limited to black and white. The best MRI resolution only begins to approximate what can be seen with the naked eye on autopsy (Innis et al., 1995).

An autopsy can also obtain tissue slices for examination with a light microscope or an electron microscope. Furthermore, on gross examination of the brain, instead of estimating tissue loss from MRI pictures, an autopsy can actually weigh and measure the brain and examine cell density under the microscope. As a result, many diseases of the brain, such as Alzheimer's, require an autopsy rather than an MRI or CT scan to make the definitive diagnosis (Caine et al., 1995).

Despite the infinitely greater sensitivity, usefulness, and relevance of autopsy examinations and microscopic pathology studies, no consistent finding of brain atrophy or any other pathology has been made despite hundreds of these studies performed on thousands of patients diagnosed

with schizophrenia prior to the use of neuroleptics (e.g., Bleuler, 1978; Nicholi, 1978; Noyes et al., 1958). Arieti (1959) concluded that hopes for finding a neuropathology of schizophrenia "have remained unfulfilled" (p. 488). Weinberger and Kleinman (1986) estimated that by 1950, more than 250 studies had claimed to find a gross pathological defect in schizophrenia, and "the overwhelming majority of these claims were either never replicated, unreplicable, or shown to be artifacts." The task proved so frustrating that "the effort stalled in the 1950s" (p. 52). When the Task Force on Tardive Dyskinesia (American Psychiatric Association, 1980b) made a brief reference to the initial CT scan findings of brain atrophy in neuroleptic-treated patients, it remarked, "This observation is quite surprising as it is not consistent with earlier neurologic evaluations of chronic schizophrenics; it requires further critical evaluation" (p. 59).

Furthermore, prior to the neuroleptics, there was no consistent dementia syndrome that could be clinically identified in association with so-called schizophrenia. In other words, until the advent of neuroleptic treatment, clinical examination of patients labeled schizophrenic had always failed to reveal anything that looks like a brain disease such as Alzheimer's or Huntington's chorea. That is why schizophrenia became known as a functional, rather than an organic, disorder and why a diagnosis of schizophrenia in fact requires first ruling out an underlying organic disorder. Schizophrenia is a diagnosis of exclusion—meaning that real diseases have been ruled out before making the diagnosis.

Meanwhile, as this chapter and earlier chapters document, the neuroleptics have indeed produced identifiable physical or organic disorders in patients labeled schizophrenic. Ironically, psychiatry has created what it always sought to find—something wrong with the brains of people diagnosed with schizophrenia. Having found it, psychiatry tends to deny the reality or to claim, once again, that the problem must emanate from the patients' preexisting schizophrenia. This claim is made despite a mountain of evidence proving that these same drugs are also toxic to the brains of animals.

In reply to the question, Do patients diagnosed with schizophrenia have cerebral atrophy, dilated ventricles, neurological deficits, or dementia? Lidz (1981) observed, "For 100 years investigators have reported a neuropathological or physiopathological cause of schizophrenia. The trouble is that no such findings have been replicated. If the patient suffers from dementia, the diagnosis is not schizophrenia" (p. 854). Lidz recommended taking into account the impact of medications and shock treatment on the brain.

In summary, the failure to obtain consistent findings of cerebral pathology on postmortem examination prior to the drug era strongly indicates that more recent findings of atrophy on brain scans are the result

not of so-called schizophrenia but of some new threat to the brains of these patients. The new threat is the widespread use of the neuroleptic drugs that are already known to cause brain diseases, including TD, neuroleptic malignant syndrome, and tardive dementia.

Other reasons to doubt that patients with schizophrenia have a deteriorating brain disorder were reviewed years ago by Manfred Bleuler (1978). First, unless caused by a toxic agent, which is then removed, organic disorders characterized by brain atrophy and dementia are usually progressive. Yet it is well documented by Bleuler and others that many patients diagnosed with schizophrenia improve over time; up to one-third or one-half show significant recovery over the years. They do not tend to show the physical signs of deterioration usually associated with progressive neurological losses, such as premature aging, infirmity, seizures, or neurological signs and symptoms. They die of the same diseases that afflict normal people. In following 208 patients for decades, Bleuler found that most of them remained in generally good health, "in spite of advanced age" (p. 450). Nowadays, of course, the widespread use of neuroleptics results in anything but "generally good health" for those unfortunate enough to experience months and years of exposure to these toxic agents.

Second, a dementing disorder, once it has progressed, would rarely, if ever, clear up spontaneously. Yet there are many examples, even before the advent of medications, of patients abruptly and spontaneously improving for years at a time or for a lifetime. In addition, many patients wax and wane, showing great clarity at one moment and extreme irrationality at another (see Bleuler, 1924; Bleuler, 1978). These older observations are entirely consistent with my own clinical experience. Without using drugs, I am often able to help patients recover from hallucinations, delusions, and other symptoms that would have earned them a diagnosis of schizophrenia and a lifetime of drug treatment from most psychiatrists. Nor am I alone in finding that this supposed biological disorder can often be reversed by psychosocial interventions (chapter 16).

As another confirmation that these patients do not suffer from an irreversible physical disorder of the brain, sometimes an emergency will temporarily arouse a seemingly chronic and incapacitated patient into a state of acute awareness and rational behavior. As a resident, I was the admitting doctor for a patient diagnosed paranoid schizophrenic. She refused to let me perform a routine physical examination as a part of her admission to the psychiatric ward, until I noticed from her breathing that she had signs of pneumonia. When I told her, in effect, "You're really sick; I need to examine you," she stopped behaving irrationally and allowed me to listen to her lungs, confirming my suspicion of pneumonia. When the exam was over, she reverted to her previous nearly catatonic behavior.

Third, patients diagnosed with schizophrenia do not suffer from the typical signs of the earlier stages of a dementing disorder such as short-term memory dysfunction. They are usually easy to distinguish, for example, from victims of Alzheimer's disease, multi-infarct dementia, and the dementias associated with Parkinson's disease, Huntington's chorea, or multiple sclerosis.

Fourth, instead of deteriorating, the intellectual functions in patients diagnosed with schizophrenia become misdirected or psychologically irrational. As I describe in *Toxic Psychiatry*, patients diagnosed with schizophrenia often speak in unusual and complex metaphors dealing with psychological and spiritual conflicts over the meaning of love, life, or God. Often they display enormous passion around the concept of their own presumed evil or exalted nature. Quite frequently, only one or two specific false ideas (delusions) will appear in an otherwise normal mental life. These delusions will be defended with intellectual vigor and a high degree of mental acuity, indicating that overall brain function itself is normal and often above average. Unless there has been exposure to neuroleptics, the patient diagnosed with schizophrenia will have an unimpaired IQ and no signs of neuropsychological deficits. For this reason, neuropsychological testing aimed at discovering organic brain deficits are of no use in diagnosing so-called schizophrenia, except to rule out other "real" diseases such as dementia.

In summary, there is little or no reason to believe that findings of brain atrophy and dementia are caused by so-called schizophrenia, while there is overwhelming evidence to indict neuroleptic therapy.

Meanwhile, the question "What is schizophrenia?" remains complicated and largely unanswered. In contrast to the biological theories now in vogue, many researchers have found that diagnosis holds little or no scientific validity, while others believe it reflects profound psychological disturbances reaching back into early childhood. This is not the place to discuss this question in any depth. However we view the diagnosis of schizophrenia, people given the label deserve to be protected from neuroleptics, a class of drugs that would probably be taken off the market if they weren't aimed at defenseless, stigmatized mental patients.

## PSYCHIATRIC DENIAL OF NEUROLEPTIC-INDUCED DEMENTIA

It took psychiatry 20 years to recognize TD as an iatrogenic illness, even as it afflicted half or more of hospitalized patients (Gelman, 1984). As noted in chapter 4, resistance to dealing adequately with TD continues (Breggin, 1983b; Brown et al., 1986; Cohen et al., 1990; Wolf et al., 1987). An even greater reluctance to recognize tardive dementia and brain

atrophy was to be anticipated since the damage is still more catastrophic. Furthermore, it is easier to overlook cognitive deficits and dementia than to ignore dyskinesias, and easier as well to mistakenly attribute the mental symptoms to the patient's psychiatric disorder.

## DRUGS TO TREAT ACUTE EXTRAPYRAMIDAL SIDE EFFECTS

A variety of drugs are used to control neuroleptic-induced acute extrapyramidal effects such as tremors, rigidity, akathisia, and dystonia. Most of these agents suppress the cholinergic nervous system. They include benztropine (Cogentin), biperiden (Akineton), procyclidine (Kemadrin), and trihexyphenidyl (Artane). These agents produce multiple anticholinergic side effects, including glaucoma, severe constipation, ileus, and the inability to empty the bladder. Since many of the neuroleptics also produce anticholinergic effects, the likelihood of these adverse reactions is increased when they are combined.

From the brain-disabling viewpoint, anticholinergic drugs can cause confusion, organic brain syndromes, and psychoses. Far too little attention has been paid to their adverse effects on memory and learning, which can interfere with everyday living, rehabilitation, or school (Marcus et al., 1988; McEvoy, 1987). Furthermore, there is concern that the use of these drugs increases the risk of TD (APA, 1992).

## WITHDRAWAL PROBLEMS AND INFORMED CONSENT

As described in chapter 4, the difficulties associated with neuroleptic withdrawal have led me to raise the issue of their potential to cause dependence (Breggin, 1989a, 1989b). Meanwhile, clinicians have become increasingly aware of the difficulty of removing patients from neuroleptics, partly because of tardive psychosis. Withdrawal from the drugs can also produce transient or persistent dyskinesias, dysphoria, and autonomic imbalances, resulting in nausea and weight loss. In addition, underlying cognitive deficits become more apparent to the patient and other observers as the neuroleptic fog is lifted. As previously described, neuroleptics possessing marked anticholinergic effects can cause a severe flulike syndrome.

Since neuroleptics are extremely spellbinding, during or more likely after withdrawal the individual will have to face a variety of persistent or permanent adverse drug effects that went unnoticed during months and years under the influence of the drugs. Many former psychiatric patients feel betrayed by the doctors who inflicted these drugs on them,

sometimes against their expressed will, and almost always without fully informing them about the risks. Am I going too far in suggesting that patients and their families are almost never fully informed by prescribing physicians about the risks associated with neuroleptics? I don't believe that I am exaggerating. Years of experience reviewing the medical records and treatment histories of other doctors, as well as their sworn depositions in legal cases, have confirmed the common sense conclusion that prescribing physicians cannot fully inform patients about the risks associated with neuroleptics because no one except the most self-destructive patient would knowingly take such toxic drugs. Doctors have to hide the mountain of risks associated with these drugs in order to get their patients to take them. In this sense, informed consent is largely a sham in regard to antipsychotic drug administration.

Chapter 15 describes how to withdraw from psychiatric drugs.

## CONCLUSION

The neuroleptic drugs, including the newer atypicals, are highly toxic to brain cells. They cause cell death and tissue shrinkage *throughout* the brain and especially impair dopamine neurons in the basal ganglia. As a result, they produce a variety of potentially irreversible motor abnormalities in the form of TD, tardive dystonia, tardive akathisia, tardive dementia, and tardive psychosis, as well as the potentially lethal neuroleptic malignant syndrome. They frequently cause a parkinsonian syndrome with retardation of both mental and motor processes. Long-term treatment frequently produces irreversible mental dysfunction in the form of cognitive deficits, dementia, a worsening mental condition, and psychosis.

The most consistent information on the prevalence of marked or obvious brain damage has been generated by animal studies that demonstrate the mechanisms of toxicity within the cells as well as cell death and brain shrinkage. The animal research findings are confirmed in humans by brain scans measuring brain atrophy. We can estimate a prevalence of 10% to 40% among neuroleptic-treated patients. It probably exceeds 50% in older patients and after more intense, long-term treatment. Not surprisingly, these figures are somewhat parallel to those for TD, which strikes the same anatomical region of the brain, and can be found in 40% to 50% or more of relatively young long-term neuroleptic-treated patients.

In addition, numerous life-threatening adverse reactions have come to the forefront with the newer atypicals, such as hypertension; cardiovascular disease, including stroke in the elderly; obesity; elevated serum cholesterol; elevated blood sugar; diabetes; and pancreatitis. Finally, there is compelling new evidence linking neuroleptic use to premature death.

As described in earlier chapters, the "antipsychotic" effect of neuroleptics such as Haldol, Zyprexa, Risperdal, Seroquel, Abilify, and Geodon is mythical. All of the neuroleptics, including the so-called atypicals or second-generation drugs, produce a lobotomy-like disability of the brain, reducing the individual's emotional responsiveness and willpower, and causing apathy and indifference (chapter 2). Consistent with the brain-disabling principles of biopsychiatric treatment described in chapter 1, these effects render the patient more manageable, less troublesome to others, and less aware or able to respond to his or her own needs and suffering. The supposed treatment in reality entails the infliction of a toxic disease process upon the patient remarkably similar to the viral disorder called lethargic encephalitis that afflicts the same regions of the brain and also caused apathy and indifference, as well as EPS.

All of the neuroleptics are profoundly medication spellbinding (chapter 1), rendering the user unable to perceive the damage being done to his or her brain, mind, and body. Because of this, the neuroleptics readily lend themselves to the creation of iatrogenic denial and helplessness, in which the doctor uses drug-induced brain damage and dysfunction to produce a more docile, less troublesome patient.

Since the mid-1950s, neuroleptic drugs have been prescribed to hundreds of millions of patients worldwide, producing an epidemic of iatrogenic brain damage, a broad spectrum of diseases, and an increased death rate among its victims. As suggested at the conclusion of chapter 4, an ethical and scientific psychiatry would devote itself to ending the use of these highly toxic agents. Instead, organized psychiatry and the pharmaceutical companies, supported by the FDA, continue to push successfully for an expanded use of these drugs, even in the treatment of children and youth.

## NOTES

1. Euphoria as well as apathy can result from frontal lobe damage and dysfunction (Bradley et al., 1991).
2. What is really needed is the kind of research that demonstrated subtle yet devastating psychological changes after lobotomy (Tow, 1955) and newer forms of psychosurgery (Hansen et al., 1982), including varying degrees of the following: inability to spontaneously generate or to write autobiographical observations; impaired insight, judgment, and self-reflection; reduced creativity, fantasy life, and imagination; loss of autonomy and self-determination with a corresponding need for increased direction and supervision in tasks; reduced abstract reasoning and increased concrete thinking; shallow affect; social insensitivity and lack of empathy; the inability to care and to love; and overall apathy and indifference. In clinically effective doses, neuroleptics produce some degree of all of these effects almost immediately. Doses sufficient to "control" psychosis or mania cause all of these lobotomy-like effects to a significant degree. To a lesser

degree, all psychiatric drugs tend to produce some or all of these effects, particularly in long-term use and especially apathy and indifference. However, medication prescribers and advocates almost never notice, record, or evaluate these effects.

3. Gualtieri and Barnhill (1988) declared that "neuroleptic treatment is considered by enlightened practitioners in the field to be an extraordinary intervention" (p. 137) requiring serious justification.
4. This subject fascinated me sufficiently for me to devote an entire article to it (Breggin, 1993).

CHAPTER 6

# Recent Developments in Antidepressant Label Changes

> Depression is a highly prevalent disorder that affects 1 in 5 women and 1 in 10 men at some time in their lives. At any point in time, 5% to 10% of adults are clinically depressed, and another 10% to 15% experience subclinical levels or milder forms of depression.

Statements like the above, this one from Johnson and Flake (2007), are frequent in the mental health field, and generally, they are taken at face value. No one asks, "Is depression different from unhappiness, because I know a lot of people, maybe most, have unhappy times in their lives?" Or if the question is asked, it will be answered with a reference to the criteria in the official diagnostic manual (American Psychiatric Association, 2000), as if fulfilling a checklist of items somehow elevates a person from the realm of human unhappiness to major depressive disorder. Few stop to realize that figures like these are concocted and generally promoted in the interest of empowering mental health professionals. And even if the particular professionals are not pushing drugs, and Johnson and Flake are not, the figures were originally generated to promote the market for psychiatric drugs. In an effort to enlarge the market, the concept of *subclinical depression* was invented to justify prescribing antidepressants to people who do not meet the standard criteria for major depressive disorder.

The market has become huge. In the United States in 2001, an estimated 24.5 million patient visits were made for depression, with 69% of these visits resulting in prescriptions for SSRIs (Fergusson et al., 2005; Stafford et al., 2001). In 2002, about 6% of all boys were taking antidepressants, and the number has continued to grow. By 2004, an estimated 1 in 10 women was taking one of the newer antidepressants (Vedantam, 2004).

The antidepressants generate gigantic revenues for the drug companies. In 2006, according to IMS Health (2007), antidepressants were the most prescribed among all classes of drugs, with a total of 227.3 million prescriptions in the United States. They were third in revenue, with a total of $13.5 billion. To give perspective to these figures, the widely prescribed lipid regulators like Lipitor were second as a class, with 203.0 million prescriptions, and first in revenue, at $21.6 billion.

Antidepressants have, however, been taking something of a licking from the Food and Drug Administration (FDA) and the media in the last few years, culminating in 2004–2005 with a black-box warning about antidepressant-induced suicidality in children and then in 2007 by another black-box warning about increased suicidality in young adults. But in reality, there was little impact on the prescription of these drugs. U.S. sales of antidepressants declined 1.4% in 2004 and 6% in 2005, followed by a 2% recovery in 2006, with industry determining that the black-box warnings were ultimately "unlikely to significantly threaten sales" (McManus, 2007). And as already mentioned, they are still number one when it comes to sales.

## WARNING SIGNS FROM THE BEGINNING

Soon after the introduction of the first SSRI, fluoxetine (Prozac), into the United States marketplace in January 1988, published reports began describing fluoxetine-induced violence against self and others.

In 1990, Teicher et al. published their classic article "Emergence of Intense Suicidal Preoccupations During Fluoxetine Treatment" in the *American Journal of Psychiatry,* describing five patients who developed akathisia and became obsessively suicidal on Prozac, who felt relief when the medication was stopped, and then a resumption of their agitation when it was resumed. In May 1990, the FDA required the manufacturer of Prozac, Eli Lilly and Company, to add *suicidal ideation* and *violent behaviors* to the Postintroduction Reports section of its label. The section that listed violence and suicide as possible adverse drug reactions began with a caveat that the reported reactions "may have no causal relationship with the drug."

On August 11, 1990, an editorial in *The Lancet* (5-HT Blockers, 1990) included "the promotion of suicidal thoughts and behaviour" (p. 346) among the adverse effects of fluoxetine. The journal was ahead of its time in its cautions:

> Fluoxetine represents US know-how at its best and has been aired in the media at a time when biological psychiatry has become supreme in North America. However, we do not know whether the drug is better than earlier antidepressants, whether 5-HT is the main neurotransmitter in depression, and whether the 5-HT uptake blockers have acceptable side effects.

The following year, the *British National Formulary,* a joint publication of the British Medical Association and Royal Pharmaceutical Society of Great Britain (1991), listed suicidal ideation and violent behavior as fluoxetine side effects. Also in 1991, I published *Toxic Psychiatry,* in which I observed for the first time that Prozac was producing a continuum of overstimulation that included akathisia, agitation, anxiety, insomnia, depression and mania, and, in the extreme, suicide and violence. I drew on previously sequestered FDA premarketing data on Prozac, the scientific literature, and my own clinical and forensic cases.

Subsequently, many books and reports have dealt with the subject of SSRI-induced violence and suicide (e.g., Breggin, 1992b, 1997, 2001a; Breggin et al., 1994a; Glenmullen, 2000; Healy, 2000; Teicher et al., 1993).

Chapter 7 will present an extensive review and analysis of the literature on antidepressant-induced mental and behavior abnormalities. This chapter will look at the evolution and importance of current changes in antidepressant labels.

## THE CLASS OF SSRIs

These selective serotonin reuptake inhibitors (SSRIs) include fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), and, most recently, escitalopram (Lexapro; see the appendix). These drugs block the removal of the neurotransmitter serotonin from the synaptic cleft. A number of other antidepressants are potent nonselective serotonin reuptake inhibitors (NSRIs). These include the atypical venlafaxine (Effexor) and the tricyclic clomipramine (Anafranil). Nefazodone (Serzone) has been withdrawn from the market due to liver damage.

When observations are made in clinical practice and in the scientific literature concerning the impact of SSRIs, they are typically treated as a single category or class of pharmacological agents. It is generally recognized that an adverse mental or behavioral reaction, such as agitation or mania, that is observed in regard to one SSRI is likely to be found with all the other SSRIs. When I initially testified about this reality in deposition and trial as a medical expert, drug company lawyers and experts criticized my position, claiming that I could not use data about one SSRI to draw conclusions about other SSRIs. Then, in 2004–2007, the FDA began issuing required class warnings on adverse psychiatric reactions such as suicidality, hostility, irritability, and mania that are identical for the entire class of SSRIs.

While usually examined as separate classes of antidepressants, the NSRIs like Effexor also share many characteristics with the SSRIs, including the capacity to induce stimulation, anxiety, agitation, and mania.

## FDA FINDS INCREASED SUICIDALITY IN CHILDREN EXPOSED TO ANTIDEPRESSANTS

On February 2, 2004, the FDA held an open meeting of the joint Psychopharmacological Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee to hear public testimony and explore the risk of suicidality associated with antidepressants in children. During September 13–14, 2004, the FDA met again to present a reevaluation of data on 4,582 pediatric patients from 24 antidepressant controlled clinical trials of 4–16 weeks in duration. With one exception, the studies were drawn from 23 industry-sponsored trials. The exception was one National Institute of Mental Health (NIMH) study, the Treatment for Adolescents With Depression Study (TADS), a 12-week trial involving 439 children age 12–17, comparing Prozac alone, cognitive therapy alone, combined therapy, and placebo (March et al., 2004). Thus industry-sponsored studies dominated the data.

Despite the handicap that the studies were largely developed and conducted with the aim of proving the value of industry products, a meta-analysis of the combined data indicated that antidepressants in children and youth increase the suicide attempt rate and that an estimated 1% to 3% of patients would be at risk of antidepressant-induced suicidality (Hammad et al., 2006). On October 15, 2004, the FDA mandated a black-box warning, and in early 2005, it was finalized (FDA, 2005a). According to FDA requirements for describing adverse drug reactions, a risk of 1% or more is considered common.

## EASY TO SHOW SERIOUS ADVERSE EFFECTS; DIFFICULT TO SHOW EFFICACY

We will find that the psychiatric establishment continues to minimize the FDA findings. Even the FDA recently described the finding as "modest" (see subsequent discussion). Thomas Insel, director of NIMH, weighed in on the side of drugs, describing them as "medications of known benefit and of questionable risks" (Vedantam, 2005), when the scientific research actually shows them to be medications of no benefit and grave risk.

The *New England Journal of Medicine* asked one of the panel members of the FDA Psychopharmacological Drug Advisory Committee, physician and epidemiologist Thomas B. Newman (2004), to comment on the results of the studies conducted in the controlled clinical trials to determine the risk of suicidality. He wrote,

> The results were striking. When all the pediatric trials were pooled, the rate of definite or possible suicidality among children assigned to receive antidepressants was twice that in the placebo group. (The summary risk ratio was 2.19; 95 percent confidence interval.) Although the FDA staff did not provide this information to the committee, according to my own calculations, such a dramatic result could be expected to occur by chance only 1 time in 20,000 ($p$ = 0.00005).... The fact that an association emerged from a meta-analysis with a P value of 0.00005, for an outcome that the sponsors of the trials were not looking for, and presumably did not wish to find, was quite convincing.

Notice that the FDA itself failed to provide the $p$ value that made the result so stunning! The panel member had to calculate it for himself.

Newman (2004) also made the point that the FDA found that only 3 of the 15 available controlled clinical trials showed efficacy for antidepressants in treating depressed children. He said that several FDA committee members spoke in favor of the antidepressants, citing either their own experience or the TADS conducted by NIMH; "however, others and I found the evidence of efficacy much less convincing than the evidence of harm." According to Newman,

> In reviewing TADS we were struck by the small size of the difference between fluoxetine and placebo as compared with the effect of placebo alone.... It is easy to see why the personal experience of clinicians and patients would lead them to believe the drug to be effective, since they would have no way of knowing that more than 85% of the benefit they observed would have also occurred with placebo.
>
> Randomized trials other than TADS have had less favorable results. The FDA indicated that only 3 of 15 trials of antidepressant use in

> children with depression had found a statistically significant benefit. The agency also provided us with a meta-analysis that showed that the estimated efficacy of antidepressants in children was minimal and likely to have been overestimated, because published studies have much more favorable results than unpublished studies. Thus, both clinical experience and published trials are likely to lead to inflated estimates of the efficacy of these drugs.

The critique provided by the FDA was by Whittington et al. (2004), described in chapter 7.

Newman (2004) also found many unanswered questions: "The FDA's meta-analysis suggested that the new antidepressants double the risk of suicidality, about 2.5 percent to 5 percent, in trials lasting two or three months. But what happens if you take them for a year?"

Epidemiologist Newman's (2004) comments summarize the essential problem of psychiatric drugs in general: easy to show their serious adverse effects; difficult to show their effectiveness.

## RECENT FDA ADMISSIONS AND WARNINGS

Thus, in 2004, the FDA began to catch up with observations I had begun making in 1991 in *Toxic Psychiatry* and more elaborately documented in the 1997 edition of this book, concerning the risks of antidepressant-induced suicide, at least in children, and later, the FDA would also affirm the risk in adults, at least young ones. However, in some ways more important, and almost entirely ignored in the press and the medical community, the FDA also confirmed my major critique of the newer antidepressants: that they produce a stimulant-like syndrome or activation that causes a whole array of disorders, from agitation, anger, and hostility to outright mania.

Following public hearings in early 2004, the FDA issued a press release for a Public Health Advisory in regard to children and adults, in which it stated, "The agency is also advising that these patients be observed for certain behaviors that are *known* to be associated with these drugs, such as, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restlessness), hypomania, and mania."

The FDA's description and its final label changes closely parallel what I had been saying for more than a decade and mimicked language from my 2003 report "Suicide, Violence and Mania Caused by Selective Serotonin Reuptake Inhibitors," in which I concluded, "Mania with psychosis is the extreme end of a stimulant continuum that often begins with lesser degrees of insomnia, nervousness, anxiety, hyperactivity and irritability and then progresses toward more severe agitation, aggression, and

varying degrees of mania." In that report, I also discussed akathisia and described the antidepressant-induced stimulant syndrome, including "hypomania/mania, insomnia, nervousness, anxiety, agitation, central nervous system stimulation, emotional lability . . . as well as paranoid reaction, psychosis, hostility, and euphoria."

## The Final Class Label on Suicidality in Children and Adolescents

The FDA published its final version of the class label for all antidepressants on January 26, 2005. The FDA applied the new label changes to all 34 antidepressants on the market, including older, more sedating antidepressants such as amoxapine (Asendin), trazodone (Desyrel), amitriptyline (Elavil), doxepin (Sinequan), and imipramine (Tofranil). The last-minute inclusion of the older antidepressant was an act of deference to the manufacturers of the newer antidepressants, in effect tarring all antidepressants with a brush meant only for the newer ones.

However, the agency's conclusions were based on a limited number of new antidepressants, including bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram, and venlafaxine, according to an FDA Talk Paper (2004a). These were the drugs most often cited by the public at the two FDA hearings.

Although the labels are currently being updated by the FDA to include a warning about antidepressant-induced suicidality in young adults, every antidepressant label until recently had a black-box warning at the top titled "Suicidality in Children and Adolescents" that begins with the following statement:

> Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

This statement was already a compromise between the FDA's original proposal and drug company feedback. The FDA's original, stronger draft read, "A causal role for antidepressants in inducing suicidality has been established in pediatric patients" (Lenzer, 2005). The draft statement went beyond the clinical trials themselves to say that suicidality had been established in general. It also used the dread phrase *causal role*. In every case in which I have testified against the drug companies in deposition, the defendant companies have tried to dismiss any scientific conclusions about drugs inducing suicidality, unless the conclusion used the term *causal*. In reality, scientific articles and FDA-approved labels rarely use the concept of causation, giving much relief to the drug

companies, who can then claim, however falsely, that causality has not been established.

Meanwhile, referring to the decision made by the FDA Psychopharmacological Drugs Advisory Committee, even staunch advocates of antidepressants have to admit that "the committee concluded that a causal link exists between antidepressant treatment and pediatric suicidality and advised that policies be implemented" (Pfeffer, 2007).

## The Stimulant Syndrome

Beneath the black box, a headline reads "WARNINGS—Clinical Worsening and Suicide Risk." Without identifying it as such, this section contains a warning about the stimulant or activation syndrome that I first described in *Toxic Psychiatry* in 1991:

> The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric.

Note the specific references to "irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania," *a virtual prescription for violence*. This new addition to the label, the implications of which having been largely overlooked, refers to children and adults. By indicating that nonpsychiatric patients can develop these reactions, the FDA class label challenges the commonly held belief that only patients with a bipolar history or vulnerability are at risk for developing antidepressant overstimulation.

The new label addresses information that should be given to patients and their caregivers who take the newer antidepressants:

> Clinical Worsening and Suicide Risk: Patients, their families and caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, and other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional,

especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Most of the symptoms described in my previous publications and by the FDA in its new label are the result of activation or stimulation, a syndrome similar to that caused by stimulants such as amphetamine, methamphetamine, and methylphenidate, especially in high doses. Compared to antidepressant-induced suicidality, activation is bolstered by a much larger scientific literature and poses a far more common, and often disastrous, level of risk (see subsequent discussion).

Activation should be at the top of the differential diagnosis list when a patient's condition deteriorates while taking antidepressants. If the physician misidentifies drug-induced activation as caused by the patient's original psychiatric disorder, the doctor is likely to continue, or even increase, the antidepressant dose, ultimately causing mania and psychosis.

## The New FDA Medication Guide

Simultaneously with the new warnings, the FDA required physicians to provide the families of children receiving antidepressants with a sheet of information titled "Medication Guide: About Using Antidepressants in Children and Teenagers" (Food and Drug Administration, 2005e). The label is currently being updated by the FDA to include young adults but otherwise remains largely unchanged.

In a section titled "You Should Watch for Certain Signs If Your Child Is Taking an Antidepressant," the information sheet states, "Contact your child's healthcare provider *right away* if your child exhibits any of the following signs for the first time, or if they seem worse, worry you, your children, or your child's teacher." It lists the following danger signs:

Thoughts about suicide or dying
Attempts to commit suicide
New or worse depression
New or worse anxiety
Feeling very agitated or restless
Panic attacks
Difficulty sleeping (insomnia)
New or worse irritability
Acting aggressive, being angry, or violent
Acting on dangerous impulses
An extreme increase in activity and talking
Other unusual changes in behavior or mood

Except for suicidality, the medication guide does not specifically state that there is a causal link between this list of reactions and the medications but clearly implies that these reactions are associated with taking medication. Each symptom is consistent with the activation or stimulation syndrome. The inclusion of *anger, aggression,* and *violence* shows the FDA's well-justified concern about antidepressants posing a serious danger to others.

## The FDA's Final Word on Antidepressant-Induced Suicidality in Children

In March 2006, Hammad et al. from the FDA Division of Neuropharmacological Drug Products Center for Drug Evaluation and Research published a summary of the agency's methods and findings. Their conclusion minimized the importance of their findings: "Use of antidepressant drugs in pediatric patients is associated with a modestly increased risk of suicidality."

Compare this conclusion of a "modestly increased risk of suicidality" to the previously mentioned observations of the epidemiologist on the FDA's Psychopharmacological Drugs Advisory Committee, Thomas Newman (2004), who said, "The results were striking.... The fact that an association emerged from a meta-analysis with a P value of 0.00005, for an outcome that the sponsors of the trials were not looking for, and presumably did not wish to find, was quite convincing."

In reality, since the short-term, company-run clinical trials were wholly unsuited to detecting suicidality, the risk had to be much more than "modest" to show up at all. In addition, Hammad et al. (2006) admitted to a fact that I had been insisting on for years in publications and testimony: that the drug company's premier measure of suicidality, the Hamilton Depression (Ham-D) Scale, is useless in that regard. The investigator asks the subject questions from the scale, only one of which is related to suicidality. Obviously, the answers will depend on how seriously the question is asked, and rote questions are likely to elicit rote answers. The inventor of the Ham-D Scale did not himself believe that it could be used as a scientific tool in the manner that the drug companies have utilized it (Hamilton, 1960).

## No Completed Suicides in the Clinical Trials

The FDA report also mentioned that no completed suicides were recorded among all the trial subjects. The agency failed to emphasize that the no suicides occurred on placebo either. Leaving depressed children drug-free did not produce a single suicide. This wholly contradicts the tendency to give drugs to prevent suicides.

The drug companies, and their promoters at the American Psychiatric Association (APA), have tried to emphasize that the clinical trials evaluated by the FDA produced "suicidality" but no actual suicides (Lenzer, 2005). Although I have never seen this point made before, it is important to realize that in general, depressed people do not commit suicide during clinical trials. Depression is essentially a loss of hope. During clinical trials, the participants are given hope that a new medication may finally relieve their suffering, they are given professional attention on at least a weekly basis, and they are monitored for any deterioration in their condition. Thus clinical trials provide the essential elements of any good therapy for depression: hope, professional attention, and close monitoring. No wonder placebo turns out to be as good as the drug; participating in the trial is itself therapeutic, at least during its brief duration.

In addition, actively suicidal patients are excluded from clinical trials. They are the most vulnerable and therefore the ones that the drugs are most likely to push into committing suicide.

The FDA authors concluded their report with an acknowledgment to "the drug companies that supplied the data needed for this work." At no point do they respond to the massive evidence that some drug companies, including the manufacturers of Prozac and Paxil, purposely provide junk data calculated to mislead, and especially to minimize, the risks associated with their drugs (see chapter 14).

## Canadian and British Regulatory Warnings

On June 3, 2004, before the FDA issued its formal label changes concerning children, Health Canada (2004)—the Canadian drug regulatory agency—issued "stronger warnings" for SSRIs and other newer antidepressants that were more encompassing than the U.S. version: "These new warnings indicate that patients of all ages taking these drugs may experience behavioural and/or emotional changes that may put them at increased risk of self-harm or harm to others." In dramatic contrast to the FDA, Health Canada applied the warning to children and adults in regard to suicidality, and it further warned about harm to self and to others (violence):

> Patients, their families and caregivers should note that a small number of patients taking drugs of this type may feel worse instead of better, particularly within the first few weeks of treatment or when doses are adjusted. For example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts that could involve *self-harm or harm to others* (emphasis added).

This is consistent with my testimony and publications, beginning with *Toxic Psychiatry* in 1991, in which I warned about both suicide and violence caused by SSRIs and with my book *Medication Madness* (in press), which will present dozens of case histories illustrating harm to self and to others induced by the SSRIs. The FDA continues to lag behind, however, mentioning hostility and aggression in the new labels as problems associated with SSRIs but without giving these dire outcomes sufficient emphasis.

In Great Britain, all SSRI antidepressants, except fluoxetine, have been banned for use in treating depression in children. The main concern surrounded suicidality that was increased with SSRIs in general, including fluoxetine (Committee on Safety of Medicines, 2003).

## Expanding the Suicide Warning to Young Adults

I warned the public and the health professions about the risk of SSRI antidepressant-induced suicidality in adults in *Toxic Psychiatry* (1991) and again in 1997 with a lengthy discussion in the first edition of this book. I elaborate in much greater detail on risk in 2003 in my scientific journal article "Suicidality, Violence and Mania Caused by Selective Serotonin Reuptake Inhibitors (SSRIs): A Review and Analysis."

In the meantime, in 2001, Houston, Texas, attorney Andy Vickery won a product liability suit against GlaxoSmithKline in a Paxil murder–suicide suit (*Tobin v. SmithKline Beecham,* 2001). Donald Schell, age 60, had taken two doses of Paxil before shooting his wife, their daughter, and his granddaughter to death. The jury awarded $6.4 million to two surviving family members (Josefson, 2001).

In fighting the case, GlaxoSmithKline claimed that there was no substantial evidence connecting Paxil to suicide. After reviewing evidence presented by both sides, the judge found that there was sufficient scientific evidence for Paxil-induced suicide to proceed with the case. Under intense pressure from the FDA to reevaluate its existing data, it would take the drug company 5 more years to come around to the same conclusion. Growing concern about antidepressant-induced suicidality led the FDA to require the drug companies to revaluate their earlier controlled clinical trials based on FDA standards for categorizing and reanalyzing data. In May GlaxoSmithKline (2006b) published a "Dear Healthcare Provider" announcement concerning Paxil-induced suicidality in depressed adults. The letter emphasized the supposedly slight increase in suicidality among *young* adults (through age 30) who take Paxil for a variety of conditions, including depression, panic attacks, anxiety, and obsessive–compulsive disorder. Far more important was the drug company's description of a statistically significant increase in

suicidality in *all ages* of adults in the controlled clinical trials for major depression. Depressed patients receiving Paxil were 6.4 times more likely to display suicidal thoughts and behavior than depressed patients taking a sugar pill. In regard to suicide—the most devastating risk associated with antidepressants—it is safer for depressed persons to stay off Paxil.

The FDA allowed the Paxil manufacturer to soft-pedal the findings by claiming, for example, that the results could be compounded by the fact that suicide is an aspect of "psychiatric illnesses." This is nonsense—and every scientist knows it. Since both groups were depressed, and since they differed only in the substances they were given to take in the blinded trials, Paxil, and not depression, was the cause of this astronomical increase in the rate of suicidality.

If depression had caused the increased suicidality, then the placebo patients—who lacked the supposed benefit of an antidepressant effect—would have suffered a much higher rate of suicidality than the Paxil patients. Instead, they had a much lower rate. In other words, because the antidepressants were supposed to be helping the depressed patients, the relative ineffectiveness of the sugar pill should have led to more suicidality than the drug, not less. The FDA, the drug company, and the media ignored this important fact. Conventional assumptions would have predicted increased suicidality on placebo, instead of increased suicidality on Paxil. It is a complete reversal of the expected outcome, underscoring the seriousness of finding increased suicidality on the drug.

Finally, in December 2006, the FDA held hearings concerning the potential addition of an adult suicide warning to all antidepressant labels. The data generated in older controlled clinical trials indicated that not only children but also young adults to age 24 were developing increased suicidal thoughts and actions when taking the newer antidepressants. The FDA's panel ended up recommending a black-box warning about increased suicidality in the 18- to 24-year-old age group. The FDA's committee was rife with conflicts of interest (Pringle, 2007).

Note that this conclusion concerning antidepressants in general ignored the Paxil data published in May 2006 by GlaxoSmithKline indicating an increase in suicidality in all ages for adults suffering from Major Depressive Disorder.

In May 2007, the FDA gave published notice of its intention to add a warning about increased suicidality aimed at "young adults" taking antidepressants. The FDA's new warnings required at the top of each antidepressant label are contained in a black box with the title "Suicidality and Antidepressant Drugs." The warning begins, "Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies

of major depressive disorder (MDD) and other psychiatric disorders" (GlaxoSmithKline, 2007).

## The FDA Helps Out the Drug Companies

The FDA's parsing of the suicidality warning into various age brackets meets drug company needs to obscure the basic reality that antidepressants cause suicide in children and adults. I don't know of another example in which a signal for a serious effect like suicidality has been divided up by age brackets, including some and excluding others. The distinctions are too fine to be made on the basis of controlled clinical trials that, at best, can provide a gross signal of a problem.

Once again, to dilute its impact on market for the newer antidepressants, the warning will be required for every drug approved for the treatment of depression, when in fact the data were generated entirely from clinical trials using the newer and more stimulating antidepressants. Because every antidepressant will carry the new warning, many doctors will be misled into believing that the older antidepressants have a similar risk to the newer ones. These doctors will conclude that there are no safer choices than the big moneymakers like Prozac, Paxil, Zoloft, Celexa, and Effexor.

The FDA not only limited its suicidality warnings to children, adolescents, and young adults in the new warning but also declared that there was no increase in antidepressant-induced suicidality in adults beyond age 24 and, furthermore, that "there was a reduction in risk with antidepressants compared to placebo in adults age 65 and older" (GlaxoSmithKline, 2007). The FDA is inviting doctors to believe, based on a small number of elderly patients in short-term clinical trials, that antidepressants might even reduce the suicide rate among older patients.

When insensitive clinical trials signal a suicide risk in both children and younger adults, it is time to admit flat out that antidepressants cause suicidality in all age groups. Besides, the number of patients 65 and older who were tested was very small.

Meanwhile, there is scientific data contradicting the FDA's suggestion that antidepressants might protect older adults against suicidality. A study published a few months before the FDA hearings evaluated coroners' records, prescription data, physician billing claims, and hospitalization data for more than 1.2 million Ontario residents age 66 and older from 1992 to 2000 (Juurlink et al., 2006). After evaluating more than 1,000 deaths by suicide, they found that "SSRI antidepressants were associated with a nearly fivefold higher risk of completed suicide than other antidepressants" (p. 813). This makes the FDA even more unscrupulous in acting as if antidepressants are safer in the older population.

As already mentioned, the FDA's new warning is actually weaker than the "Dear Healthcare Provider" letter sent out by GlaxoSmithKline earlier in May 2006. *The Paxil trials as disclosed in the letter showed an increased rate of suicidality in all ages of adults with major depressive disorder.*

## Paxil Is the Most Dangerous for Adults

The FDA's own analysis of all the adult controlled clinical trials found that Paxil was the most dangerous in regard to causing suicide attempts (Stone and Jones, 2006, p. 26). With the exception of Paxil, the individual antidepressants did not show a statistically significant increase in adult suicidality. The significant result came only after the data were pooled for all antidepressants. But in regard to Paxil, *in adults of all ages and in all psychiatric disorders, there was a statistically significant increase in suicidality* (OR 2.76, 95% CI 1.16-6.60, $p = 0.02$).

Paxil stood out from the pack in terms of dangerousness despite GlaxoSmithKline's efforts over many years to hide cases of Paxil-induced suicidality, to misidentify suicide attempts as emotional lability in their computerized coding system, and to manipulate the suicidality data to make it seem less menacing (chapter 14; Breggin 2006a–c). Despite the company's efforts to thwart the truth, even in short-term controlled clinical trials that were skewed to avoid demonstrating Paxil-induced suicidality, there was a statistically significant increased rate of suicidality in patients taking the drug compared to patients taking the placebo in all ages and all diagnostic categories.

## The Real-Life Risk Is Much Greater Than Described

Keep in mind that controlled clinical trials are planned by the drug companies, supervised by the drug companies, and carried out by paid doctors known to cooperate with the drug companies. Keep in mind that all the data analysis is done at drug company headquarters by drug company executives. Independent scientists play no role anywhere along the process. Keep in mind that the trials are constructed to prove the usefulness of the drug and to minimize adverse effects such as suicidality. Keep in mind that the controlled clinical trials are very short, usually 4–6 weeks long, and that prescreening excludes suicidal and psychotic patients from participating in the studies. Given these caveats, it is surprising that the suicidal signal was so strong that it could shine in the context of these trials.

In real-life medical practice, the rate of drug-induced suicidality will be much higher than in the research-oriented, controlled clinical trials.

In actual practice, many patients are already suicidal when they are started on the drug, increasing the likelihood that the drug will push them over into self-injurious behavior. Similarly, in real-life clinical practice, compared to controlled clinical trials used for research, busy doctors provide much less supervision or monitoring, the patients are almost never tested or evaluated for suicidality, multiple drugs are often given at once, and the doctors know little about looking for adverse effects on the mind.

Given that Paxil increased the rate of suicidality by more than 6 times in the drug company's controlled clinical trials, it will be considerably increased in actual practice. We cannot determine exactly how much greater the risk will be in clinical practice, but it will be much higher than in the brief, highly selective, and closely monitored controlled clinical trials.

## THE PSYCHOPHARMACEUTICAL COMPLEX RESPONDS

### The American College of Neuropsychopharmacology

The American College of Neuropsychopharmacology (ACNP) considers itself the premier organization in the world of professionals concerned with research and practice in the field of psychiatric medications. What was its response to the disclosure that antidepressants in children are ineffective in treating depression but that they can worsen the youngsters' overall condition and cause increased suicidality? This organization, bloated with doctors on the payrolls of drug companies, warned that the FDA was causing a potential disaster. In what the journal *Psychiatric Services* called a "chilling summary paragraph," the ACNP concluded ("ACNP Releases," 2006; Mann et al., 2006),

> The FDA's recent black box warning could serve to initiate a natural public health experiment. The change in labeling may be accompanied by a reduction in antidepressant prescriptions, particularly for youth. An unintended consequence of this policy could be an increase in youth suicide. That is an empirical question to be examined in the near future.

The real chilling experiment has been the drugging of millions of America's children with toxic so-called antidepressants, with no proven efficacy and with proven adverse effects, including mania and suicidality. Of course, it should be *hoped* that the change in label reduces the number of children exposed to these drugs. As for the empirical question concerning any potential increase in youth suicide from a reduction in antidepressant use, it is hard enough to draw conclusions from

placebo-controlled clinical trials, let alone from societal experiments, where the variables are literally infinite, subjectivity can run rampant, and the controls are nonexistent. There is already a plethora of such epidemiological studies, some claiming that suicide has increased, and some claiming that it has decreased (Van Pragg, 2003), since the advent of antidepressant treatment for adults.

Society-wide epidemiological studies cannot realistically answer empirical questions about drug efficacy and adverse effects; it is hard enough to do so in carefully controlled clinical trials. And besides, the empirical question has already been answered by the clinical trials. Antidepressants increase suicidality in children and youth as well as adults. But it is guaranteed that these same ACNP so-called experts will start producing flimsy and even ridiculous epidemiological studies in an attempt to undermine the far more reliable data generated in controlled clinical trials.

Is it unfair to say that the ACNP represents the drug companies, rather than America's children? At the end of the ACNP report, there is a list of Task Force members (the report authors), with their disclosures concerning potential conflicts of interest (Mann et al., 2006). The list of industry affiliations fills one and three-fourth pages. Of the 11 authors, only 1, William Beardslee, the fourth name in the list, claims no industry affiliation. Every one of the other 10 authors acknowledges several drug company affiliations, most have many affiliations, and *all 10 have connections to the manufacturers of antidepressants.* And these are the professionals, the supposedly top experts, who set the standards for the prescription of psychiatric drugs in America and worldwide!

I am familiar with a number of these men as a result of my work as a medical expert in product liability suits against the drug companies. For example, the lead author, J. John Mann, listed affiliations with two of the leading manufacturers of antidepressants, GlaxoSmithKline (Paxil) and Pfizer (Zoloft). He noted that he had been an expert trial witness on behalf of Pfizer, and I have read his prodrug company reports in that context. But he does not include an equally interesting connection under his list of industrial affiliations: the pharmaceutical giant, Janssen, funds his professorship at Columbia. He is the Paul Janssen Professor of Translational Neuroscience in Psychiatry and Radiology. Janssen is now a part of Johnson & Johnson, the second largest pharmaceutical company in the world, with revenues of $50.514 billion in 2006 (CNN Money, 2007).

The Department of Neuroscience (December 2006) Web page for the Columbia University Medical Center describes the Paul Janssen Professorship and the Paul Janssen Scholars program as resulting from a "partnership" between the university and Johnson & Johnson. It is a frightening illustration of how deeply embedded the pharmaceutical industry has become in the nation's leading medical centers.

Why would Mann fail to list his professorship as one of his industry affiliations? I am sure he takes great pride in his professorship, and he lists it as his university credential. I suspect that this kind of hand-in-glove connection to industry is so commonplace and so inherent in the lives of men like Mann that they hardly consider that it might be a conflict of interest to have your job funded by a partnership between your university and the world's second largest pharmaceutical company, even when that job ostensibly involves providing objective, independent evaluations of pharmaceutical products.

As another example of someone familiar to me from my work as a product liability expert, Jan Fawcett has conducted numerous clinical trials for drug companies over the years. He lists himself as a consultant to ten pharmaceutical companies, as a Speaker's Bureau member for eight pharmaceutical companies, and as recipient of grants and research support from eight pharmaceutical companies. Curiously, Fawcett lists a ninth institution, the NIMH, under industry affiliations, confirming my view that NIMH is now a part of the psychopharmaceutical complex and might as well be considered a branch of the pharmaceutical industry.

For readers who want to see all this, and more, for themselves, the article, including the list of industrial affiliations, can be found through the *Neuropsychopharmacology* Web site (http://www.nature.com/npp).

## The American Psychiatric Association

The APA has also been busy trying to dampen, and even to obliterate, the effects of the FDA black-box warnings. A June 2007 editorial in the association's *American Journal of Psychiatry* (Pfeffer, 2007) lamented, "these policy actions may have had the unintended effect of discouraging the prescription of antidepressants for pediatric patients and pediatric utilization of antidepressants without compensatory increases in other specific treatments" (p. 845). What was the purpose of warning about suicidality, if not to discourage the use of antidepressants?

The viewpoint of the editorial is so warped that it does not even mention that the FDA also found that the vast majority of clinical trials showed that antidepressants are ineffective in treating depression in children. As already noted, only 3 of 15 placebo-controlled clinical trials showed any efficacy. (Two of the three positive studies were sponsored by Eli Lilly, with Graham Emlsie, a close Lilly collaborator, as the first author; see subsequent discussion.) Also remember FDA committee member and epidemiologist Thomas Newman's (2004) observations that the adverse effects of the antidepressants were much better established than their efficacy, which could largely be accounted for by the placebo effect.

Dangerous and ineffective—that *should* discourage the use of a treatment in children.

## ANTIDEPRESSANTS LACK EFFICACY IN CHILDREN

There was no need to wait for the FDA to conclude that most studies with children fail to display any antidepressant efficacy. The issue had been decided in the scientific literature years earlier, and additional confirmation was unfolding at the same time as the FDA hearings.

I have observed for more than a decade (Breggin, 1991c, 1997a) that there is no scientific evidence that antidepressants are helpful for depressed children. But as a headline in *Clinical Psychiatry News* indicated a dozen years ago, "Though Data Lacking, Antidepressants Used Widely in Children" (Baker, 1995).

Sommers-Flanagan and Sommers-Flanagan (1996) reviewed all double-blind, placebo-controlled efficacy trials for tricyclic antidepressants (TCAs) with depressed young people published during the period 1985–1994. They summarized, "Results indicate that neither TCAs nor SSRIs have demonstrated greater efficacy than placebo in alleviating depressive symptoms in children and adolescents, despite the use of research strategies designed to give antidepressants an advantage over placebo" (p. 145). They concluded, "There has never been a double-blind, placebo controlled study published indicating that antidepressant medications are more effective than placebo in treating child or adolescent depression" (p. 151).

Fisher and Fisher (1996) explored the ethical issues surrounding the use of antidepressants in children. They pointed out how published recommendations for the use of antidepressants fly in the face of data within the same publications. They observed, "The prescribing of antidepressants for children clearly illustrates how a significant group of practitioners (child psychiatrists and pediatricians) can persist in using a procedure that is actually contradicted by research data and at the same time muster justifications for doing so" (p. 101).

A meta-analysis study by Whittington et al. (2004) in *The Lancet* found that the combination of published and unpublished studies led to the conclusion that with the possible exception of Prozac, there was no indication of efficacy for the antidepressant treatment of children. In addition, not noted in the article is the fact that the two key studies in favor of Prozac were supported by Eli Lilly, one directly and the other indirectly through funds funneled through NIMH,[1] and that the lead author in both was Graham Emslie (Emslie et al., 2002, 1997). Emslie was task force cochair and second author of the ACNP's infamous defense of antidepressants. Emslie's industry affiliations included "Grants/Research Support: Eli Lilly, Novartis,

Organon" and "Consultant/Speaker's Bureau: Bristol-Myers Squibb, Eli Lilly, Forest Laboratories, GlaxoSmithKline, McNeil, Otsuka, Pfizer, Inc., and Wyeth-Ayerst."

Whittington et al.'s (2004) meta-analysis led *The Lancet* to publish an editorial titled "Depressing Research" (2004), in which the world's oldest medical journal described the anguish of families who lose a child to suicide. It went on:

> That such an event could be precipitated by a supposedly beneficial drug is a catastrophe. The idea of that drug's use being based on the selective reporting of favourable research should be unimaginable. In this week's issue of *The Lancet,* however, a meta-analysis by Craig Whittington and colleagues suggests that this is what has been happening for research into the use of antidepressants in childhood. Their results illustrate an abuse of the trust patients place in their physicians.

In the same year, the *British Medical Journal* (*BMJ*) published another review of studies and an overall critique of antidepressant research in regard to children (Jureidini et al., 2004). Its summary points stated the following:

- Improvement in control groups is strong; additional benefit from drugs is of doubtful clinical significance.
- Adverse effects have been downplayed.
- Antidepressant drugs cannot confidently be recommended as a treatment option for childhood depression.

This report was followed by yet another editorial, this time in the *British Journal of Psychiatry* (Tonkin et al., 2005). Concerning antidepressants in children, it summed up the following:

> The evidence for efficacy is weak. At least five unpublished trials using a placebo control have failed to show an advantage of antidepressants over placebo. Among eight published trials, four found no statistically significant advantage for antidepressants over placebo on any primary outcome measure, and only about a third (17/52) of all published measures show an advantage for drug over placebo. Even the statistically significant improvements are of dubious clinical importance.

This editorial in Britain's major psychiatric journal concluded, "The currently available evidence indicates that the SSRIs should not be recommended as first-line treatment in children with depression."

Given these striking research reports and editorials in major journals in Great Britain, why would an editorial in America's major psychiatric

journal, in defiance of the FDA, recommend the use of antidepressants in children? The answer, simply, is that psychiatrists in the United States are much more in the pocket of the drug companies than psychiatrists in Great Britain.

### So-Called Alternative Treatments

The editorial in the *American Journal of Psychiatry* is miffed that the FDA warned about antidepressant-induced suicidality without providing another alternative. But the so-called alternatives for treating depression in children—psychosocial and educational interventions—should have already become the *only* treatments for childhood depression.

As I describe in *The Heart of Being Helpful* (1997b) and in *The Antidepressant Fact Book* (2001a), depression ultimately is loss of hope. It is despair over ever having a worthwhile or happy life. A depressed, unhappy child has lost hope and begun to give up trying to handle life successfully.

In children, the causes of this despair and loss of hope are almost always apparent in the first consultation session, providing it involves the family and includes an evaluation of the child's school life. In children, depression almost always revolves around problems at school and in the home, everything from bullying at school and abuse at home to academic school failure, painful peer relationships, and family conflicts over how to raise the child. The treatment of depression in children requires, first, finding out how and why the child became depressed and, second, helping the child, the family, the school, and all the other participants in the child's life restore hope in the child. Children have many needs, including a stable family, rational discipline, unconditional love, stimulating educational environments, physical security, and emotional safety. The object of therapy is to identify the unmet needs and to help adults meet them.

There is nothing in this *American Journal of Psychiatry* editorial about the child's basic needs and how to meet them. It is all about promoting drugs. There is nothing about children as human beings in the editorial. American psychiatry's dependence on drugs has led to moral bankruptcy and therapeutic nihilism. When it comes to America's children, psychiatry is doing far more harm than good.

## CONCLUSION

Overall, there has been an important movement at the FDA in the direction of warning the public and the medical profession about the risks associated with antidepressants, but it has taken much too long, and

the agency remains unable to come to grips with the reality that antidepressants are lethal and ineffective. Meanwhile, organized psychiatry has fought mightily against making any changes or accommodations in response to increased knowledge about the lack of efficacy and extreme hazards associated with antidepressant treatment. Individual health care practitioners too often seem undaunted by the latest negative information about antidepressants. At the least, these drugs should be contraindicated in the treatment of depressed children, and in a more ideal world, doctors would stop prescribing them for children or adults, instead turning to more effective and less risky psychosocial interventions in the treatment of depressed people of all ages.

## NOTE

1. Jureidini et al. (2004) stated that the funding for Emslie et al. (1997) was attributed to the National Institute of Mental Health in the article, but "[Food and Drug Administration] data show that study was sponsored by Eli Lilly" (p. 880).

CHAPTER 7

# Antidepressant-Induced Mental, Behavioral, and Cerebral Abnormalities

This chapter reviews the scientific literature on adverse *psychiatric* effects associated with antidepressants, especially the SSRIs and newer antidepressants. Many of the adverse psychiatric reactions produced by the newer antidepressants can be viewed as occurring along a continuum of activation or stimulation, culminating in mania and psychosis. In addition, these drugs can produce a blunting or lobotomy-like deactivation in the form of an apathy syndrome, especially after longer periods of use. They can also cause an obsessive syndrome that can lead to violence or suicide. Few drugs are as medication spellbinding as the newer antidepressants. All antidepressants cause mania, and mania is an acknowledged adverse effect in the FDA–approved label of all antidepressants. As noted in chapter 6—and now built into the FDA–approved labels for antidepressants—mania is the extreme expression of drug-induced overstimulation that includes insomnia, anxiety, agitation, irritability, hostility and aggression, emotional lability, akathisia, and hypomania and mania. It can lead to crashing into depression and suicidality.

At one end of the continuum, the individual becomes mildly irritable, a little emotionally labile, or slightly agitated. At the other end of the continuum, the individual becomes classically manic, at times perpetrating violence or crashing into depression and suicidality. On occasion an

individual will traverse the whole continuum, starting with irritability or insomnia, for example, and ending up in a manic state. At other times the individual may experience only one of the drug-induced stimulant symptoms, such as agitation, akathisia, or hostility.

SSRI labels tend to be organized in ways calculated to avoid any implication that the medications can cause a pattern of overstimulation, but detailed analyses of the labels disclose that these drugs do in fact produce a continuum of stimulation (see Breggin, 2002a, for an analysis of the Luvox label; Breggin et al., 1994a, for an analysis of the Prozac label). Table 7.1 was compiled to illustrate the spectrum of SSRI-induced adverse drug reactions and illustrate the frequency of stimulant-like effects. All of the effects listed in the table can also occur with stimulants such as amphetamine and cocaine, and many are typical of these stimulants, including hypomania/mania, euphoria, insomnia, nervousness, anxiety, agitation, central nervous system stimulation, emotional lability, tremor, sweating, and palpitation. They also include paranoid

**TABLE 7.1 Mental and Behavioral Adverse Drug Reactions in Adults Caused by Paroxetine**

| Frequent[a] | Infrequent[b] |
|---|---|
| Mania/hypomania (2.2% of bipolar patients) | Paranoid reaction |
| Mania/hypomania (1% of depressed patients) | Psychosis |
| Insomnia (13%) | Hostility |
| Nervousness (5%) | Euphoria |
| Anxiety (5%) | Delirium |
| Agitation (1%) | Hallucinations |
| Drugged feeling (2%) | Abnormal thinking |
| Confusion (1%) | Depersonalization |
| Central nervous system stimulation | Neurosis |
| Emotional lability | Lack of emotion |
| Concentration impairment | Libido increased |
| Amnesia | |
| Depression | |
| Tremor (8%) | |
| Sweating (11%) | |
| Palpitation (3%) | |

*Note*. From the 2001 FDA-approved label for Paxil. Table compiled from the label by Peter R. Breggin.

[a]Frequent means at a rate of 1% or greater. [b]Infrequent means at a rate between 1% and 0.1%. All adverse drug reactions (ADRs) with percentages (%) are for depressed patients in placebo-controlled clinical trials. ADRs without percentages are taken from the entire data pool of 7,678 patients administered Paxil, including 6,145 depressed patients.

reactions, psychosis, and hostility, all of which are also associated with stimulant drugs.

Confirmation of the stimulant syndrome was provided in a previously undisclosed internal document from Eli Lilly and Company, the manufacturer of fluoxetine (Prozac). The document was obtained during discovery in product liability suits against the company and is now available on my Web site (http://www.breggin.com; Beasley, 1988; Fentress Trial Exhibit 70, 1993). Charles Beasley, of the company's Division of Clinical Neurosciences, evaluated what he called *activation* in patients taking fluoxetine or placebo in the controlled clinical trials used for FDA approval of Prozac for depression. Beasley defined *activation* as including any of the following: nervousness, anxiety, agitation, and insomnia. Beasley found that 38% of fluoxetine-treated patients developed activation, but only 19% of placebo patients developed these symptoms. The proportion of patients activated by fluoxetine would have been higher if other expressions of stimulation had been included such as akathisia, hyperactivity, euphoria, and mania. It would have been further increased if many of the patients had not been prescribed sedative tranquilizers to quiet their symptoms of stimulation (Breggin et al., 1994a).

## THE RISK OF AGITATED DEPRESSION

Reports authored by psychiatrist Richard Kapit (1986b, 1986c), the FDA official in charge of evaluating adverse drug effects during the approval process of Prozac for depression, repeatedly warned that fluoxetine had a stimulant profile similar to amphetamines. He was concerned that stimulant effects such as insomnia, nervousness, anorexia, and weight loss would produce agitated depression and worsen the condition of some depressed patients (details about Kapit's reports are in chapter 14).

Clinically, agitated depression is an unstable condition that can lead to violence against self or others more frequently. A number of reports cited in the following sections will mention agitation in patients who behave abnormally as a result of antidepressant effects.

Koukopoulos and Koukopoulos (1999) provided a remarkable discussion of varied manifestations of agitated depression and suggested that it should be viewed as a separate diagnostic entity called *mixed depression*. They warned about the risk of giving antidepressants to patients with agitated depressions:

> Today's extensive use of antidepressant drugs in the treatment of all forms of depression makes the question of the real nature of agitated depression a critical issue. Many of these patients are seen to have such

> *adverse outcomes as increased agitation, intractable panic, heightened risk of suicide, manifestation of psychotic symptoms, and worsening of subsequent course of the illness.* (p. 547, emphasis added)

In other words, antidepressants can worsen agitated depression.

Koukopoulos and Koukopoulos (1999) proposed a definition of agitated depression as a major depressive episode with one of the following: motor agitation, psychic agitation or intense inner tension, and racing or crowded thoughts. This condition, which has also been referred to as *black mania,* "can worsen dramatically under the effect of antidepressants."

Unfortunately, Koukopoulos and Koukopoulos (1999) do not grasp that antidepressants, regardless of the patient's condition, can by themselves *cause* an agitated depression, with all of the associated unfortunate outcomes. In chapter 6, we found this clinical reality embedded and expressed in the new class labels for antidepressants that describe the association between antidepressants and insomnia, agitation, anxiety, hostility, aggression, and mania as well as an overall worsening of the patient's condition. We will find illustrative cases in the review that follows.

## SIMILARITY OF ADVERSE DRUG REACTION PATTERNS AMONG SSRIs

In general, the pattern of adverse reactions is similar among all the SSRIs and some of the other new antidepressants that block the reuptake of serotonin, especially venlafaxine. As a result, the FDA has required class label warnings for them in regard to suicidality and to the array of stimulant adverse reactions, from agitation and hostility to mania.

A British study conducted on the basis of prescription-even monitoring (PEM) involved cohorts exceeding 10,000 patients for paroxetine, fluvoxamine, sertraline, and fluoxetine (Mackay et al., 1997). The study confirmed the general similarity of reported adverse events, with two possible exceptions: Fluvoxamine (Luvox) had an increased number of reported adverse events, and paroxetine (Paxil) had an increased number of reported withdrawal reactions.

A Norwegian study by Olav Spigset utilizing that country's Adverse Drug Reactions Monitor Center reviewed 1,202 reports describing 1,861 adverse reactions to SSRIs. Again, the pattern of reports for the individual SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) was very similar, with three exceptions. Fluvoxamine reports were comparatively elevated for gastrointestinal symptoms, fluoxetine

reports were increased for dermatological symptoms, and sertraline reports were elevated for psychiatric symptoms. There was a broad range of antidepressant-induced psychiatric symptoms, with anxiety the most frequent, followed by confusion, hallucinations, sleep disturbances, hypomania/mania, depersonalization, amnesia, nightmares, aggression, insomnia, psychosis, concentration impairment, agitation, personality change, euphoria, and pathological inebriation. There were 13 reports of aggression, and they occurred more often in men.

SSRIs cause a wide range of neurological impairments. Spigset (1999) found the following neurological reports in order of frequency: parethesias, headache, dizziness, tremor, seizures, acute dystonia, dyskinesia, muscle cramps, muscle weakness, parkinsonism, muscle stiffness, akathisia, myoclonus, extrapyramidal reactions, increased muscle tone, and migraine. There have been reports of irreversible tardive dyskinesia caused by SSRIs (see subsequent section).

## STUDIES RELATED TO SSRI-INDUCED DEPRESSION AND SUICIDALITY IN ADULTS

### Epidemiological Studies and Clinical Trials of SSRI-Induced Depression and Suicidality in Adults

Chapter 6 described the FDA-mandated studies of suicidality in adults that found an increased rate of suicidality in young adults taking SSRIs in placebo-controlled clinical trials. The chapter also evaluated the May 2006 letter concerning Paxil sent by GlaxoSmithKline to health care providers describing an increased suicidality risk for adults of all ages with major depressive disorder when taking Paxil. In addition, chapter 6 examined evidence from the FDA's analysis (Stone and Jones, 2006) that Paxil was the one antidepressant that by itself demonstrated a statistically significant increase in suicidality and that this increase occurred in all diagnostic categories and all age groups. The following section deals with additional cogent evidence for a causal connection between SSRI antidepressants and suicidality.

An unpublished document obtained during discovery in product liability suits against the drug company disclosed that Eli Lilly, the manufacturer of fluoxetine (Prozac), had evaluated the comparative rates of suicide attempts on fluoxetine, amitriptyline, and placebo (the documents are available from http://www.breggin.com). The data were generated during controlled clinical trials conducted for the FDA approval process for Prozac for depression. On the basis of the company's data for controlled clinical trials, patients taking fluoxetine were 12 times more

likely to attempt suicide than a similar group of patients taking older antidepressants or placebos (details in chapter 14). An evaluation by a consultant to the company, Avery Winokur, concluded that the increased rate might be due to fluoxetine-induced overstimulation of the depressed patients.

Aursnes et al. (2005) discussed how the inclusion of unpublished data had been shedding new light on the risk of suicide associated with antidepressants prescribed to children in controlled clinical trials. They located unpublished data from controlled clinical trials not previously available for a total of 16 studies in which Paxil had been randomized against placebo. They found a statistically significant total of seven suicide attempts among 916 patients given Paxil and one among 550 patients receiving placebo. The data revealed that Paxil "is connected with an increased intensity of suicide attempts per year." Together with other published meta-analyses of antidepressant-induced suicidality, they found "a strong case for the conclusion, at least with a short time perspective, that adults have an increased risk of suicide attempts" on Paxil. Aursnes et al. concluded, "Our findings support the results of recent meta-analyses. Patients and doctors should be warned that the increased suicidal activities observed in children and adolescents taking certain antidepressant drugs may also be present in adults."

Fergusson et al. (2005) searched the literature and found 702 randomized clinical trials (87,650 patients) comparing SSRIs with either placebo or an active non-SSRI control medication. They found a statistically significant, more than two-fold increased risk of suicide attempts on SSRIs compared to placebo. The odds ratio of suicide attempts in SSRI-treated patients versus placebo patients was 2.28 ($p = 0.02$) and a 95% confidence interval (CI) of 1.14-4.55. They also found an increased suicide risk between SSRIs and other medications, excluding tricyclic antidepressants. There was no difference between the SSRIs and tricyclics in suicide risk. Overall, their results "documented an association between suicide attempts and the use of SSRIs."

Fergusson et al. (2005) estimated the risk at 5.6 suicide attempts per 1,000 patient years. They observed, "Although small, the incremental risk remains a very important population health issue because of the widespread use of SSRIs." They also believed that suicide attempts were underreported. In addition, the trials averaged 10.8 weeks in duration, with only a fraction of patients (fewer than 7%) followed for more than 6 months. Because individual trials were relatively small, they decreased the likelihood of a particular risk being identified.

Healy (2003) reviewed and reanalyzed data comparing the number of suicides and suicide attempts per patient in worldwide placebo-controlled clinical trials used for the FDA antidepressant approval process

(Khan et al., 2001; Khan et al., 2000). The drugs included four SSRIs (sertraline, paroxetine, citalopram, and fluoxetine). As a percentage of patient numbers, there was a statistically significant difference between combined suicides and suicide attempts among all SSRIs patients (1.55%) and among all SSRI trial placebo patients (0.48%). There were also a significantly greater number of completed suicides on SSRIs in the combined suicide and suicide attempt group as well as in the paroxetine group individually, compared to placebo. One set of data showed a 3 times greater rate for suicide attempts on SSRIs compared to other antidepressants.

Donovan et al. (1999) found a significantly increased rate of suicide among patients treated with SSRIs compared to those treated with tricyclic and other antidepressants. After correcting the data for the number of prescriptions for each drug, SSRIs were 3.5 times more likely to be associated with suicide. The authors concluded, "The overall occurrence of suicide by any method was lowest in patients prescribed TCAs [tricyclic antidepressants] and highest in those prescribed SSRIs. This difference was statistically significant ($p < 0.01$)." The study was conducted in three regions of England and Ireland and involved 222 suicides.

Donovan et al. (2000) conducted a prospective study of 2,776 consecutive cases of deliberate self-harm among subjects age 17 and older who were seen at the accident and emergency department of Derbyshire Royal Infirmary as a consequence of any act of deliberate self-harm during a 2-year period (1995–1996). Acts of deliberate self-harm included overdoses, other forms of suicide attempts, and cutting oneself. Of the 2,776 cases, 307 had received an antidepressant 30 days or less prior to the incident of deliberate self-harm. With the rate of prescribing in Derbyshire taken into account, the relative incidence of deliberate self-harm was significantly higher ($p < .001$) in patients who were prescribed the SSRIs fluoxetine, paroxetine, and sertraline compared to patients who were prescribed the tricyclics amitriptyline, dothiepin, and imipramine. The relative incidence of deliberate self-harm per 10,000 prescriptions was broken down in a table, as follows: fluoxetine (19.8), sertraline (14.8), paroxetine (12.1), all SSRIs (16.6), imipramine (3.5), amitriptyline (3.0), and all tricyclics (5.6). Compared to amitryptyline, the relative risk for all SSRIs was considerably higher: fluoxetine (6.6), sertraline (4.9), paroxetine (4.0), and all SSRIs (5.5). Patients on Paxil were 4 times more likely to harm themselves than patients on the older non-SSRI antidepressants. Of interest in regard to causation, the risk for the tricyclic clomipramine was very high as well, with a relative incidence of 13.8 and a relative risk compared to amitryptyline of 4.6. Among the tricyclics, clomipramine has the strongest inhibitory effect on serotonin reuptake and a great tendency toward overstimulation (see, e.g., *Drug Facts and Comparisons,* 2003). Jick et al. (1995) conducted an epidemiological study

of reports from general practices (primary care) in the United Kingdom involving 172,598 patients, including 143 who committed suicide, who had at least one prescription for 1 of 10 antidepressants. Rates of suicides were compared for patients on the various antidepressants. Patients taking fluoxetine were twice as likely to commit suicide compared to patients on other antidepressants. In comparison to three more sedating antidepressants—doxepin, imipramine, and amitryptyline—fluoxetine was 4 times more likely to be associated with suicide. The relative risk for patients taking Prozac compared to patients taking the non-SSRI antidepressant dothiepin was 3.8 (95% CI of 1.7–1.86).

Jick et al. (1995) stretched beyond reason to take their position that Prozac might not be the cause of the suicides.[1] They found that "when the analysis was restricted to those without a history of having felt suicidal or who had taken only one antidepressant, the increased risk for those who took fluoxetine was reduced." Thus, the increased risk was reduced by these manipulations but not eliminated. Data in a table show that after taking into account a past history of suicidal behavior and/or antidepressant use, Prozac remained *twice* as likely to be associated with suicide as any other antidepressant. In fact, Prozac became the *only* antidepressant that was associated with *increased* risk of suicide.

Jick et al. (2004) examined data on suicide attempts among 159,810 adults and children taking Prozac, Paxil, and the non-SSRI antidepressants amitriptyline or dothiepin. They found that the risk of suicide was increased during the first month of medication exposure, "especially during the first 1 to 9 days." Comparing the first 9 days to the first 90 days, there was a statistically significant increase in both suicide attempts and completed suicides. This is consistent with observations that I have made, as well as the recent FDA label changes, and is consistent with the drugs causing suicidality.

Juurlink et al. (2006) reviewed more than 1,000 cases of suicide and found that during the first month of therapy, SSRI antidepressants were associated with a nearly fivefold higher risk than other antidepressants. The results were statistically significant (OR 4.8, 95% CI 1.2–12.2.) The authors concluded that "initiation of SSRI therapy is associated with an increased risk of suicide during the first month of therapy compared with other antidepressants."

Muijen et al. (1988) conducted a 6-week double-blind study comparing fluoxetine, mianserin, and placebo with 26, 27, and 28 starters, respectively, and 14, 14, and 16 finishers, respectively. Two of the fluoxetine patients "took an overdose within two weeks of starting the study, and in both cases this was related to a deteriorating clinical state that necessitated hospitalization" (p. 386). None of the patients in the other drug group or the placebo group suffered from this decline and suicidality.

Remarkably, the authors did not include these reactions among the adverse drug effects. At this point in time, few researchers were aware of the connection between SSRIs and suicidality.

Gorman et al. (1987) conducted an open trial of fluoxetine involving 16 patients with panic disorder. They reported, "Two of the nonresponders became depressed and had suicidal ideation while taking fluoxetine. Only one of the two had a history of depression" (p. 331). Still in the era before recognition of SSRI-induced suicidality, the authors did not comment on this finding.

## Coroner Studies of Adult Suicidality

Frankenfield et al. (1994) conducted a retrospective case review of all deaths in Maryland where either fluoxetine or tricyclic antidepressants was forensically detected. The study covered a 3.5-year period of time. They found a statistically significant increase in *violent* suicides in association with fluoxetine (65% vs. 23%). Violence was defined to include "gunshot or shotgun wounds, suffocation, stabbing, strangulation, drowning, falls and jumping in front of a moving vehicle" (p. 109). The evaluations of the suicide attempts were blind to which medications were involved.

Bost and Kemp (1992) reviewed a series of coroner's reports in Dallas, Texas, involving 15 suicides associated with fluoxetine treatment. The study covered a 9-month period. While they appreciated that their data were impressionistic, they warned that the proportion of patients taking fluoxetine and committing suicide was high enough to be of concern to health care providers.

## NIMH Confirms That SSRIs Cause Suicidality

On November 13, 2006, NIMH announced a new NIMH initiative aimed at studying the connection between SSRIs and suicidality and in the process made clear that consensus exists within the psychiatric establishment that SSRI antidepressants cause suicidality. NIMH director Thomas Insel, M.D., was quoted: "These new multi-year projects will clarify the connection between SSRI use and suicidality" and "they will help determine why and how SSRIs may trigger suicidal thinking and behavior in some people but not others, and may lead to new tools that will help us screen for those who are most vulnerable."

## Case Reports of Mania, Violence, and Suicide in Adults

There are many case reports in the scientific literature documenting the capacity of SSRIs to cause mania in adults, often in association with

irritability and aggression. Some cases display overstimulation that falls short of mania.

Medwar et al. (2002) reviewed e-mails sent to the British TV show *Panorama* and described cases of suicidality and withdrawal reactions associated with SSRIs. Medwar et al. (2003–2004) continued their observations, comparing patient and physician reports, and discussed the public health implications of using these kinds of sources. The researchers were impressed with the great numbers of responses that were received in response to the TV show, and they advocated making greater use of these kinds of public responses as signals of adverse drug reactions. In reality, for many years Web sites throughout the world have been describing adverse psychiatric reactions to SSRI antidepressants, including mania, violence, and suicide, while the pharmaceutical industry and organized medicine ignored these "signals" that the drugs were causing disastrous reactions. As another, similar use of public data, *Talking Back to Prozac* (Breggin et al., 1994a) listed dozens of newspaper reports describing violence and suicide in association with taking Prozac; but the FDA, psychiatry and the drug industry dismissed these data.

Healy et al. (2006) described nine cases in England, Scotland, Australia, and the United States as illustrations of antidepressant-induced violence. Two paroxetine, three sertraline, and one fluoxetine case resulted in homicide. One paroxetine case resulted in assault, one venlafaxine case resulted in attempted murder, and one fluoxetine case resulted in assault and robbery. Some were associated with maniclike symptoms. They also evaluated clinical trial data (see subsequent discussion).

Okada and Okajima (2001) described three cases of aggressive and violent behavior induced by fluvoxamine. On 150 mg/day, a 32-year-old woman became both irritable and aggressive, and she expressed impulsive violence during arguments with her family. She improved after her fluvoxamine was reduced (but not stopped). A 29-year-old woman on 150 mg of fluvoxamine daily became nervous and irritable and then impulsively violent and was admitted to a psychiatric hospital. She improved with discontinuation of the drug and further treatment with other medications. A 28-year-old woman receiving 150 mg of fluvoxamine daily exhibited signs of irritability and aggressive behavior and expressed violence toward her mother. She improved when the fluvoxamine was stopped and other medications instituted. They warned about the existence of impulsive and aggressive behavior induced by fluvoxamine.

Severe stimulation reactions were reported in four of six fluoxetine-treated patients with posttraumatic stress disorder, requiring three of them to withdraw from the study: "Two experienced agitation and worsening of hyperarousal symptoms; one patient's panic symptoms markedly

worsened. A fourth patient also suffered severe agitation and greater anxiety" (Marshall et al., 1995, p. 1238).

Mania and hostility frequently go together, and mania is one cause of Prozac-induced violence. Crashing after mania can cause depression and suicide as well. There are many other reports of varying degrees of psychosis caused by Prozac (Chouinard et al., 1986; Lebegue, 1987; Settle et al., 1984; Turner et al., 1985). LaPorta et al. (1987) described two cases and Mendhekar et al. (2003) described one case of mania caused by Zoloft.

Ramasubbu (2001) described five cases of hypomanic reactions on SSRI antidepressants, including paroxetine (two) and citalopram (three). A man who had a prior history of depression associated with "one minor stroke and one transient ischemic attack" was put on citalopram and became "increasingly verbally abusive, aggressive and excitable in social situations." He also admitted to becoming "more angry and irritable in social situations for trivial reasons." But he also justified his angry outbursts on the basis of other people's behavior. (A typical medication spellbinding effect.) Reducing the dose from 40 to 20 mg/day "resolved his verbal aggression." Ramasubbu (2004) also described two cases of dose-dependent mania in response to sertraline in patients with no bipolar history.

Mundo et al. (1993) gave a general description of their experience with patients who developed mania while taking clomipramine, fluoxetine, or fluvoxamine in their obsessive–compulsive disorder (OCD) clinic. According to the authors, "when these patients were treated with proserotonergic antiobsessional drugs, they experienced reduced impulse control, dysphoria, and increased aggressiveness and reckless acts, symptoms similar to those found in mania."

During the seventh week of citalopram, a patient developed "a manic episode with insomnia, euphoria, psychomotor agitation, logorrhea, flight of ideas, disinhibition, injudicious spending, and delusional ideas of megalomania and persecution developed" (Bryois et al., 1994). Bobo and Grammer (2003) described a florid mania caused by escitalopram. Christensen (1995) reported on the case of a 32-year-old man who developed his first manic episode while taking paroxetine. He became psychotic and "threatened his parents with physical harm" (p. 1400). Vesely et al. (1997) presented six cases of SSRI mania, one on paroxetine and five on citalopram. Other reports cite fluvoxamine as a causative agent (e.g., Burrai et al., 1991; Dorevitch et al., 1993; Okada et al., 2001).

Dorevitch et al. (1993) described three cases of fluvoxamine-induced mania. Each case was recognized quickly, and the drug was reduced in dose or stopped so that potentially disastrous outcomes were avoided. Had the patients been more secretive or the monitoring less effective,

the results could have been more drastic in outcome. In the first case, the patient developed a psychotic manic state with auditory hallucinations. In the second case, the patient became euphoric; displayed increased energy and inappropriate behavior, with sexual advances toward other patients; was irritable; and had fears that people were out to kill him. In the third case, the patient developed multiple signs of mania, from excessive sexual activities to excessive talking and argumentativeness. Manic patients who are argumentative can sometimes become very aggressive when thwarted.

In another case report, a woman taking fluvoxamine became suicidal and had to be hospitalized (Bastani et al., 1996). In the hospital, the fluvoxamine dose was increased from 50 mg/day to 150 mg/day, whereupon her condition worsened and she began to experience auditory hallucinations. The fluvoxamine was discontinued, and she recovered within 24 hours, confirming that the medication had caused the depression and psychosis.

## Case Reports of SSRI-Induced Akathisia, Suicidality, and Aggression in Adults

This chapter has already mentioned cases in which SSRI-induced akathisia played a role in the worsening of the patient's condition and suicidality. *Akathisia* is a painful inner agitation that manifests as the inability to sit still or stop moving. The hyperactivity may manifest itself subtly as a feeling of jitteriness or grossly as frantic pacing or repeatedly sitting up and down.

Akathisia was first described in association with neuroleptic drugs. The inner agitation associated with akathisia can become extremely uncomfortable, causing the individual to feel tortured from within (see vivid descriptions in Van Putten, 1974, 1975a&b; Breggin, 1997a), leading to extreme irritability and suicide or violence.

In the neuroleptic literature, Crowner et al. (1990) drew a direct connection between akathisia and violence. They filmed activities on a psychiatric unit 3 days a week, from 8:00 A.M. to noon, for 2 years. They screened the films for incidents of violence "resulting in injury or with the potential to do so." They only rated segments where the participants, and at least two nonparticipating bystanders, were visible for at least 2 min of the 5-min rating period. Their findings are remarkable: "The assailants were akathisic before about half of all the assaults, as were the victims." Only 4 out of 24 nonparticipants displayed akathisia. This confirms an observation I have made over the years: that most violence on psychiatric wards stems from the treatments, including drug toxicity and (unstudied in this project) provocation by staff.

Although akathisia by definition usually involves a hyperactive movement component, clinical experience indicates that it may be accompanied with a feeling of jitteriness without actual physical movement; that is, the same jittery, agitated subjective experience, accompanied by irritability, violence, or suicidal feelings, can occur without the specific component of feeling driven to move about. Indeed, on earlier occasions, the individual may have experienced the associated compulsion toward hyperactivity. Healy (1994) made similar observations.

Adler and Angrist (1995) described a case of a depressed patient who developed akathisia with pacing and rocking foot to foot. The symptoms appeared 7 days after starting Paxil and 4 days after the dose was increased to 20 mg/day. The patient reported difficulty standing still and was so distressed that he considered signing out of the hospital because of worsening depression. Rather than reducing the medication, he was treated with the addition of propranolol and lorazepam to subdue the akathisia. This unfortunate practice bombards the nervous system and continues exposure to an agent that is causing neurological dysfunction.

Bonnet-Brilhault et al. (1998) also presented a case of paroxetine-induced akathisia. They terminated the treatment with a complete resolution of the problem. They observed that in most cases the first and best option is to discontinue the offending agent. LaPorta (1993) treated two cases of sertraline-induced akathisia that cleared up after terminating the medication. Olivera (1996) described a case of paroxetine-induced akathisia that was mistaken for an exacerbation of the patient's so-called panic anxiety: The dose was doubled, and the condition worsened. The akathisia resolved when paroxetine was replaced by clomipramine.

Baldassano et al. (1996) described a depressed 18-year-old student who was started on paroxetine 20 mg/day and clonazepam 0.5 mg at night who developed worsening insomnia, a need to move about, restlessness, physical tiredness, and anxiety. The akathisia resolved on propranolol. The authors reviewed their charts and found 3 cases of akathisia among 67 patients (4%) treated with paroxetine. They concluded,

> The gravest consequence of akathisia is its reported association with suicide. The patient population receiving antidepressants for affective illness are *[sic]* at high risk for suicide, and the additive effect of untreated akathisia could be tragic.

Lipinski et al. (1989) reported on five cases of akathisia caused by fluoxetine. They also reviewed the literature and found rates of 9.7% to 25% for fluoxetine-induced akathisia. They concluded, "In summary, fluoxetine, and perhaps other antidepressant drugs as well, may produce

the side effect of akathisia fairly frequently" (p. 342). The Public Citizen Health Research Group (1990) estimated a rate of 15% to 25%. While studies of SSRI-induced akathisia vary greatly in the frequency with which this disorder is observed, they confirm that it is common.

Lane (1998) observed, "SSRI-induced akathisia may represent a form of serotonergic overstimulation or serotonin toxicity" (p. 203). He also cited research linking the phenomenon to the impact of SSRIs on the dopaminergic system. He warned, "The emergence of symptoms of akathisia could be mistaken for a worsening of depression, especially the conversion of a non-agitated depression to an agitated form" (p. 206). This error in judgment could lead to the prescription of increased doses of the offending medication, resulting in a severely worsened condition. Lane cited studies indicating that "fluoxetine is not an appropriate choice of antidepressant for depressed patients with agitation and restlessness" (p. 206) because it can lead to increased rates of agitation, anxiety, and manic reactions. He noted that patients may feel "death is a welcome result" when suffering from unbearable Prozac-induced akathisia.

Rothschild and Locke (1991) reported on three cases of fluoxetine-induced suicidality associated with akathisia. Each case of suicidality developed on fluoxetine *(challenge)* and then resolved when the drug was stopped *(dechallenge)*. The suicidality then returned when the drug was started a second time *(rechallenge)* and stopped again when the drug was stopped (a second dechallenge). During rechallenge, each of the patients developed akathisia and reported that this feeling had caused them to become suicidal each time.

Wirshing et al. (1992) reported on five cases of a fluoxetine-induced syndrome consisting of akathisia and suicidality. In all five cases, the akathisia and the suicidality remitted when the drug was stopped or reduced in dosage. In one case, a rechallenge with an increased dose of fluoxetine again produced the syndrome. They concluded, "Our cases appear to confirm that certain subjects experience akathisia while taking fluoxetine and that this effect is dose-related in the individual patient. . . . Furthermore, like the akathisia in the neuroleptic-treated schizophrenic population, 'fluoxetine akathisia' can apparently be associated with suicidal ideation, sometimes of a ruminative intensity" (p. 581).

Masand et al. (1991) reported on two cases of suicidality in association with fluoxetine. One of the patients suffered from akathisia. In both cases, the suicidal feelings subsided shortly after stopping the medication. Neither patient had prior suicidal ideation. Both developed violent fantasies (hanging and jumping out a window).

Hamilton and Opler (1992) wrote about the clinical qualities and potential biological mechanisms of antidepressant-induced akathisia. They

described a depressed woman who developed "panic-like symptoms, anxiety, and palpitations" 10 days after starting fluoxetine 20 mg/day. The dose was reduced to 5 mg, with resolution of those symptoms; but within 3 more weeks, she complained of symptoms she had never before experienced, "feeling restless and out of control. . . . I feel like I need to hold onto my chair or else I'll jump out of the window." Although she said she felt good, "she was afraid that she would kill herself because of these restless and out-of-control feelings." While she had experienced mild to moderate suicidal feelings in the past, without any intent or attempts, she now felt suicidal in a more "frightening manner." Her fluoxetine was stopped, and within several days, the restlessness and suicidal feelings stopped.

Hamilton and Opler (1992) suggested that akathisia results from the influence of the serotonergic system on the dopaminergic system, with inhibition of the nigrostriatal dopamine tract, impacting on the extrapyramidal system. They identified the disorder as "Extrapyramidal-Induced Dysphoric Reaction, one extreme manifestation of which is the emergence of suicidal ideation."

Leo (1996) discussed the possible biological mechanisms underlying akathisia in some detail and concluded that "SSRI-induced EPS [extrapyramidal symptoms] are probably related to agonism of serotonergic input to dopaminergic pathways within the [central nervous system]."

In various case reports in this chapter, we will find that akathisia can be found in combination with SSRI-induced mania and aggression.

## Case Reports of SSRI-Induced Obsessive Suicidality and Aggression in Adults

A number of clinical reports have described a syndrome of obsessive SSRI-induced suicidality and aggression that seems particular to these drugs, starting with Teicher et al. (1990). These cases bear some similarity to akathisia-driven suicidality, but compulsion toward self-harm is not accompanied by the specific symptoms of akathisia. They summarized, "Six depressed patients free of recent serious suicidal ideation developed intense, violent suicidal preoccupation after 2–7 weeks of fluoxetine treatment" (p. 207). Additional cases and potential mechanisms of action were analyzed by Teicher et al. (1993).

Dasgupta (1990) described a similar case of "intense suicidal preoccupation" (p. 1570) after 4 weeks of fluoxetine treatment in a woman who had not been previously suicidal. She, too, rapidly recovered on stopping the fluoxetine. Hoover (1990) described another similar case in which the patient developed intense, violent suicidality on the two occasions that he was exposed to fluoxetine.

Creaney et al. (1991) described two patients who became suicidal on SSRIs. One patient developed dysphoria and manic symptoms on fluoxetine and then developed a similar syndrome, this time with suicidal feelings, on fluvoxamine. Another patient became intensely and violently suicidal 16 days after starting fluoxetine.

Gualtieri (1991) described the "case of a mentally handicapped gentleman whose rates of self-injurious behavior doubled on fluoxetine, and then fell to baseline after the drug was withdrawn" (p. 393). Gualtieri pointed out that fluoxetine can cause apathy and indifference in some patients and, conversely, mania in others.

Goder et al. (2000 ) reported that a 32-year-old man with OCD with preexisting obsessive, aggressive impulses developed "nausea, a strong sense of guilt, aggression, fear of losing control and increasing restlessness" after his first dose of 10 mg of paroxetine. He also had severe restlessness. He was prescribed neuroleptics and continued on paroxetine for 4 days, after which he had to be transferred to a closed ward because of his fear that he would give way to impulses to kill other people. On the following day, he attempted to kill himself by jumping off a wall and was severely injured. The paroxetine was terminated, he was treated with neuroleptics, and he recovered.

## SSRI-Induced Apathy Syndrome in Adults

The clinical phenomenon of SSRI apathy and indifference has become of increasing interest in the literature. The mixture of apathy and disinhibited aggressiveness reported by Healy (2006) and other researchers is found in a portion of patients who act uncharacteristically suicidal or violent as a result of taking SSRIs (Breggin, in press). In my clinical experience, feelings of apathy and loss of interest are among the main reasons patients seek help in trying to withdraw from SSRIs. Unfortunately, by the time the spellbinding apathy syndrome is recognized, the individual has often been taking the drugs for years and thus has considerable difficulty withdrawing from them.

Hoehn-Saric et al. (1990), who were among the first to report it, described "apathy and indifference in patients on fluvoxamine and fluoxetine" as well as loss of initiative and disinhibition with and without hypomania in five patients. Levine et al. (1987) reported that 7% of 59 nondepressed obese patients became depressed following a rapid increase in fluoxetine to a dose of 80 mg/day, but they did not identify apathy as an aspect of this drug-induced depression.

Apathy was reported as an "infrequent" adverse reaction during the testing of Prozac for depression (*Physicians' Desk Reference,* 2000). However, it has become sufficiently common to be described in *The*

*American Psychiatric Publishing Textbook of Clinical Psychiatry* (Marangell et al., 2003; see also Marangell et al., 1999):

> Apathy syndromes: We and others have noted an apathy syndrome in some patients after months or years of successful treatment with SSRIs. Patients often confuse this syndrome with a recurrence of depression, but the two conditions are quite distinct. The syndrome is characterized by a loss of motivation, increased passivity, and often feelings of lethargy and "flatness." . . . Mistakenly interpreting the apathy and lethargy for a relapse of depression, and hence increasing the dose of medication, will worsen the symptoms.

Note that the apathy syndrome is so spellbinding that patients "often confuse this syndrome with a recurrence of depression." As the textbook indicates, doctors can make the same mistake of failing to identify the drug as causal.

In my clinical experience, apathy or indifference is one of the main reasons patients want to stop taking SSRI antidepressants. Over months and years, they became increasingly unable to respond to loved ones and to the world around them, losing interest in favorite subjects and activities and existing in an emotionally dulled state. Usually, they have felt a return of their normal interest in life after stopping the medications. The lobotomy-like effect usually renders people passive, rather than aggressive, but it may be mixed with irritability and anger that more often occur during the start of treatment, dose changes, or withdrawal.

Barnhart et al. (2004) reviewed the literature on apathy syndrome and found 12 relevant case reports and one open-label treatment trial. They pointed out the difficulty in distinguishing apathy from clinical depression but noted that patients can often tell the difference. In my experience, patients suffering from SSRI-induced apathy experience an indifference or lack of interest, even when their own rational assessment tells them that they do not feel sad or depressed, when in fact they would *like* to feel more involved in life. Whereas depressed patients typically lapse into feeling helpless and withdrawn, these individuals want to become more interested in their loved ones, friends, work, or hobbies but find themselves unaccountably stifled in their capacity to do so. They often feel frustrated rather than depressed. Or if spellbound, they may actually claim to feel "fine," even while they display indifference to their surroundings.

Furthermore, as Barnhart et al. (2004) pointed out, "cerebral blood flow changes, evidenced by single proton emission computed tomography, as well as the pattern demonstrated in neuropsychological testing, support the hypothesis that the effect in question is a reversible front lobe syndrome rather than a residual component of mental illness." The

evidence in this regard is very preliminary but, in my opinion, probably will be confirmed.

In their review of 12 reported cases, Barnhart et al. (2004) found three cases associated with fluvoxamine, seven with fluoxetine, and two with paroxetine. The apathy states improved or resolved with dose reduction or discontinuation. The authors believed that the syndrome frequently goes undetected "despite its significant clinical impact." Opbroek et al. (2002) reported that 80% of patients with SSRI-induced sexual dysfunction reported suffering from "treatment-emergent emotional blunting." This is consistent with my clinical observations that so-called sexual dysfunction in patients receiving antidepressants often involves a more generalized loss of interest in both sex and loved ones.

The syndrome has been described in children (see subsequent sections).

## IDENTIFYING ANTIDEPRESSANT-INDUCED COMPULSIVE VIOLENCE AND SUICIDALITY IN ADULTS AND CHILDREN

On the basis of the literature and my clinical experience, the syndrome of SSRI-induced obsessive suicidality and violence includes many, and sometimes all, of the following:

- A relatively sudden onset and rapid escalation of the compulsive aggression against self and/or others
- A recent (typically within a few months or less) initial exposure to the medication, a recent change in the dose of the medication, or a recent addition or removal of another psychoactive substance to the regimen
- The presence of other adverse drug reactions, often involving akathisia or stimulation along a continuum from irritability and agitation to agitated depression and mania, as well as indifference and apathy
- Resolution of the syndrome after termination of the causative medication, often with a marked overall improvement in the individual's mental status
- An extremely violent and/or bizarre quality to thoughts and actions
- An obsessive, compelling, unrelenting quality to thoughts and actions

- An out-of-character quality for the individual, as determined by the individual's history
- An alien or ego-dystonic quality, as determined by the individual's subjective report

Concerning the extremely violent and/or bizarre quality of patients overcome with this syndrome, Grounds et al. (1995) made interesting observations based on several of their own cases:

> A striking feature of this syndrome is that most of the patients do not want to die—they just want to kill or harm themselves. None of our patients have actually suicided. . . . The sufferers do not usually become preoccupied with taking overdoses, just with violent self injury. Quotes which illustrate this include: "I didn't want to die, I just felt like tearing my flesh to pieces." "I suddenly found myself purposely driving dangerously—such as driving through a red light and driving on the wrong side of the road. I got frightened but I had to do it." "I got my cane cutters' knife in my right hand and wanted to cut my left hand off at the wrist."

They also pointed out that the syndrome "tends to occur soon after commencement of treatment, or a dose increase. Cessation of fluoxetine results in abatement of the problem, and it usually recurs on rechallenge."

In my clinical experience, the sudden compulsion to harm oneself or others can occur after the first one or two doses of the antidepressant or within a day or two of a dose change, especially an increase. It can also occur shortly after the addition of another stimulating drug to the treatment regimen.

## EPIDEMIOLOGICAL STUDIES AND CLINICAL TRIALS OF SSRI-INDUCED MANIA AND AGGRESSION IN ADULTS

The clinical syndrome of mania is commonly associated with increased irritability, aggressiveness, physical violence, and a variety of antisocial and criminal behaviors (American Psychiatric Association [APA], 2000, pp. 357–362). Many studies of antidepressant-induced mania involve aggression.

### Studies of Antidepressant-Induced Aggression in Adults

Healy et al. (2006) evaluated data produced by GlaxoSmithKline (2006b) in response to a recent review by British regulators. They also examined

the company's data on controlled clinical trials for children. The authors summarized,

> In these trials, hostile events are found to excess in both adults and children on paroxetine compared with placebo, and are found across indications, and both on therapy and during withdrawal. The rates were highest in children with obsessive compulsive disorder (OCD), where the odds ratio of a hostile event was 17 times greater (95% confidence interval [CI], 2.22–130.0).

Healy et al. (2006) posited a variety of possible mechanisms for SSRI-induced violence, including akathisia, emotional blunting (a lobotomy-like apathy syndrome), and manic or psychotic reactions.

Healy (2000) conducted a randomized double-blind crossover study comparing the effects of sertraline to a non-SSRI antidepressant (reboxetine) in a group of healthy volunteers. Many of the 20 individuals developed adverse mental and neurological effects while taking the sertraline, and two became severely disturbed. Case A, a 30-year-old woman, became withdrawn and ruminated over impulsive, disinhibited actions. She was also tearful and did not feel like herself. In addition, her diary recorded impulsiveness, irritability, oversensitivity, and marked suspicion. She became obsessed with killing herself and almost threw herself beneath a car or train. Case B, an otherwise peaceful 28-year-old woman, experienced severe road rage and actually grabbed a teenage boy and threatened to knock him down. On the SSRI, she felt aggressive and fearless. While emotionally disturbed and out of control (disinhibited), the two individuals nonetheless felt and appeared emotionally blunted.

The FDA conducted an epidemiological study comparing fluoxetine to a more sedating antidepressant, trazodone, in regard to spontaneous reports concerning hostility and intentional injury (Food and Drug Administration [FDA], 1991; available from http://www.breggin.com). When the FDA factored in the greater number of prescriptions for fluoxetine, it still had a higher frequency of reports for aggressive and violent behavior than trazodone. Furthermore, the reports began to accumulate before the controversy surrounding fluoxetine and violence had become public.

Fisher et al. (1993) conducted a phone survey of pharmacy patients taking various antidepressants and compared fluoxetine to trazodone. They concluded that fluoxetine caused "a higher incidence of psychologic/psychiatric adverse clinical events, including delusions and hallucinations, *aggression,* and *suicidal ideation*" (p. 235, emphasis added). In a follow-up study, Fisher et al. (1995) found that many of the same side effects reported in regard to Prozac were also reported for Zoloft. Both drugs

had equal numbers of reports for suicidality. Their research confirmed the hazards of SSRIs as a single class of drug with similar adverse effects.

## Antidepressant-Induced Mania in Nonbipolar Adult Patients

The following studies make clear that the newer antidepressants very commonly cause mania. Too many prescribing health care providers seem oblivious to this risk or explain it away as an "unmasking" of an underlying mania, a rationalization that has no scientific justification.

The initial euphoria associated with mild cases of drug-induced mania often offer relief and hope, however unrealistic, to the patients who experience it. If the euphoria does not progress to full-blown mania, it is likely to wear off, and then apathy becomes more dominant over time. This often leads patients to ask for one antidepressant after another in the hope of recapturing that brief "high."

Some of the most tragic medical-legal cases I have evaluated began with the patient in effect telling the doctor shortly after starting the medication, "I've never felt better in my life." Too often this signals the start of a drug-induced manic reaction, technically called a substance-induced mood disorder with manic features.

As documented in the FDA-approved labels for SSRIs, clinical studies conducted for the FDA approval process have shown increased rates of mania, but usually the rates are much less than those found in scientific reports based on prescribing practices and conditions in community settings. For example, in the relatively short 4- to 6-week trials used for the approval of Prozac for depression, slightly more than 1% of patients developed hypomania and mania (see, e.g., the 1990 label for Prozac for depression). An unpublished FDA report obtained through the Freedom of Information Act indicated that fluoxetine caused mania at a 3 times greater rate than tricyclic antidepressants given in the same studies (Kapit, 1986c). Furthermore, in 23 of the 33 cases, fluoxetine caused mania in patients with no past history of mania. In no cases did the older antidepressants cause mania in patients with no prior history. This data contradicts the commonly held clinical notion that SSRI-induced mania is limited to patients with an underlying bipolar disorder.

Martin et al. (2004) used an administrative national database of more than 7 million privately insured individuals, aged 5–29 years, to find new diagnoses of bipolar illness made in association with antidepressant treatment. They found a statistically significant correlation between exposure to all categories of antidepressants and the subsequent diagnosis of bipolar disorder. During a median follow-up of 41 weeks, manic conversion occurred in 5.4% of patients. The highest risk was

in 10- to 14-year-olds. This latter finding highlights the risk of treating children with antidepressants and helps to explain the escalating rate of bipolar disorder diagnoses in children. In my clinical experience, nearly all maniclike episodes in children, especially preadolescents, occur in reaction to prescribed medications, usually antidepressants and sometimes stimulants.

Preda et al. (2001) carried out a retrospective study of 533 psychiatric hospital admissions over a 14-month period and found that 43 (8.1%) could be attributed to antidepressant-induced mania and/or psychosis. The SSRIs (70%) were the predominant offenders, but Effexor, Serzone, Wellbutrin, and the other antidepressants were also represented. Twelve of the cases were new-onset mania or psychosis, again contradicting the mistaken notion that antidepressants only unmask preexisting mania. The three illustrative cases were severe, including two with marked suicidal potential. A 52-year-old married woman with a past history of bipolar disorder developed "command auditory hallucinations with suicidal content" (p. 31) while taking desipramine and fluvoxamine as well as risperidone, zolpidem, and oxazepam. A 42-year-old woman with a 1-year history of depression "began to experience derogatory and then command auditory hallucinations to kill herself" (p. 31) while on fluoxetine as well as lithium and thioridazine. Finally, a 49-year-old woman taking venlafaxine for "low mood and anxiety" (p. 31) developed symptoms of paranoia, feelings of doom, and a delusion that television messages were being directed at her. All three patients improved rapidly with treatment that included termination of the antidepressants.

Morishita and Arita (2003) carried out a retrospective review of 79 patients treated for depression with paroxetine and found that 7 (8.6%) developed hypomania or mania. Three of the seven patients were suffering from unipolar depression.

Howland (1996) found 11 cases of SSRI-induced mania among approximately 184 (6%) patients treated at a university clinic and hospital with a variety of SSRIs, including fluoxetine, paroxetine, and sertraline. The episodes were "generally quite severe" (p. 426). Eight of the 11 patients became psychotic, and 4 were so agitated that they had to be put in seclusion, even though they were probably receiving additional medication to control their iatrogenic mania.

Ebert et al. (1997) attempted to develop a rate estimate for severe mental aberrations caused by fluvoxamine. They carried out a prospective study of 200 inpatients over a total of 8,200 treatment days with the SSRI. Fourteen patients (17%) developed hypomania according to *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–IV*; APA, 1994) criteria. Three patients (1.5%) developed insomnia, agitation, confusion,

and incoherent thoughts. These patients became potentially violent and suicidal. One, a 35-year-old man, developed agitation and restless legs that progressed to insomnia, confusion, paranoid ideas, and hallucinations. He recovered after fluvoxamine was stopped. Another patient, a 38-year-old man, developed psychomotor agitation with insomnia that progressed to aggressiveness, incoherent thoughts, confusion, auditory hallucinations, and paranoid ideas. He also recovered when fluvoxamine was stopped. A third patient, another 35-year-old man, developed insomnia and then became agitated with restless legs and severely depressed with suicidal ideas. He was also incoherent and confused with paranoid ideas. He, too, recovered within a few days after stopping the medication. On the basis of the clinical descriptions, all three patients may have suffered from akathisia.

Ebert et al. (1997) summarized the syndrome of SSRI-induced manialike symptoms as consisting of insomnia, confusion, incoherent thoughts, agitation, hallucinations, and paranoid ideas. They observed that it was especially frequent in combination with other drugs. They considered it rare, but their data indicate that it was common. Adding up the 14 hypomanic patients and the 3 psychotic and aggressive patients, there were at least 17 severe psychiatric adverse reactions among 200 patients, for a rate of 8.5%.[2]

Troisi et al. (1995) used 20 mg/day of fluoxetine to treat 19 inpatients with mental retardation and epilepsy and a current or recent history of aggressive behavior. All of them were taking other medications as well. Using a standardized rating scale for assessing behavior before, during, and after treatment with fluoxetine, they found an increase in aggressive behavior in nine patients while taking the medication. Unexpectedly, the behavior decreased to *below* pretreatment levels after withdrawal of the fluoxetine. The authors concluded that fluoxetine can worsen aggression in patients with mental retardation and impulsive aggressive behavior.

Peyre et al. (1992) reviewed the histories of 189 patients treated with fluvoxamine and found a rate of 2.5% for *manic switches,* that is, the development of mania during treatment for major depression.

Henry and Demotes-Mainard (2003) reviewed the literature covering all categories of antidepressants in regard to conversion of depression to mania in unipolar as well as bipolar patients and during antidepressant withdrawal. They found that with tricyclic antidepressants, switches occurred shortly after the start of antidepressant treatment, with a mean of 5.8 weeks and a range from 3 to 10 weeks; with SSRIs, switches occurred later (mean of 12 weeks), and even later with second-generation antidepressants when given with mood stabilizers. They confirmed that patients with a personal or family history of manic episodes are more

prone to switch from depression to mania when taking antidepressants (see the following section).

Levy et al. (1998) carried out a blind retrospective chart assessment of 167 patients with anxiety disorders, rather than depressive disorders, to see if antidepressants were related to emergence of hypomania or mania in these patients. They reported, "Five patients (2.99%) were identified as having an episode of antidepressant-associated mania within 3 months of initiation of treatment."

Henry and Demotes-Mainard (2003) cited Koukopoulos and Koukopoulos (1999) concerning the dangerousness of driving an ordinary depression into a more serious agitated depression. They discussed the role of agitation in depression in causing aggression and suicidality. Many cases of violence and suicide occur when an otherwise apathetic depression is converted into an agitated depression by antidepressants.

Although the labels for all antidepressants mention the risk of inducing mania, none of them mention the high frequency of this adverse drug reaction, and none describe its potentially devastating impact on the victim's life.

## Manic Conversion (Switching) in Adult Bipolar Patients

There are many studies of patients diagnosed with bipolar disorder converting from depression to mania when being treated with antidepressants. The rates are astonishingly high, contradicting the common practice of giving antidepressants to patients who have had previous hypomanic or manic episodes.

Henry et al. (2001) followed 44 patients meeting *DSM–IV* criteria for bipolar disorder. They found that switches from hypomania to mania occurred in 24% of patients treated with SSRIs. Most (16%) had frank manic episodes. Goldberg and Truman (2003) reviewed the literature and found that about 20% to 40% of bipolar patients were converted into manic states by antidepressants of all classes. They concluded, "About one quarter to one-third of bipolar patients may be inherently susceptible to antidepressant induced manias."

Bipolar patients with so-called breakthrough major depressive episodes, despite adequate treatment, were placed in a randomized double-blind 10-week study and treated with bupropion, sertraline, or venlafaxine augmentation (Post et al., 2001). Switches to hypomania or mania occurred in 14% of the patients. Those who responded positively to the treatment were continued for 1 year in a blinded maintenance trial, and 33% switched into hypomania or mania. In a second phase of their antidepressant augmentation studies, 18.2% switched into hypomania or

mania during the acute phase of treatment and 35.6% during the continuation phase (Post et al., 2003).

Ghaemi et al. (2002), who reviewed 85 charts of outpatients with affective disorder seen in a clinic, concluded that 37% had an undiagnosed bipolar disorder and that 23% of them had developed "a new or worsening rapid-cycling course attributable to antidepressant use." They concluded, "Antidepressants seem to be associated with a worsened course of bipolar illness." Ghaemi et al. (2003) reviewed the literature and looked further into the issue of manic conversion. They drew the following conclusions:

> (i) There are significant risks of mania and long-term worsening of bipolar illness with antidepressants, (ii) Antidepressants should generally be reserved for severe cases of acute bipolar depression and not routinely used in mild to moderate cases and (iii) *Antidepressants should be discontinued after recovery from the depressive episode,* and maintained only in those who repeatedly relapse after antidepressant discontinuation (a minority we judge to represent only about 15–20% of bipolar depressed patients). (emphasis added)

Unfortunately, health care providers tell many of their patients, whether diagnosed with unipolar or bipolar depression, that they must take antidepressants for the remainder of their lives. Recognition that this promotes future manic reactions and even rapid cycling episodes should greatly reduce or stop this practice.

## COMPARING ANTIDEPRESSANT-INDUCED MANIA AND SPONTANEOUS MANIA

Stroll et al. (1994), from Harvard's McLean Hospital, compared the blinded charts of 49 consecutive inpatient admissions with antidepressant-induced mania with 49 matched cases of spontaneous mania over a 1-year period, from March 1, 1990, to February 28, 1991. The patients had been exposed to tricyclics ($n$ = 19), fluoxetine ($n$ = 13), monoamine oxidase inhibitors ($n$ = 8), bupropion ($n$ = 6), and mixed antidepressants ($n$ = 3). (It is striking that these doctors were already aware of the risk of Prozac-induced mania approximately 2 years after the January 1988 introduction of Prozac into the market. Meanwhile, too many health care providers remain in denial about this significant risk.)

The patients with antidepressant-associated manic states required monitoring and restrictions for shorter periods of time and had "significantly less severe levels of delusions, hallucinations, psychomotor

agitation, and bizarre behavior" than patients with spontaneous mania. Stroll et al. (1994) concluded, "Antidepressant-associated mania appears to be a milder and more time-limited syndrome than spontaneous mania and may represent a distinct clinical entity."

This study confirmed my own observations from dozens of cases, many seen for medical-legal evaluations, that patients with antidepressant-induced mania recover quickly when the offending agent is removed (Breggin, in press). The study also confirmed that antidepressant-induced mania is not merely an unmasking of a preexisting manic tendency; its clinical course is actually different.

Stroll et al. (1994) also observed that "MAOIs and bupropion may be associated with milder manic states than either tricyclic drugs or fluoxetine.... Clinical lore suggests that fluoxetine produces a more severe and prolonged manic state than other antidepressants, mainly because of its long duration of action." This underscores a risk seldom considered within psychiatry: that longer-acting medications, including extended-release delivery systems, cause a more severe risk of lengthy adverse reactions.

## ANTIDEPRESSANT-INDUCED MANIA DESCRIBED IN TWO STANDARD SOURCES

In a variety of forensic activities, including criminal and civil cases, the courts sometimes rely on authoritative or standard texts to demonstrate that the opinions rendered are supported by a significant portion of the medical or scientific community.

### *The Diagnostic and Statistical Manual of Mental Disorders*

The *DSM–IV* (1994) and the fourth edition text revision (*DSM–IV–TR*; APA, 2000) are written by committees made up of professionals considered experts by many of their colleagues in their respective fields. The conclusions therefore provide a professional consensus or body of conventional wisdom in psychiatry that can at times be useful in clinical practice and in forensics. Many aspects of the *DSM–IV* are controversial. However, when such an essentially conservative consensus document provides evidence for SSRI-induced adverse reactions related to mania, suicide, and violence, it should alert clinicians to the existence of these clinical phenomena and can provide an avenue for communicating in the courtroom concerning these risks.

The *DSM–IV* was published in 1994, several years after the advent of SSRI antidepressants, and makes clear that all antidepressants can

cause mania. The first SSRI, fluoxetine, was approved by the FDA in December 1987 and was in widespread use when the following observations about antidepressants were published in the manual.

The *DSM–IV* makes multiple references to the fact that antidepressants can cause mania or maniclike behavior. It states, for example, "Symptoms like those seen in a Manic Episode may be due to the direct effects of antidepressant medication" (p. 329). Similarly, it observes, "Symptoms like those seen in a Manic Episode may also be precipitated by antidepressant treatment such as medication" (p. 331). References to antidepressant-induced mania and mood disorder can also be found elsewhere in the manual as well (e.g., pp. 332 [note at bottom of table], 334, 336, 337, 351, 371, and 372). The *DSM–IV–TR* contains the same statements. It emphasizes that a diagnosis of mania or bipolar disorder should not be made when the symptoms hypomania or mania first appear while taking a medication that can cause them and "usually disappear when the individual is no longer exposed to the substance." Of great clinical importance, it adds, "but resolution of symptoms can take weeks or months and may require treatment" (p. 191).

The association between mania and antisocial behavior, including violence, is underscored in the *DSM–IV.* Aggression is specifically mentioned as a feature of manic behavior. It is noted that "antisocial behaviors may accompany the Manic Episode," "ethical concerns may be disregarded even by those who are typically very conscientious," "the person may become hostile and physically threatening to others" and "physically assaultive," and "the mood may shift rapidly to anger or depression" (p. 330). The very next page in the *DSM–IV* repeats the reminder that "symptoms like those seen in a Manic Episode may also be precipitated by antidepressant treatment such as medication" (p. 331).

Mania is characterized by "increased involvement in goal-directed activities" (*DSM–IV,* p. 328). Therefore the individual does not lack the capacity to plan and carry out inappropriate or destructive actions or to attempt to cover them up once they have been enacted. To the contrary, individuals undergoing mania often feel driven to carry out elaborate plans, however bizarre, violent, or doomed they may be.

According to the *DSM–IV,* an "elevated, euphoric or irritable mood" is sufficient to qualify for a diagnosis of substance-induced mood disorder with *manic features* (pp. 370, 375; *DSM–IV–TR,* pp. 405–406). This descriptor for manic features is sufficiently broad to encompass some or all symptoms associated with stimulation and aggression. Therefore an SSRI-induced stimulant-like or aggressive reaction can often be diagnosed as a drug-induced mood disorder with manic features. When drug-induced mood swings occur from mania to depression, sometimes

accompanied by switches from violence to suicidality, the diagnosis can include both *depressive* and *manic* features.

*Irritability,* as used in the *DSM–IV,* has a more ominous meaning than *irritability* as used in ordinary language. During a discussion of depression, the *DSM–IV* refers to the symptom of "increased irritability (e.g., persistent anger, a tendency to respond to events with angry outbursts or blaming others, or an exaggerated sense of frustration over minor matters)" (p. 321). Many individuals who commit aggression while under the influence of SSRIs will qualify for a substance-induced mood disorder with manic features on the basis of their obvious increase in irritability while taking the drug.

The capacity for SSRIs to induce akathisia—and for akathisia to cause suicidality, aggression, and a worsening mental condition—is also recognized in the *DSM–IV* and the *DSM–IV–TR* in the section dealing with neuroleptic-induced akathisia. The *DSM–IV–TR* observes, "Akathisia may be associated with dysphoria, irritability, aggression, or suicide attempts." It also mentions "worsening of psychotic symptoms or behavioral dyscontrol." It then states, "**Serotonin-specific reuptake inhibitor antidepressant medications** may produce akathisia that appears identical in phenomenology and treatment response to Neuroleptic-Induced Acute Akathisia" (p. 801).

### *Practice Guidelines for Major Depressive Disorder in Adults*

The APA (1993) practice guidelines, like the *DSM–IV,* attempt to arrive at a consensus among experts. The emphasis, however, is on treatment, rather than diagnosis. Like the *DSM–IV,* the practice guidelines were published after the SSRIs were in use.

Using several citations from the literature, the practice guidelines state the following:

> All antidepressant treatments, including ECT, may provoke manic or hypomanic episodes. Individuals with a history of mania or hypomania are at particular risk for this untoward effect, although it may occur even in patients with no such history; this complication is estimated to occur in 5%–20% of depressed patients treated with antidepressants. (p. 22)

Recognition of antidepressant-induced maniclike reactions and akathisia in two of the most commonly used manuals of psychiatric diagnosis spanning 1993–2000 has important implications for clinical practice and forensics. Practitioners should be aware that these adverse drug reactions occur and that the patient should be diagnosed with

a substance-induced disorder or with akathisia, rather than with a primary psychiatric disorder such as bipolar I disorder or an anxiety disorder. It should alert practitioners to the need to stop antidepressants at the first sign of initial or recurring hypomanic and manic symptoms or akathisia. In forensics, recognition of the existence of these adverse drug reactions can help establish causality in malpractice, product liability, and criminal cases when SSRIs induce abnormal mental and behavior reactions. The body of literature reviewed in this report and the confirmation found in the *DSM–IV* and *DSM–IV–TR* help to establish a standard requiring that physicians be aware of the potential for these drugs to cause mania and akathisia with the associated risks of suicidality, violence, and extreme or bizarre behavior.

## STUDIES RELATED TO SSRI-INDUCED ABNORMAL BEHAVIOR IN CHILDREN

Many cases of SSRI-induced violent or suicidal behavior involve children or young adults. However, even in regard to cases involving older persons, the literature on children and youth is important. Adverse behavioral effects tend to show up more frequently and severely in children, providing a magnified view of the same or similar effects that the drugs are causing in adults.

### Clinical Case Studies Involving Children

As previously noted, Medwar et al. (2002) and Medwar et al. (2003–2004) described numerous public reports involving adults and children that were sent by e-mail to the British TV show *Panorama*.

An example of Prozac-induced mania with potential violence was presented by Jerome (1991), who described a 10-year-old boy who became depressed when his family moved to a new neighborhood. The youngster was placed on 20 mg of Prozac by his family physician and immediately became "hyperactive, agitated . . . [and] irritable," with pressured speech. He gained energy, required less sleep, and developed a "somewhat grandiose assessment of his own abilities." Then he began to make anonymous phone calls, threatening to kill a stranger in the neighborhood. When the telephone calls were traced back to him, the Prozac was discontinued, and all of the hypomanic symptoms resolved within 2 weeks.

A single case study involving paroxetine described a 16-year-old who became manic with angry outbursts after 3 weeks on the drug (Oldroyd, 1997). Beech (2000) described an 8-year-old girl who became hypomanic

on sertraline. The adverse drug reaction had been originally misdiagnosed as attention-deficit/hyperactivity disorder. Diler and Avci (1999) described three cases of paroxetine-induced mania in children, two aged 9 and one aged 10, who were being treated for obsessive–compulsive disorder. Guile (1996) described a case of activation that fell short of the standards of hypomania in a 15-year-old treated with sertraline. Kat (1996) reported on two teenage girls who became manic on sertraline. One, age 14, developed the mania after two doses and rapidly remitted after stopping the drug.

Heimann and March (1996) reported about a 15-year-old with a long history of "chronic, low grade depression" who became manic after 1 month on sertraline. Her behaviors included "physical aggression toward a peer, intoxication with alcohol, and sexual promiscuity." Behaviors such as this can, unfortunately, ruin a child's life.

Jafri and Greenberg (1991) described the case of a 15-year-old boy who became psychotic "directly related to his receiving fluoxetine." After his medication was stopped, he improved over about 1 week's time. Hersh et al. (1991), physicians from Cornell University Medical College, described an 11-year-old girl who developed a delusional system on Prozac.

In another single case study, a 17-year-old with mild retardation was started on fluvoxamine 50 mg to treat depression and anxiety (Sim, 2000). After a single dose, he developed increasing agitation and insomnia, followed in the next 24 hours by auditory and visual hallucinations, a fearful mood, and paranoid delusions about the devil. He required hospitalization and was treated with an antipsychotic drug. The authors believed that fluvoxamine caused the acute psychosis. As a third example of single-case clinical reports, Wilkinson (2000) described a character change with increased aggression in a 15-year-old boy taking fluoxetine. Uncharacteristically, he struck another youngster in the face. Fluoxetine was stopped, and within a week, he was no longer aggressive. The author identified blunting, rather than akathisia, as the motivational state.

Koizumi (1991) described a 13.5-year-old boy who developed manic symptoms on 40 mg/day of fluoxetine. These side effects disappeared when the dose was lowered to 15 mg/day. However, after 15 months of fluoxetine treatment, he then developed "explosive, angry outbursts over minor matters, which was totally unlike him" (p. 695). He then experienced a "weird" and ego-alien voice telling him to kill himself. He recovered from these symptoms within 10 days of stopping fluoxetine.

Pravin et al. (2004) described four patients, age 6–15, who developed mania on citalopram. One child first developed mania when exposed to fluoxetine and then again when given citalopram. Three of the children required additional treatment with lithium or antipsychotic drugs, and the fourth ended up being given ECT.

## Epidemiological Studies and Clinical Trials Involving Children

Chapter 6 described the meta-analyses used by the FDA to determine that the rate of suicidality was doubled in children taking SSRIs in placebo-controlled clinical trials.

Earlier, this chapter reviewed Healy et al.'s (2006) finding that clinical trials in paroxetine for children found an increased number of hostile events and that "the rates were highest in children with obsessive compulsive disorder (OCD), where the odds ratio of a hostile event was 17 times greater (95% confidence interval [CI], 2.22–130.0)."

Numerous epidemiological and clinical study reports confirm that SSRIs cause a high rate of mania in children and youth. Again, as noted earlier in this chapter, Martin et al. (2004) used a national database of more than 7 million privately insured individuals, aged 5–29 years, and found that the highest risk of manic conversion while taking antidepressants was in the 10- to 14-year-old group.

According to the FDA-approved label for fluvoxamine (Luvox in the *Physicians' Desk Reference,* 2001), the SSRI causes a 4% rate of mania in children under age 18, compared to no cases of mania produced in a similar group of children on placebo. The rate was at least 4 times greater than in adults (see Breggin, 2002a, for a more complete analysis of the Luvox label). Moore (2004) analyzed adverse event reports made to the FDA concerning children and adults in association with the six most commonly prescribed antidepressants: Zoloft, Paxil, Prozac, Celexa, Wellbutrin, and Effexor. He reported the following:

- Suicidal/aggressive behaviors were reported in children at more than twice the expected rate given the drugs' medical use in this age group. Suicidal/aggressive behaviors were also reported more frequently in children when compared to other types of adverse events, which were reported in similar proportions in both adults and children.
- Taken together, suicidal/aggressive behaviors and mania/euphoria describe potentially dangerous changes in mood or personality suspected of being associated with the six target drugs. In children, such reports accounted for 24% of all reported adverse events.

A controlled clinical trial found that fluoxetine caused a 6% rate of mania in depressed children and youngsters age 7–17 (Emslie et al., 1997). The reactions were severe enough to cause the children to be dropped out of the trials. By contrast, none of the depressed youngsters

on placebo developed mania. Emslie, as already noted, is closely tied to drug companies and heavily promotes their products. The 6% mania rate is, of course, extremely important and deserved to be mentioned in the abstract, discussion, and conclusion, but it is buried in the discussion of dropouts. I only found it, after a careful search of the article, because I had been alerted in advance by a report he gave to a psychiatric newspaper 2 years earlier (Sherman, 1995). In that earlier report, Emslie also mentioned that several children became aggressive on Prozac, but that is nowhere to be found in the published report.

In a most remarkable study, especially given the prodrug bias of the investigative team, Wilens et al. (2003), of the Clinical and Research Program in Pediatric Psychopharmacology at the Massachusetts General Hospital and Harvard Medical School, systematically evaluated 82 charts of children treated with SSRIs for depressive or OCD symptoms over a mean period of 26.9 months. The drugs included sertraline, paroxetine, fluoxetine, fluvoxamine, and citalopram. The mean age of the children was 12.2 years. Psychiatric adverse events (PAEs) were found in 22%, "most commonly related to disturbances in mood." The onset was typically 3 months after the beginning of treatment. Remarkably, "re-exposure to an SSRI resulted in another PAE in 44% (n = 13) of the group."

The breakdown of PAEs caused by SSRIs in this study was ominous. Of the 82 children, 21% developed *mood disorders*, including 15% who became *irritable,* 10% who became *anxious,* 9% who became *depressed,* and 6% who became *manic*. In addition, 4% of the children became *aggressive*. *Sleep* disorders afflicted 35% of the children, including 23% feeling *drowsy* and 17% experiencing *insomnia*. Finally, 10% became *psychotic!*

In a sane medical community, this one study would have raised a hue and cry of concern, leading to the complete abandonment of SSRI antidepressants for children, especially given their lack of efficacy. There is not a hint from this Harvard research team that these findings ought to slow down the drugging of children.

A team at the University of Pittsburgh (Go et al., 1998) reviewed the cases of 40 youths, age 11–17, treated with SSRIs for OCD. Twenty received SSRIs, and 20 did not. In an open-label clinical treatment regimen, 30% (6 of 20) of the patients treated with SSRIs developed hypomanic or manic symptoms. Five were on fluoxetine and one on sertraline.[3] According to the authors, "symptoms included impulsivity, grandiosity, pressured speech, and disinhibition." They concluded, "Clinicians are advised to be aware of the risk and to be vigilant in monitoring manic and hypomanic behaviors when using SRIs [*sic*] to treat OCD in youth, even with low doses and gradual dose elevation."

Jain et al. (1992) made a retrospective examination of the medical charts of children and young men age 8–19 who had taken fluoxetine in a university clinic setting. The researchers found that 23% of fluoxetine-treated young people developed mania or maniclike symptoms. Another 19% developed drug-induced hostility and aggression, including a grinding anger with short temper and increasing oppositional behavior.

Constantino et al. (1997) prospectively studied the course of aggressive behavior in 19 SSRI-treated psychiatrically hospitalized adolescents who were not preselected for potential aggressiveness. They reported symptoms of physical aggression toward self or others in 12 of 19 patients on SSRIs. Of the 19 patients, 13 were assessed both on and off SSRIs. On the SSRIs, there was increased verbal aggression ($p = 0.04$), increased physical aggression toward objects ($p = 0.05$), and increased physical aggression toward self ($p < 0.02$). No increase was observed in physical aggression toward others. The authors warned against using SSRIs to treat aggression in children.

Another study of children and youth age 8–16 in a university setting found that 50% developed two or more abnormal behavioral reactions to fluoxetine, including aggression, loss of impulse control, agitation, and maniclike symptoms (Riddle et al., 1990–1991). The effects lasted until the fluoxetine was stopped.

A second research study from the same university setting described a number of youngsters (6 of 42, or 14% in their cohort) who became aggressive and even violent while taking fluoxetine (King et al., 1991). The researchers hypothesized that fluoxetine caused aggressive behavior by means of drug-induced activation (stimulation) or a specific serotonergic-mediated effect.

The report by King et al. (1991) provided a clinical window into the development of obsessive violence and a school-shooter mentality. A 12-year-old boy on fluoxetine developed nightmares about becoming a school shooter and then began to lose track of reality concerning these events. This case occurred in a controlled clinical trial, and the investigators did not know that the child was getting fluoxetine until they broke the double-blind code. The child's reaction occurred long before any of the well-known school shootings had taken place. Therefore his reaction was not inspired by the school shootings—it was not a copycat fantasy:

> Thirty-eight days after beginning the protocol, F. experienced a violent nightmare about killing his classmates until he himself was shot. He awakened from it only with difficulty, and the dream continued to feel "very real." He reported having had several days of increasingly vivid "bad dreams" before this episode; these included images of killing

> himself and his parents dying. When he was seen later that day he was agitated and anxious, refused to go to school, and reported marked suicidal ideation that made him feel unsafe at home as well. (p. 180)

The child was hospitalized first for 3 days, and then for 17 days. He gradually improved. Then, 3 weeks after his last hospitalization, his local physician—not one of the clinical investigators—put him back on fluoxetine. The child became acutely suicidal, until the fluoxetine was stopped a second time.

This individual report is important for a variety of reasons:

- It took place in a double-blind controlled clinical trial.
- Entirely new symptoms related to violence developed on the drug (challenge).
- The symptoms terminated after stopping the drug (dechallenge).
- Some of the symptoms resumed on starting the drug again (rechallenge).
- The symptoms cleared for a second time after the drug was again stopped (demonstrating dechallenge for a second time).

## Antidepressant-Induced Apathy in Children

Reinblatt and Riddle (2006) stated, "Selective serotonin reuptake inhibitor (SSRI)-induced apathy is characterized by a lack of motivation that is not a result of sedation or symptoms of depression." In a review of 43 participants in a fluvoxamine pediatric research project, the authors identified two (5%) cases of apathy, one in a 9-year-old and the other in a 16-year-old, neither of whom was depressed. They found that "similarities to existing reports included: Lack of insight, delayed onset, dose dependency, and reversibility with SSRI dose reduction or discontinuation."

The 16-year-old girl's personality changed in ways that I witnessed, with more tragic results. Her friends worried that her personality had changed as she became socially withdrawn, began to take unusual risks, and was overly confident with strangers (a grave danger in a teenage girl). Meanwhile, according to Reinblatt and Riddle (2006), "she was paradoxically simultaneously amotivated to do her usual daily activities." In the case of a 9-year-old boy, when his dose was increased he "presented with extreme amotivation and apathy, not caring about anything; he did not want to go to school and didn't care about typical interests."

Reinblatt and Riddle (2006) concluded, "SSRI-induced amotivational syndrome is a more important and frequent clinical issue than suggested by the paucity of published reports. It may go undetected in its milder forms owing to delayed onset and variable severity of presentation."

Garland and Baerg (2001) described cases of apathy, one accompanied by disinhibition, in a child and four adolescents. A 14-year-old boy on paroxetine became so flat that his face became masklike, similar to parkinsonism, but without any other signs of that disorder. His parents and the clinician were concerned about his loss of interest, but typical of severe medication spellbinding, "the patient was quite satisfied with his life and did not recognize a problem."

A 15-year-old boy on fluoxetine became "bizarrely" blasé about his participating in competitive sports and lost interest in schoolwork. He began neglecting his chores, losing items of clothing, and was generally criticized as irresponsible by the adults in his life, until the syndrome was recognized. He remained unconcerned. According to Garland and Baerg (2001), "when the parents confronted him about these behaviors, he was calm, unconcerned, and did not seem to perceive a problem." His medication was discontinued, and he gradually returned to normal over a month. However, he then asked to be resumed on the medication at a lower dose to control his anxiety, and "positive benefits returned without the amotivational features." Consistent with the brain-disabling principle, I strongly suspect, however, that the boy was simply experiencing a relatively small induction of apathy that he perceived as reducing his anxiety.

A 14-year old boy taking fluoxetine again demonstrated medication spellbinding (Garland et al., 2001):

> In a follow up visit 6 weeks after the dose increase, his affect was flat, and he appeared emotionally disconnected and apathetic. However, he reported that he felt "fine" and was not in any way unhappy or distressed about his situation despite a large drop in his grades.

A 10-year-old female taking paroxetine developed disinhibited behavior after a dose increase (Garland et al., 2001):

> She had interpersonal boundary problems, asking people inappropriate personal questions, having poor judgment and thereby insulting and alienating both peers and adults. This was quite out of character for her, as she previously had been quite polite and sensitive to others. She did not seem to have insight into how inappropriate her statements were at the time.... When describing her actions to the psychiatrist, she showed no appropriate embarrassment. She appeared unusually unconcerned and flat in affect.

Consistent with the other cases in this section, she showed no signs of mania to account for her disinhibition. She was, instead, apathetic in appearance and affect.

The fifth case, concerning a 17-year-old girl, described how she lost interest in socializing and in sports, even though she was realistically working toward a college athletic scholarship. She appeared apathetic and flat but had few complaints, except for tiredness and mild hypersomnia. Consistent with the brain-disabling principle, her parents were "far less concerned about her as she was no longer volatile and there was less conflict about curfews as she was less interested in going out with her friends" (Garland and Baerg, 2001). Fortunately, her psychiatrist became concerned about her and reduced the medication (while adding bupropion). However, according to Garland and Baerg (2001), "her lack of participation in sports during a crucial part of the session had a lasting impact on her career plans." She did not go to college.

As all of the above cases indicate, patients commonly lack insight into how apathetic they have become. In my clinical experience, even when they identify apathy and ask to be withdrawn from their antidepressants, most children and adults are surprised and even mortified as they realize in what an apathetic state they had been when medicated. SSRI-induced apathy is a profound example of the brain-disabling effects of psychiatric medications, including medication spellbinding. The disabling effects occur along a continuum so that a mild degree of apathy is often perceived by others and by the patient as an improvement, while a severe degree will be seen by others, but not necessarily by the patient, as an adverse drug effect. When accompanied by disinhibition, apathy can lead to especially tragic results (Breggin, in press). As in the case of the girl who lost out on her scholarship and never went to college, even without disinhibition, even a relatively brief period of apathy can have lifelong negative results.

## DO ANTIDEPRESSANTS WORK AT ALL?

As documented in chapter 6, the scientific literature demonstrates, and the FDA admitted at its 2004 hearings, that there is no substantial evidence supporting the usefulness of antidepressants in treating depression in children. What about the treatment of adults? Is it possible that the antidepressants are not antidepressants at all?

At the height of enthusiasm for the older tricyclic antidepressants, Baldessarini (1978) found little scientific confirmation. Spontaneous remission and placebo effect, he concluded, might account for why it usually takes several weeks to obtain a positive response. Even in more severe depressions, he noted, the spontaneous remission rate can exceed 50% in a few months. Similarly, Klerman and Cole (1965), strong drug advocates, recognized that "depressions, on the whole, are among the

psychiatric conditions with the best prognosis for symptomatic recovery, with or without treatment." They cited data predating the drug era that show improvement rates of "44% of all patients within the first year and 56% recovery eventually over a longer time period." Like Baldessarini (1978), they observed that the time lapse before the antidepressants are alleged to work may coincide with the period of spontaneous recovery.

Fisher and Greenberg (1989, 1995) approached the subject of antidepressant efficacy with a systematic analysis of the existing controlled studies. They found that antidepressants were little or no better than placebo. When the placebo had side effects, such as dry mouth or sedation, it convinced the observers and the subjects that the placebo was really an active drug. As a result, in these studies involving a placebo with side effects (an active placebo) there was no difference between the medication and the placebo. Researchers lead by David Antonuccio have reviewed the existing clinical studies and literature concerning antidepressant effectiveness and have found that any positive drug effect is negligible (Antonuccio et al., 1994, 1995; Antonuccio et al., 2002). Their research also confirmed that psychotherapy is as good as, or better than, antidepressants. It is obviously much safer.

In 1994, in *Talking Back to Prozac,* I first brought to light the failure of Prozac to prove its effectiveness in the studies done for FDA approval (see Breggin et al., 1994a). Then, in 2002, a team led by psychologist Irving Kirsch at the University of Connecticut published an analysis of efficacy data submitted to the FDA between 1987 and 1999 for six of the most commonly prescribed antidepressants: Prozac, Paxil, Zoloft, Effexor, Serzone, and Celexa (Kirsch et al., 2002).

Each of the drugs had been approved based on a drug company submitting *two* positive studies to the FDA. But all of the companies conducted numerous additional studies before they were able to obtain the required two that seemed positive. So Kirsch et al. looked at *all* the antidepressant studies—not just the ones submitted for approval.

Kirsch et al. obtained 47 studies, an average of almost eight per drug, conducted as a part of the FDA approval process. After examining all of the studies, they found that any beneficial or positive effects in comparison to placebo were negligible.

## THE ELDERLY

This chapter has emphasized the poor risk:benefit ratio in giving antidepressants to children and adults, but the elderly are probably most vulnerable of all to their adverse effects. The practice of prescribing antidepressants to older patients with dementia is particularly inappropriate

since the drugs worsen their cognitive function (Deakin et al., 2004). In a study of patients over age 55 seen at a day hospital from 1986 to 2005, including 824 patients, 600 of whom received antidepressants, apathy subscales of two depression-rating instruments were significantly correlated with the use of SSRI antidepressants (Wongpakaran et al., 2007). Wongpakaran et al. (2007) concluded, "Even though depression was improved in elderly patients receiving antidepressants, the degree of apathy appeared to be greater in patients who were treated with SSRIs than in patients who were not. Frontal lobe dysfunction due to alteration of serotonin was considered to be one of the possibilities."

## PROFESSIONAL REACTIONS

How do psychiatry and the psychopharmaceutical complex react to the mounting evidence that antidepressants are not only dangerous, but also useless for both adults and children? They generally ignore it. However, the Kirsch et al. (2000) study has received positive recognition from those few professionals brave enough to face the facts, including Angell (2007), the former editor of the *New England Journal of Medicine,* and Charles Medwar (Medwar et al., 2004, p. 57), the respected British researcher and public safety advocate.

In 2006, British psychiatrist Joanna Moncrieff and Kirsch published another review and analysis of antidepressant effectiveness in the *BMJ*. They focused on studies conducted on SSRIs such as Prozac, Zoloft, and Paxil and concluded that these drugs "do not have a clinically meaningful advantage over placebo."

It is a sad, ironic, and tragic tale: It is impossible to prove that antidepressants actually relieve depression, but it is relatively easy to demonstrate that they can worsen depression and cause mania, violence, and suicide. If my colleagues wanted to be scientific about it, they would call them *depressants,* rather than *antidepressants,* and take them off the market.

## UNDERLYING ANTIDEPRESSANT-INDUCED BRAIN DAMAGE AND DYSFUNCTION

### Permanent Neurological Adverse Effects

A large percentage of patients suffer from neurological sexual dysfunction as a result of taking the SSRI antidepressants. Estimates vary widely but are way beyond the small percentages suggested on SSRI labels. Baton (2006) noted rates as high as 80% and suggested that a realistic estimate probably lies between 30% and 50%.

In my clinical experience, many, and probably most, patients taking SSRIs suffer from drug-induced sexual dysfunction due to suppressed sexual appetite, inhibited sexual function, and emotional withdrawal, but the SSRIs often make them too apathetic or disinterested to complain to their doctors. They are too medication spellbound to care about their sexual and love life or the effects on their loved ones and partners.

Unfortunately, reports have appeared suggesting that these sexual disorders may remain persistent after termination of the drug, leaving an otherwise recovered individual suffering from lifelong sexual dysfunction (Csoka et al., 2006).

The risk of causing EPS, another SSRI-induced neurologist disorder, was apparent from early on. The FDA's Kapit (1986) warned, "It is possible that a tardive syndrome related to fluoxetine may exist. It will be necessary to be on the lookout for such events" (p. 32). By January 1993, more than two dozen reports of Prozac-induced tardive dyskinesia had reached the FDA (1993), but the profession has not taken much notice. Numerous case reports confirm that the SSRIs can produce persistent extrapyramidal reactions, including tardive dystonia with painful and disabling spasms of the neck and shoulder musculature.

In his review of the literature published in 1996, Leo already found 42 articles reporting 71 cases of motor symptoms that appeared for the first time during SSRI use. Akathisia was reported in 32 cases, dystonia in 20, parkinsonism in 10, tardive dyskinesia–like movements in 8, and tremors in 7. Several patients had combined disorders.

Gerber and Lund (1998) reviewed the literature and located 127 case reports of SSRI-induced abnormal movements. These included akathisia (agitation with hyperactivity), tardive dyskinesia, parkinsonism, dystonia (muscle spasms), bruxism (tooth grinding), and related disorders. They found many additional case reports from the drug manufacturers, including 516 cases of parkinsonism and 76 cases of tardive dyskinesia. The term *tardive dyskinesia* is usually reserved for cases that are irreversible.

SSRIs can cause most of the neurological disorders associated with the neuroleptic drugs, including a serotonergic syndrome that resembles neuroleptic malignant syndrome. The similar result is probably due to the capacity of SSRIs to impact the dopaminergic system. Recent studies (e.g., Miura et al., 2007) continue to confirm the early clinical suspicion that SSRIs were not quite as selective as their name implies and in fact impinge on other neurotransmitter systems.

## The Brain Resists the Impact of SSRIs

Theoretically, Prozac is supposed to make more serotonin available in the synapses, but the brain tries to overcome its effects. When an SSRI

antidepressant blocks the removal of serotonin from the synapse, the brain senses that too much serotonin is pooling in the region, and it shuts down the production and release of the serotonin into the synapse. Two of Eli Lilly's top researchers, Ray Fuller and David Wong, published a paper in 1977—more than a decade before Prozac reached the marketplace—showing how the brain compensated for SSRI overstimulation by inhibiting the production and release of serotonin and the overall activity of the serotonergic system. When Prozac and similar drugs were given to animals, instead of the anticipated overstimulation, there was a tendency for the system to shut down:

> When fluoxetine or other effective but less specific serotonin uptake inhibitors are given, a rapid decrease in serotonin turnover occurs and the rate of firing of single neural units in the serotonin rich raphe area of the brain is reduced. This decrease in serotonin turnover and release may be a compensatory mechanism in response to an enhanced action of serotonin on the synaptic receptors.

Notice that the actual results are completely contrary to what most health care providers imagine. Prozac and the other SSRIs do not cause an immediate enhancement (e.g., overstimulation) of the serotonergic system; they cause a compensatory shutdown of the system. On the basis of the drug company–sponsored theory that sluggish serotonin causes violence and suicide, this means that an initial dose, and probably dose changes, can cause extreme sluggishness in the system, with the potential for violence and suicide.

Later studies showed that the inhibition lasts about 10 days, but there is evidence that it may last longer in other parts of the brain. Thus, from the start, Eli Lilly knew that it was creating complex, unpredictable biochemical imbalances and a roller-coaster situation in which the drug would block the removal of serotonin and the brain would resist the process.

Then, in 1999, Wegerer and a team from Germany and the United States discovered that the brain had yet another way of compensating for the SSRI-induced blockade of the transporter system that removes serotonin from the synapse. To envision the chemical transporter system and the antidepressant blockage, imagine a conveyor belt that removes valuable rocks from deep within a quarry. Putting other rocks onto the transporter system (conveyor belt) to take up the space would obviously interfere and slow down the conveyer process. In effect, Prozac, Zoloft, Effexor, and other SSRIs jump onto the transporter system, blocking its function of removing serotonin from the synapse.

SSRIs are potent occupiers (blockers) of the serotonin transporter system (Meyer, 2007; Meyer et al., 2004). Meyer et al. (2004) used PET

to study the degree of occupancy in normal volunteers and in subjects with mood and anxiety disorders after 4 weeks of exposure to four commonly prescribed SSRIs. They achieved 80% occupancy of the transporter system receptors at "minimum therapeutic doses." They believed that this blockade was important for the "therapeutic effect." But how does the living brain respond to being occupied in this manner?

When antidepressants block the function of the transporter system, Wegerer et al. (1999) found, the transporter system grows strong in response by increasing in density. This effect was found in young rats after only 2 weeks of exposure to Prozac.

The Wegerer et al. (1999) study found that the increased transporter system density persisted for at least 90 days into the adulthood of the rats. These abnormalities were found in the most highly developed portions of the rat brain, the frontal lobes. Wegerer et al. were unusually brave and ethical in pointing out that these findings indicated a risk for children taking SSRIs.

After exposure to Prozac and other SSRIs, yet another compensatory biochemical mechanism called *down-regulation* quickly begins reducing the number of receptors in the brain for serotonin (de Montigny et al., 1990; Wamsley et al., 1987; Wong et al., 1981; Wong et al., 1985). After weeks or months of exposure, a large percentage of the receptors actually become undetectable; that is, they disappear, resulting in reduced responsiveness to serotonin *(subsensitivity)*. Wamsley et al. (1987) found that at lower doses, there were both increases and decreases in receptor density in various areas of the brain, indicating the complexity of the brain's response (see also Fuller et al., 1974).

Down-regulation begins as soon as 2 days after exposure to Prozac in rats. Up to 60% of some subtypes of serotonin receptors can disappear. The reduction in receptors and the resulting down-regulation of serotonergic activity is widespread throughout the brain, involving the frontal lobes and cortex—the centers that regulate the emotional and intellectual life of the individual. In the process, the capacity of the serotonin system for activation is reduced, theoretically producing a sluggish system.

A number of studies show lengthy periods of time—weeks and months—during which receptor loss does not recover, but no systematic attempts have been made to determine if recovery ever occurs. Longer studies would not be hard to conduct. Nonetheless, Ray Fuller, Lilly's head of research, declared in deposition testimony that he knew of no studies concerning recovery of down-regulated serotonin receptors. Asked if he thought these experiments were important, Fuller sounded a little flummoxed as he responded, "I don't see that that would be of any value to know that" (Fuller, 1994, p. 266). Oblivious of the potential

consequences, health care providers too often urge their patients to stay on SSRI antidepressants indefinitely.

Clearly antidepressants do not correct biochemical imbalances in the brain; they cause them. They change the brain for the worse in ways that can persist indefinitely after the drugs are stopped. At no point in time can we know what the exact biochemical imbalance in the brain looks like, and it probably varies in different regions and at different times as the drugs produce their effects and the brain fights back in its varied ways.

Advocates of SSRI antidepressants often assert that depression and suicide, and even violence, may be linked to an underactive serotonin system, and that SSRIs activate the system by blocking the removal of serotonin from the synapse. In reality, the antidepressants produce unpredictable results with an overall impact that cannot be measured in the living brain, even with animal experiments. At times, when the brain's compensatory mechanisms overcome the drug effects, the result of taking SSRIs is likely to be a sluggish serotonergic system. This might account for why so many bizarre and destructive acts are committed shortly after starting the medication, when the initial compensatory shutdown takes place in the serotonin system. All this is speculation, but it is worth underscoring that the biochemical justifications for using antidepressants make no scientific sense.

## Causing Brain Dysfunction and Shrinkage

A group from Wayne State University School of Medicine studied the volume of the thalamus in children diagnosed with OCD before and after being exposed to Paxil and found a loss of brain tissue (Gilbert et al., 2000). Instead of raising an alarm, the authors tried to justify the use of drugs in children on the grounds that in OCD children, the thalamus is too large, and the drugs correct the problem by shrinking it. This is very similar to the argument that lobotomies killed bad brain cells or dampened an overactive emotion-regulating system, and indeed, the thalamus connects to the frontal lobes through some of the same nerve tracts that are attacked in lobotomy. Shrinking the thalamus of children is very likely to have lobotomy-like effects, an especially dreadful example of the brain-disabling principle of psychiatric treatment.

By contrast, Yale researchers found that Prozac given to rats for a mere 2–4 weeks caused a proliferation of neurons in the temporal lobes (Malberg et al., 2000; Weaver, 2000, for the accompanying press release quoting the researchers). While the Wayne State researchers argued that loss of neurons might be good for children, the Yale researchers argued that an abnormal increase in the growth of brain cells might be good for

people. To prove their point, the researchers pointed out that shock treatment causes an abnormal growth of cells in the same temporal region. They do not make the obvious connection: The temporal lobe plays a major role in memory function, shock treatment damages the temporal lobe, and postshock patients have devastating, often permanent memory loss (chapter 9). The abnormal growth in the temporal lobes may explain why, in my clinical experience, many patients begin to complain that their memory no longer functions as well after prolonged exposure to SSRI antidepressants.

Another study of the impact of Prozac on the rat brain found grossly suppressed cerebral function as measured by sugar metabolism in the brain (Freo et al., 2000). In two regions of the brain, metabolism was reduced by 23% and 32%, indicating a substantial compromise of function. Reductions occurred throughout the brain, including the cerebral cortex and basal ganglia. The authors opined that these gross malfunctions may be the source of the so-called therapeutic effect, indirectly confirming the brain-disabling principles of psychiatric treatment.

It is not likely that neurons or other cells will turn out to appear or function normally when they were stimulated to grow by a toxic agent. A study in *Brain Research* found that single doses of Prozac, Luvox, or the older antidepressant desipramine caused abnormal neuronal growth in the temporal region of rats (Norrholm et al., 2000). The abnormalities persisted until the end of the study 3 weeks after the last doses. The authors offered the opinion that these effects could disrupt neuronal development into young adulthood. Kalia et al. (2000) found that 4 days of high doses of serotonin-stimulating drugs, including Zoloft and Prozac, caused abnormalities in the body and the axons of neurons. Prozac more often produced a large swelling of the neuronal body. Zoloft caused swollen and truncated axons and, in some cases, made the cells look corkscrew in form. The study raises questions about the survivability of the damaged cells, but there can be no doubt that they were severely injured and malfunctioning. The researchers suggested that their research may reflect on the potential effects of chronic SSRI use in humans.

Meanwhile, researchers and medical publicists continue to spin SSRI-induced abnormal neuronal growth as evidence of a therapeutic mechanism. A December 19, 2005, headline in a promotional bulletin called *Johns Hopkins Medicine* declared, "Popular Antidepressants Boost Brain Growth, Hopkins Scientists Report." From the university's Office of Corporate Communications, this Johns Hopkins public relations release boasted about a newly published study by the medical center (Zhou et al., 2006).

One of the authors, Vassilis Koliatsos, MD, explained, "It appears that SSRI antidepressants rewire areas of the brain that are important

for thinking and feeling, as well as operating the autonomic nervous system." It required only 4 weeks for fluoxetine to accomplish this rewiring of the rat's brain. Dr. Koliatsos stated that these abnormal growths of neurons should provide patients "more tangible evidence of a real effect in the brain." Yes, but how many patients would welcome a potentially permanent rewiring of their brains by a toxic drug?

The study itself showed very widespread abnormalities, increasing the density and branching of axons in the dorsal raphe (the origin point for serotonergic nerves) and in the limbic forebrain and neocortex, the most highly evolved areas of the brain. If one were not committed to justifying psychiatric drugs, findings such as these would be viewed as indicators of a widespread, severe disease process with ominous if as yet undetermined implications for the function of the brains and minds of human beings exposed to these drugs. Instead, paralleling the press release, the scientific report suggested that these brain changes caused by the antidepressants "may play a role in their clinical efficacy."

The brain is the focus of this book but it is not the only organ injured by SSRI antidepressants. A recent study of 2,722 older women (mean age 78.5) found that the SSRIs drastically reduced their bone densities (Diem et al., 2007). The bone mineral density (BMD) decreased by 0.82% per year in SSRI users, compared to 0.47% in nonusers ($p < .001$). On the other hand, women using tricyclic antidepressants had the same BMD as nonusers. One wonders how this form of SSRI toxicity might be rationalized as therapeutic. Meanwhile, it is yet one more reason not to prescribe the drugs, especially to older people.

Stimulant drugs also impair serotonergic function, contributing to the widespread damage that they also produce in the brain (chapter 11). Particularly in regard to the mood stabilizers and the highly toxic drug lithium, researchers are claiming that the gross neuronal damage found in animals might have a so-called protective function in living, human patients (chapter 8). There is a veritable research industry growing up around this theory, which must prove pleasing to the drug companies, who never want brain damage caused by their drugs to be viewed as harmful.

## OLDER ANTIDEPRESSANTS

The tricyclics, such as clomipramine (Anafranil), amitriptyline (Elavil), and imipramine (Tofranil), have been used for several decades. I have previously described their central nervous system toxic effects in some detail (Breggin, 1983b; see also Breggin, 1991b). This section will therefore be abbreviated. A list of some of the older antidepressants can be found in the appendix.

Most of the older antidepressants are called *tricyclic* because their chemical nucleus has the basic tricyclic structure of the original phenothiazine neuroleptic, chlorpromazine, or Thorazine (Bassuk et al., 1977; Pauker, 1981). Of extreme importance, the antidepressant amoxapine (Asendin) is turned into a neuroleptic in the body, producing the same problems as any other neuroleptic, including tardive dyskinesia (chapters 3 and 4).

Bassuk and Schoonover (1977) noted that tricyclic antidepressants can cause a toxic syndrome similar to the neuroleptics:

> Tricyclics may also cause psychomotor slowing and difficulties in concentration and planning. Although more attenuated than with the phenothiazines, some of these properties are similar to the neuroleptic syndrome. These effects should be explained to the patient if he is in a setting where active physical or mental performance is required. Weakness and fatigue, nervousness, headaches, agitation, vertigo, palsies, tremors, ataxia, paresthesia, dysarthria, nystagmus, and twitching are central symptoms that occasionally occur. Tricyclics also lower the seizure threshold in a manner similar to the phenothiazines.

In discussing animal behavior, Jarvik (1970) noted, "Despite its clinical antidepressant effects, imipramine produces a depression of spontaneous motor activity in laboratory animals." He noted that it produces "difficulty in concentrating and thinking comparable to that experienced during the course of similar treatment with chlorpromazine" and stated that "its effect has been described as a dullness of depressive ideation." Byck (1975) took the same position in a later edition of the same book, including the observation that "imipramine seems to produce greater impairment of cognitive and affective processes and less reduction in physical movement than does chlorpromazine." Other studies of tricyclics indicate that they produce "measurable cognitive impairment in normal subjects following acute or chronic administration" (Judd et al., 1987).

In my clinical practice, I have occasionally seen otherwise normal patients who were put into states of apathy or lethargy by very small doses of tricyclic antidepressants (e.g., 10 mg to 25 mg of amitriptyline) given to them for nonpsychiatric purposes, especially to treat headache or diarrhea. Depressed patients are frequently made more depressed by these drugs without the spellbound patients or their doctors perceiving that the drug is causing the worsened condition.

As already described, the FDA now requires a broad range of warnings on antidepressant labels. There should no longer be any scientific doubt about the range and frequency of abnormal reactions in children

taking SSRIs and other potentially stimulating antidepressants. The older antidepressants are also known to cause a variety of expressions of behavioral toxicity in children. In discussing the use of tricyclic antidepressants in children, Dulcan (1994) observed,

> Behavioral toxicity may be manifested by irritability, worsening of psychosis, mania, agitation, anger, aggression, forgetfulness, or confusion. CNS toxicity may be mistaken for exacerbation of the primary condition. (p. 1222)

Tricyclic antidepressants commonly produce abnormalities in cardiovascular function in children and adults, and there are reports of cardiac arrest and death in children. Cardiovascular function should be carefully monitored in children taking these drugs (Dulcan, 1994).

Prescribing dangerous, ineffective antidepressants for children is especially tragic because depression in children is almost always a readily identifiable product of their environment. Helping a child overcome depressed feelings involves helping the adults attend better to the needs of the child. Children get depressed because of depressing circumstances in their lives. Sometimes these circumstances may be buried in the past in the form of neglect or physical, emotional, or sexual abuse. Sometimes they are the obvious product of current circumstances.

## Tricyclic Antidepressants and the Brain-Disabling Principle

The so-called therapeutic effect of tricyclics can result from any number of effects that vary from individual to individual, including emotional blunting, sedation, and stimulation. They frequently cause organic brain syndromes, which—as in the case of electroshock treatment—tend to relieve the gross signs of depression by burying them beneath emotional apathy or an artificial high. A study from the Yale University Department of Psychiatry by Davies et al. (1971) indicated that acute organic brain syndromes are very common during routine tricyclic antidepressant therapy (reviewed in detail in Breggin, 1983b). Symptoms included "forgetfulness, agitation, illogical thoughts, disorientation, increased insomnia, and, at times, delusional states."

Especially in earlier decades, many clinicians purposefully administered tricyclics until they produceed toxic reactions. Goodwin and Ebert (1977) advised giving the tricyclics in doses that produce "confusion" and other signs of toxicity. Amphetamine-like toxic effects were considered a good sign. Wells and Mendelson (1978) observed, "In our practice, an adequate trial often constitutes the highest dose that the patient can tolerate."

As described in chapter 1, the patient who experiences drug-induced brain dysfunction and the psychiatrist who induces it collaborate in a mutual denial of what is going on. Both end up denying the patient's drug-induced brain dysfunction and the patient's real-life personal problems. When euphoria is present, it becomes especially easy for the patient and the psychiatrist to deny the reality of what is happening. A drug with sufficient neurotoxicity to produce a mild to severe organic brain syndrome is especially suited to creating the illusion of improvement in depressed patients.

## Tricyclics: More Cause Than Cure for Suicidality?

There is no substantial published evidence that any antidepressants, new or old, ameliorate suicidal tendencies. Instead, there is clinical evidence that the tricyclic antidepressants, like the SSRIs, can cause suicide. Baldessarini (1978) warned, "The risk of suicide may even increase with initial improvement, since activity usually increases before mood elevation." Baldessarini's explanation for drug-induced suicidality, formulated many years ago, is oversimplified; but the observation remains correct, that antidepressants cause suicidality, especially early in treatment or during dose changes.

Damluji and Ferguson (1988) reviewed paradoxical worsening of depressive symptomatology caused by antidepressants in an article of the same title and reported four cases of their own caused by the older antidepressants amoxapine, desipramine, nortriptyline, and trazodone. The APA National Task Force on Women and Depression (1990) report on benzodiazepines also cited the problem of depression and suicide from tricyclic antidepressants.

Tragically, while the older antidepressant drugs cannot prevent suicide and can cause it, in relatively small amounts, they can become lethal instruments in the hands of suicidal patients. As little as 1 week's supply of most tricyclics can cause death, often due to cardiac dysfunction. In combination with other drugs, their lethality increases. Thus millions of depressed, suicidal patients are given the tool with which to kill themselves. By 1981, the tricyclics were overtaking the barbiturates as the medications most frequently involved in serious overdoses ("Tricyclics," 1981). The tricyclics remain a major public health problem as agents of suicide (Henry et al., 1995).

## Other Antidepressants

Monoamine oxidase inhibitors such as tranylcypromine (Parnate) for a time went into disfavor because of their extreme toxicity to the central

nervous system, their stimulating impact, and their tendency to cause severe hypertension crises when combined with a wide variety of foods and medications. They are reviewed more extensively in the 1997 edition, but in this era of excessive overmedication, they are enjoying something of a comeback.

Several so-called atypical antidepressants are currently on the market in the United States. This brief review is not intended to be comprehensive in regard to their adverse effects.

Venlafaxine (Effexor), approved by the FDA in December 1993, was described in more detail early in this chapter. It is one of the newer antidepressants implicated in causing suicidality. It is a NSRI that also strongly inhibits the reuptake of epinephrine. Its profile is very similar to the SSRIs in producing stimulation, including anxiety, nervousness, insomnia, anorexia, and weight loss. It causes the various emotional and behavioral abnormalities that go along with stimulation, such as agitation and mania, and has been associated with hostility, paranoid reaction, psychotic depression, and psychosis. It can cause hypertension.

Trazodone (Desyrel) and buproprion (Wellbutrin) are somewhat older atypical antidepressants that do not fit the pattern of other groups of agents. Buproprion has an unusually high rate of seizures associated with its use. It can be very stimulating and agitating. Trazodone tends to cause sedation and can also cause dizziness and fainting. It can cause cardiac difficulties for recovering heart patients. It also produces the potentially disastrous side effect of priapism: uncontrolled, irreversible penile erection, sometimes requiring surgical intervention.

In my experience, any of the antidepressants can produce a variety of unexpected and sometimes severe emotional reactions, including apathy, lethargy, and depression, or euphoria, paranoia, and mania. Frequently, these adverse effects are mentioned as possibilities on the FDA-approved label.

Keep in mind that as a group, antidepressants affect diverse neurotransmitter systems in a complex, little understood manner. Even the supposedly selective SSRIs end up producing generalized dysfunction in the brain and hence the mind.

## ANTIDEPRESSANT WITHDRAWAL REACTIONS, INCLUDING MANIA

It is counterintuitive that a drug that causes mania would also cause it during withdrawal. However, there are case reports that most types of antidepressants can cause mania during withdrawal, especially the SSRIs (Goldstein et al., 1999; Sherese et al., 2003). Benazzi (2002) reported

on a case of sertraline-induced withdrawal mania. He also summarized some of the problems associated with SSRI withdrawal:

> Discontinuing selective serotonin reuptake inhibitors (SSRIs) may induce a syndrome wherein the main neuropsychiatric symptoms are dizziness, shock-like sensations, anxiety, irritability, agitation, and insomnia. These symptoms usually develop 1 to 7 days after abrupt or gradual discontinuation. Antidepressant discontinuation may also induce mania, mainly reported with tricyclics and monoamine oxidase inhibitors but also observed with SSRIs.

Patients with a history of bipolar disorder are probably more vulnerable to this adverse drug reaction. I have observed patients becoming euphoric during withdrawal from SSRIs, but none have become manic. During withdrawal from antidepressants, I advise patients and their families that withdrawal reactions are highly variable and unpredictable and that they should be alert for any significant change in psychological and emotional functioning.

Meanwhile, Benazzi's (2002) brief summary does not capture the severity or wide variety of withdrawal reactions associated with drugs that block the reuptake of serotonin (SSRIs), especially the overwhelming feelings of depression and despair, with uncontrollable weeping (Shipko, 2002; see chapter 15 for more details).

Psychiatry has yet to face the fact that it has trapped millions of patients into taking SSRI and SRI drugs for years on end because they are unable to endure the withdrawal symptoms. Sometimes the brain changes are so persistent or irreversible that the individuals feel compelled to remain on the drugs indefinitely. Often the withdrawal symptoms lead them mistakenly to believe that they suffer from an underlying mental illness that requires medication, when instead they have persistent brain dysfunction caused by medication.

In reality, most patients quickly stop taking the newer antidepressants because of their painful adverse effects, thereby protecting themselves from long-term adverse effects, including withdrawal reactions. Others stay on them mainly because of pressure from their doctors, including the lie that they have so-called biochemical imbalances. The more disturbed or distressed the individual before starting the medication, they more the individual is likely to deteriorate while taking it.

Paxil is probably especially punishing in regard to causing both acute adverse effects and withdrawal. In a double-blind study, Zanardi et al. (1996) administered Zoloft and Paxil to inpatients diagnosed with depression with psychotic features. Within 2 weeks of starting treatment, 41% of the Paxil patients dropped out "because of unpleasant side effects

such as anxiety, agitation, and insomnia." Prescribing Paxil is a formula for making psychotic patients even more disturbed.

The older tricyclic antidepressants and monoamine oxidase inhibitors also cause withdrawal mania and a variety of other adverse withdrawal effects, including cognitive and emotional disturbances and psychosis. Many of them have strong anticholinergic effects and therefore produce severe anticholinergic rebound on withdrawal, including cardiovascular and gastrointestinal symptoms. I have seen patients who have taken tricyclics for many years and then been unable to withdraw from them.

Chapter 15 discusses SSRI withdrawal symptoms in more detail and describes how to successfully withdraw from psychiatric medications.

## MY CLINICAL AND FORENSIC EXPERIENCE

I have been a medical expert in dozens of criminal, malpractice, and product liability legal cases in which children and adults have developed bizarre, irrational, and violent behavior while taking SSRI antidepressants (Breggin, 2006d; Breggin, in press). In one case in California, a man drowned himself and his two small children in a bathtub a few days after starting on paroxetine (see http://www.breggin.com for this and other legal cases). Also while taking paroxetine, a man in Pennsylvania drove his car into a policeman to obtain the officer's gun to kill himself. In a fourth case involving paroxetine, in Vermont, a 17-year-old boy who had missed one or two doses of paroxetine bludgeoned a close friend for no apparent reason. In Florida, a teenage girl taking Fluoxetine fired a pistol point-blank at another youngster, but the gun fortunately failed to function. None of these individuals had any history of violence prior to taking SSRIs. I have described several dozen cases of SSRI-induced mania, mayhem, murder and suicide in my book *Medication Madness* (in press).

## DISCUSSION: "THE DRUG MADE ME DO IT"

There is a reluctance to attribute so-called bad behavior or loss of ethical restraint to a psychoactive substance. Western philosophy, religion, and tradition tend to hold human beings responsible for their harmful behaviors and eschew excusing such behavior on the basis of so-called mental illness. Indeed, the concept of mental illness has been subject to challenge by this author and many others. Nonetheless, the weight of considerable evidence indicates that psychoactive substances can play a role in causing suicide, violence, and other forms of disinhibited criminal

conduct. The effect should not be attributed to the vague and misleading concept of "mental illness." Instead, the effect is neurological in origin—a genuine brain disorder cause by toxicity. Terms with ethical connotations tend to be expunged from psychiatry as unscientific, and so the change in ethical restraint caused by medications is referred to by various more neutral terms, such as *disinhibition*, *dyscontrol,* or *loss of impulse control.*

The two chapters on antidepressants and upcoming chapters on stimulants and benzodiazepine tranquilizers provide ample evidence for how medications can cause an adverse change in ethical behavior. In general, the evidence falls into four categories:

First, controlled clinical trials comparing any psychoactive drug to a placebo will typically produce evidence for a pattern of central nervous system adverse drug effects with mental symptoms that are specific for the drug and not for the placebo. For example, SSRI antidepressants and amphetamine-like agents both tend to produce a continuum of central nervous system stimulation. This physical stimulation will be associated with mental manifestations that range from mild euphoria and irritability to depression and mania and ultimately to increased rates of both aggression and suicidality. The studies confirming SSRI-induced suicidality in this chapter should leave no doubt about the capacity of psychiatric medications to disrupt the function and the brain and mind, leading to destructive behavior that would not otherwise have occurred.

Second, patterns of reports made to the FDA's spontaneous reporting system also make apparent that certain drugs are associated with specific patterns of extreme mental and behavioral reactions (for additional examples and an analysis of methodology, see Breggin, 1997a, 1998b). Even nonpsychiatric medications have been implicated in causing depression and suicidality. Isotretinoin (Accutane), a medication used to treat severe acne, has been found to produce depression and suicidality, as demonstrated in numerous clinical reports and in individual case studies. In some clinical cases, "depression subsided with discontinuation of the therapy and recurred with reinstitution of therapy" (*Physicians' Desk Reference,* 2003, p. 2872).

Third, many physical disorders also affect mental attitudes and behavior. Hyperthyroidism as well as overdoses of thyroid hormone can increase anxiety, irritability, and other emotions that the individual would not ordinarily experience and that can lead to behavioral abnormalities. There are, of course, many similar examples involving hormones such as testosterone and cortisone. More to the point, accidental brain injury to the frontal lobes and surgical lobotomy usually impair judgment, ethical restraint, and self-reflection. The character of the injured individual is often viewed as changed and worsened.

Fourth, as an expert in criminal and civil cases, I have studied the lives of many individuals who—under the influence of psychoactive drugs such as SSRIs, nonselective serotonin reuptake inhibitors (NSRIs), and benzodiazepines—have committed acts of aggression that were wholly alien to their character and antithetical to their prior behavior. It is, of course, well known that the illegal use of stimulant drugs, such as methamphetamine and cocaine, can be associated with paranoid reactions and violence.

The example of *involuntary intoxication* under the law helps elucidate the issue of responsibility while under the influence of psychoactive substances. Under the law, an individual is held responsible for behavior committed under the influence of alcohol or other nonprescription intoxicants because it is presumed that the individual knew that he or she was taking a psychoactive substance that can impair judgment and self-restraint. However, in most states, an individual can claim *involuntary* intoxication as a mitigating or exonerating factor in a criminal case. For example, if the individual *unknowingly* drank alcohol from spiked punch, the involuntary nature of the intoxication might become a mitigating or exonerating factor under the law. Similarly, when an individual is prescribed an antidepressant without knowing that it can cause mania, he or she may be exonerated from the consequences of maniclike behavior.

If an individual involuntarily intoxicates another person, the perpetrator may be guilty of a crime, and the victim may be absolved of any contributory responsibility. For example, a man can be judged guilty of rape if he has impaired the consciousness and self-restraint of his victim by surreptitiously slipping a sedative into her drink. The victim, even if physically conscious during the sexual act, may be exonerated of seeming acquiescence to the assault on the basis of involuntary intoxication.

The debate over human responsibility will always remain at root ethical and philosophical. However, empirical data must be taken into account. A mountain of experimental and clinical data, some of it reviewed in this report, supports the concept that psychoactive substances are frequently associated with an increased rate of disturbed mental and behavior reactions, causing some individuals to act as if they have lost their customary ethical restraint and self-control.

It may be argued that some individuals will not lose ethical restraint regardless of the nature or intensity of an involuntary intoxication. However, even if some individuals are relatively immune to behaving badly under the influence of drugs, while others seem especially susceptible, this merely reflects human variation, a factor that complicates most research in medicine and behavioral science. The reality of human variation does not undermine the validity of the association between certain drugs and

the relatively frequent production of certain kinds of dangerous mental states and behaviors.

I want to reemphasize that drug-induced disturbances in mood or in behavior should be viewed as genuine neurological disorders rather than as vague mental illnesses. The capacity of speculative biochemical imbalances or genetic factors to cause or contribute to mania or depression remains unproven. Nor do we know the specific biochemical or neurological mechanisms whereby psychoactive substances cause mental disturbances. But the capacity for psychoactive substances to disrupt brain function and hence mental function is beyond dispute. Furthermore, a great deal of empirical data confirm their capacity to cause disinhibition, mania, depression, and other mental phenomena associated with violence toward oneself and others, as well as other destructive behaviors.

## WHAT DO THE SPECIALISTS KNOW?

In my clinical experience, including reading innumerable depositions given under oath by psychiatrists in legal cases, I have come to the dismal conclusion that most psychiatrists know little more than what they are told by drug company salespersons who visit their offices and drug company spokespersons who address them at industry-sponsored seminars. At the 2005 annual meeting of the American Psychiatric Association (Strong, 2007), a survey was conducted of pediatric psychopharmacologists. The great majority of these professionals are psychiatrists who identify themselves as specializing in prescribing medications to children and adolescents. These are the doctors to whom other doctors refer their more difficult patients. These are the doctors who write papers and teach their colleagues about how to use psychiatric drugs. It was an experienced group who had been in practice on average for approximately 20 years.

Although these specialists knew that the FDA had recently issued a black-box warning about antidepressant-induced suicidality in children and youth, hardly any of them took it seriously. Only 22% thought that any specific medication was more likely to worsen suicidality, with two-thirds of them naming the SSRIs. Thus, less than 15% of the experts (two-thirds of 22%) thought that SSRIs increased the risk of suicidality in their patients. So much for the impact of research and the black-box warning!

By contrast, 60% continued to believe that some medications were more likely to *improve* suicidality, with "the vast majority" citing the SSRIs as most helpful in relieving suicidality in children and youth. This flew in the face of evidence from controlled clinical trials and observations by the FDA indicating that antidepressants are no better than placebos in treating childhood depression.

In summary, only a small percentage of the so-called experts thought that the SSRIs increased the suicide risk, while most thought they reduced it. This survey confirmed my experience that the vast majority of specialists and experts in the use of psychiatric medication (psychopharmacologists) are little more than drug-company-inspired drug pushers. Tragically, the medication specialists have become the most dangerous people in regard to the cavalier promoting of drugs for children and youth, as well as for adults.

## CONCLUSION

The newer antidepressants, especially the SSRIs, frequently cause medication spellbinding (intoxication anosognosia) with the associated risk of violence, suicide, mania, and other forms of psychotic and bizarre behavior. Because of the spellbinding effect, the victims of these drug-induced reactions often do not realize that their mental outlook or behavior has been drastically changed. They typically attribute any changes in how they feel to something other than the medication, often blaming themselves or other people. At times they believe they are doing better than ever when they are in reality deteriorating. And in the extreme, they can become driven by suicidal, violent, or bizarre ideas that would otherwise seem alien to them.

Teicher et al. (1993) suggested nine possible mechanisms for SSRI-induced suicidality: (a) energizing the depressed and suicidal patient, (b) paradoxically worsening the individual's depression, (c) causing akathisia, (d) causing panic and anxiety, (e) causing manic or mixed manic-depressive states, (f) causing insomnia or disturbances in the sleep architecture, (g) causing obsessive suicidal preoccupations, (h) causing borderline states with hostility, and (i) causing alterations in electroencephalogram (EEG) activity. Teicher et al. (1993) document each of these phenomena in their review of the literature and, as their article indicates, the scientific evidence has grown considerably stronger in the intervening decade.

With the exception of the alteration in EEG activity, the scientific literature and my clinical and forensic work have confirmed that each of the previously mentioned antidepressant-induced phenomena can cause violent and suicidal behavior. However, my clinical and forensic experiences and reviews of the literature indicate that five syndromes encompass most of the phenomena and describe most of the individual cases:

1. The production of a *stimulant continuum* that often begins with lesser degrees of insomnia, nervousness, anxiety, hyperactivity, and irritability and then progresses toward more severe agitation,

aggression, and varying degrees of mania. Mania or maniclike symptoms include disinhibition, grandiosity, sleep disturbances, and out-of-control aggressive behavior, including cycling into depression and suicidality.

2. The production of a combined state of *stimulation and depression*—an *agitated depression*—with a high risk of suicide and violence. Often the overall depression becomes markedly worsened.
3. The production of *obsessive preoccupations* with aggression against self or others, often accompanied by a worsening of any preexisting depression.
4. The production of *akathisia,* an inner agitation or jitteriness that is usually (but not always) accompanied by an inability to stop moving. It is sometimes described as psychomotor agitation or restless leg syndrome. The state causes heightened irritability and frustration with aggression against self or others, and often a general worsening of the mental condition.
5. The production of *apathy and indifference,* usually causing or worsening depression, but sometimes resulting in disinhibition from normal restraints, leading to actions that would otherwise appall the individual.

The above syndromes, all of which are medication spellbinding, often appear in combination with each other. Often the syndromes will abate within days after stopping the antidepressant, but sometimes they persist, leading to hospitalization and additional treatment over subsequent weeks or months. Reported rates for these syndromes very widely, but each of them appears to be relatively common. They frequently occur in individuals with no prior history of similar problems or behaviors (Breggin, in press).

In summary, there is incontrovertible evidence that antidepressants cause suicidality, irritability, violence, and mania as well as a wide range of other psychiatric adverse drug reactions often related to overstimulation, such as insomnia, anxiety, agitation, emotional instability, and akathisia. They can also cause apathy and emotional indifference. There is also strong evidence that they cause lasting abnormalities in brain function and even brain anatomy, including abnormal brain cell proliferation, death of brain cells, and shrinkage of brain tissue.

To compound the problem, these drugs can cause severe withdrawal problems, including agitation and a worsening of depression (see chapter 15). A substantial portion of my psychiatric practice involves working with patients who suffered frightening and sometimes agonizing withdrawal symptoms before coming to me for help in stopping the newer

antidepressants and, on occasion, the older ones. Sometimes these withdrawal symptoms persist for months, or even years, after stopping the drug.

Furthermore, even the FDA has admitted that these drugs are ineffective in children, and meta-analyses have shown that they are ineffective in adults as well. They are no better than placebo, they cause severe adverse reactions, and they cannot bring about the positive benefits associated with psychotherapy and other life experiences that can truly improve the individual's quality of living.

It bears repeating that antidepressants are dangerous to start taking and dangerous to stop taking as well as ineffective. The best advice is to stay away from them. In 40 years of psychiatric practice, I have never started a patient on an antidepressant, although I do prescribe them during the withdrawal process or if the patient is unable to go through withdrawal. Although good fortune undoubtedly plays a role as well, I believe that my refusal to start patients on these drugs has contributed to my success in never having a suicide in my practice. In addition to preventing antidepressant-induced suicidality, by not giving the medications I encourage myself and my patients to work together to find more effective and hope-inspiring ways of living.

## NOTES

1. According to the Food and Drug Administration, an adverse drug reaction rate of 1% is frequent or common.
2. A footnote explains that the "drug surveillance programme" is supported in part by 10 different drug companies, at least one of which makes an SSRI. However, Eli Lilly was not among them.
3. The title of this article does not correspond with its findings: "Manic behaviors associated with fluoxetine in *three* 12–18-year-olds with obsessive–compulsive disorder." The article did present detailed information on only 3 cases but described the occurrence of mania in 6 of 20.

CHAPTER 8

# Lithium and Other Drugs for Bipolar Disorder

Lithium for the treatment of manic episodes or bipolar disorder was originally promoted to the public and to the mental health profession as the ultimate example of a specific biochemical treatment for a specific psychiatric disorder. To bolster this claim, it was said that lithium lacks any brain-disabling effects on either patients or normal volunteers. This view of lithium directly challenges the concept of medication spellbinding and brain-disabling principle of psychiatric treatment. Although a number of new drugs have now been added to the mood stabilizer armamentarium, lithium remains the prototype.

## CLAIMS OF LITHIUM SPECIFICITY FOR MANIA

In 1970, a booklet published by the National Institute of Mental Health (NIMH) and intended for public consumption claimed that lithium produces "no unwanted effects on mood and behavior" and "only the symptoms are leached out while the rest of the personality remains unaffected." The NIMH report concludes that "the drug is unique among psychopharmaceuticals in that it rarely produces any undesirable effects on emotional and intellectual functioning." It calls the substance "the first specific chemical treatment for a mental disease."

Five years later, the American Psychiatric Association (APA, 1975) published "The Current Status of Lithium Therapy: Report of the APA Task Force." Without citing evidence, the authors stated, "The task force has concluded that lithium is a more specific anti-manic agent than neuroleptics and that its therapeutic results are achieved in a unique pharmacologic effect rather than nonspecific calming action."

Ronald Fieve became one of the leading advocates of lithium. In his book *Moodswing* (1989), he stated, "I have not found another treatment in psychiatry that works so quickly, so specifically, and so permanently as lithium for recurrent manic and depressive mood states" (p. 4). He describes this extraordinary therapeutic effect as occurring with no discernible adverse effects. The evidence will reveal that instead that lithium is neither quick nor specific nor permanent in its impact. Nor is lithium relatively free of adverse effects. It is one of the more deactivating, disabling drugs in the psychiatric armamentarium.

## BRAIN-DISABLING EFFECTS ON ANIMALS, INFANTS, PATIENTS, AND VOLUNTEERS

### Subduing Effects on Animals

Cade (1949) discovered the potential therapeutic value of lithium accidentally while experimenting with guinea pigs and immediately decided to try administering it to human beings. In his own words, here is the deductive leap he made:

> A noteworthy result was that after a latent period of about two hours the animals, although fully conscious, became extremely lethargic and unresponsive to stimuli for one to two hours before once again becoming normally active and timid.
>
> It may seem a long distance from lethargy in guinea pigs to the excitement of psychotics, but as these investigations had commenced in an attempt to demonstrate some possibly excreted toxin in the urine of manic patients, the association of ideas is explicable.

Cade's leap from producing a toxic lethargy in animals to "treating" human beings shows his intuitive recognition of the central role of deactivation in psychiatric treatment. As reviews by Schou (1957, 1968, 1976) indicated, no large studies on primate behavior were conducted before the widespread use of lithium in humans. One reason for this may be indicated in Schou's summary of how lithium affected mice and rats.

In a 1957 review, he noted, "A certain apathy and slowness of reaction have been frequent symptoms in the experimental animals." Or, as he remarked in a later review (Schou, 1976), there is "decreased spontaneous and exploratory activity."

This suppression of "spontaneous and exploratory activity," as well as the suppression of other expressions of volition and vitality, are the hallmarks of most biopsychiatric treatments and helped to inspire my concept of deactivation and the brain-disabling principles of psychiatric drugs. In studies of lobotomy and in the early and most forthright early studies of neuroleptic drugs, the primary or essential effect was identified as the production of indifference. In the antidepressant literature, this same effect is gaining recognition in regard to how these drugs produce apathy in long-term use. Stimulant advocates have failed to recognize these same effects in regard to Ritalin, Adderall, and other drugs used for the control of behavior in children; but the scientific literature will confirm that their primary effect is the crushing of spontaneity with a loss of interest in autonomously generated, imaginative, creative, and social activities.

Lithium is toxic in rats at the same serum concentrations as in humans (Schou, 1976). In a rat study by Smith and Smith (1973), lithium was administered in the low therapeutic range for a period of only 1 week. The authors summarized, "The most consistent effect of lithium was to decrease the voluntary activity of the rats."

The consistent finding of generalized behavioral suppression in animals undermines the claim that lithium is a specific magic bullet for mania. Suppression of voluntary or spontaneous activity is perhaps the most concise description of the primary impact of all brain-disabling therapies on animals and humans alike.

## Subduing Effects on Normal Infants

If a drug subdues the human fetus or infant, it is likely that its effect is not specific for a particular psychiatric disorder. Lithium freely crosses the placental barrier in utero and can be passed through breast milk (Ananth, 1978). The effects of lithium in producing lethargy and *hypotonia* (loss of muscle function) in babies at relatively low serum levels has been thoroughly documented (Rane et al., 1978; Strothers et al., 1973). Hollister (1976) noted that lithium causes "lethargy, cyanosis, poor suck and Moro reflexes." Lethargy in an infant describes the primary brain-disabling effect. As in animal studies, clinical reports concerning newborn and nursing babies demonstrate that lithium suppresses, and even disables, the central nervous system.

## Disabling Effects on Normal Volunteers

Because they considered lithium to be disease-specific for mania, advocates of the drug initially claimed that it had little or no effect on normal individuals (Dempsey et al., 1977; Hollister, 1976). Even van Putten (1975a), usually a keen observer of drug effects, stated that "lithium prophylaxis does not affect normal mental functioning or deprive a patient of normal human sorrow or elation."

Claims that lithium has no effect on normal volunteers are often based on a study by Schou et al. (1968), who stated: "The most striking observation seems to be how little lithium affects normal mental functions: in prophylactic dosage not at all and in higher therapeutic dosage only moderately."

However, Schou et al.'s (1968) own data do not support this view. It is true that the researchers found no impact in six volunteers when the drug was given at low doses for only 1 week. However, the authors also administered lithium to *themselves* within the therapeutic range (1.0 mEq/L) for 1–3 weeks. The authors, who now became the subjects of the experiment, experienced the common initial somatic side effects, including "transient nausea, diarrhea, slight tremor of the hands, etc." In addition, they suffered from a straitjacketing effect: "A feeling of muscular weakness or heaviness was prominent in all the subjects. They had to overcome a certain resistance against rising and moving and also had a feeling that mental effort was needed to undertake any physical task."

The most remarkable effects were subjective. Keep in mind that Schou et al. (1968) are trying to substantiate how little effect lithium has on normal mental function when they described the following effects on themselves:

> Psychological effects were, on the whole, subtle and ill defined. There was no consistent change of the mood level, but irritability or emotional lability could at times be noted. There might be hypersensitivity to everyday sights and sounds. On other occasions responsiveness to environmental stimuli was diminished; this was in one of the cases welcomed by the family ("Dad is much easier and nicer than usual"), while the families of the two other subjects complained about their being so dull. The subjective experience was primarily one of indifference and slight general malaise. This led to a certain passivity. The subjects often had a feeling of being at a distance from their environment, as if separated from it by a glass wall. The subjective feeling of having been altered by the treatment was disproportionately strong in relation to objective behavioral changes. The subjects could engage in discussions and social activities but found it difficult to comprehend and integrate

> more than a few elements of a situation. One of the subjects noted, for example, that whereas he had unaltered ability in a game such as chess with only two participants, he was less good at bridge with its four players. Intellectual initiative was diminished, and there was a feeling of lowered ability to concentrate and memorize; but thought processes were unaffected, and the subjects could think logically and produce ideas. The assessment of time was often impaired; it was difficult to decide whether an event had taken place recently or some time ago.

References to diminished "responsiveness to environmental stimuli," diminished "intellectual initiative," "indifference and a slight general malaise," and "a certain passivity" definitively describe the deactivating, brain-disabling effects of lithium (chapter 1). The language used is identical to that used to describe lobotomy effects.

Most interesting, perhaps, the authors, in writing about themselves, seem medication spellbound. That is, they fail to recognize how much harm the drugs are doing to their mental capacities, even as they report them. They used their study as the basis for their widely publicized claim that lithium has little or no effect on normal volunteers. Their study was published in such an obscure foreign-language journal that it was not even available in the National Library of Medicine, and therefore other researchers and professionals had to rely upon their claims concerning their results.[1]

That one of the author's children thought he was improved by deactivation confirms the brain-disabling principles. At least from this child's viewpoint, it was a relief to have her father become subdued and withdrawn.

Small et al. (1972) examined the mental effects of lithium on 11 normal volunteers in a more systematic fashion. Three had such serious reactions that there were "objective indications of impairment in work and school performance." A fourth developed a "severe, precipitous toxic delirium on the tenth day of taking lithium." A fifth volunteer dropped out of the study in the first week with "severe muscle weakness, confusion, and depression," which, the authors argue, without evidence, was "more likely" related to psychological factors than to the drug.

Linnoila et al. (1974) focused on behavioral reactions in simulated automobile driving and found lithium-induced impairment in response and reaction times, and in judgment.

Judd et al. (1977a&b) also studied the reactions of normal volunteers to lithium (mean, 0.9 mEq/L) over a 2-week period. In one study (Judd et al., 1977) they reported the effects of lithium on mood and personality in 23 subjects. They expressed surprise at their findings, which included a decreased "sense of well-being" among their volunteers and

a "large number of spontaneous complaints." The authors described their results in no uncertain terms:

> These subjective changes are not mood elevating, but rather mood lowering. In general, these feeling-tone alterations are dysphoric and characterized by lassitude, lethargy, and feelings of negativism and depression. In addition, feelings of agitation, anxiety, tension, and restlessness are related to lithium carbonate maintenance. There is also some evidence that subjects indicated they did not want to have to deal with the demands of interacting with their human environments. Finally, there are consistent self-reports of inability to concentrate, mental confusion, feeling muddleheaded, and a loss of clear-headedness.

Although not as picturesque as Schou et al.'s self-described lithium effects, the impression of brain-disabling effects is similar. In 1979, Judd summarized the results of studies with 42 healthy young men. He concluded that lithium produces a "general dulling and blunting of various personality functions" and a "generalized subjective dysphoria." Consistent with the brain-disabling principles, he attributed the therapeutic effect of lithium to a general slowing of cognitive processes.

An especially interesting aspect of Judd's research confirms that trained independent observers are not likely to report adverse drug effects, even when they are apparent to those who administered the drug and to those personally associated with the persons receiving the drug (Judd et al., 1977a):

> It was of interest to find that the effects of lithium carbonate in normal subjects were not perceptible to trained independent observers in the experimental situation. We initially speculated that these changes, although profound to the individual experiencing them, were not such that they were easily discernible, even to trained observers. In contrast to this was the fact that the "significant other," an individual who had a much more extensive interpersonal experience with the subject, was able to identify alterations in behavior and mood during the time the subjects were being maintained on lithium carbonate. Further, their observations were completely consistent with qualitative changes obtained from the self-rating data from the subjects themselves. Thus, these changes due to lithium carbonate are not just subjectively experienced, but are apparent to independent observers who are well acquainted with the normal range of behavior of each of the subjects.

The adverse effects most frequently noted by personal associates of the subjects included "increased levels of drowsiness and lowered ability to work hard and to think clearly" (Judd, 1979). The group who reported these changes in the subjects consisted of "friends, roommates,

girlfriends, etc." The background of the "trained independent observers" is not described, but presumably they are mental health professionals.

It is striking that the trained observers were "unable to detect any behavioral changes in the subjects induced by lithium" when they were apparent to personal associates and could be measured on testing. Judd (1979) attributed their failure to a lack of familiarity with the subjects in their normal surroundings. But various findings in this book confirm that this failure to observe adverse drug effects is characteristic of the vast majority of research reports and review articles in the drug literature. It is the doctor's part in iatrogenic denial: the tendency to deny the brain-disabling effects of psychiatric treatments (chapter 1).

Studies have continued to demonstrate adverse effects of lithium on normal subjects (Glue et al., 1987; Kroph et al., 1979; Muller-Oerlinghausen et al., 1977; Weingartner et al., 1985). Schatzberg and Cole (1991) appropriately warned that the patient's subjective experience of mental dysfunction should be taken seriously:

> Some patients on lithium complain of slowed mentation and forgetfulness and, on testing, a memory deficit has been found. Although such patients are often suspected or accused of "using" such symptoms to avoid necessary lithium therapy, our impression is that these complaints are often real and constitute a basis for lowering the dosage or trying another therapy. (p. 159)

Jefferson (1993) summed up the deactivating effect of lithium,

> Neurologic adverse effects of lithium include reduced reactivity, lack of spontaneity, intellectual insufficiency, memory problems, difficulty in concentration, dysphoria. Some of these effects may be related to the therapeutic action of lithium in reducing hypomania. However, hypothyroidism, weakness and fatigue due to hypercalcemia, and breakthrough depression must be considered in the presence of these symptoms.

The production of thyroid disorders by lithium is common and requires constant concern throughout the treatment. Lithium-induced hypothyroidism can produce depression and other mental dysfunction, greatly confusing and complicating the patient's clinical picture.

In a review of the literature concerning the impact of psychiatric drugs on cognition in normal subjects, Judd et al. (1987) found the following:

> In summary, lithium often induces subjective feelings of cognitive slowing together with decreased ability to learn, concentrate and memorize. In addition, controlled studies have consistently described small

> but consistent performance decrements on various cognitive tests, including memory tests. The available data suggest that the slowing of performance is likely to be secondary to a slowing in the rate of central information processing. (p. 1468)

Studies of normal volunteers should lay to rest the claim that lithium only affects a disease process. It should also put an end to the claim that lithium has a specific antimanic effect, rather than a generalized brain-disabling, deactivating effect. This effect may at times reduce the occurrence of manic episodes, but it does so by reducing overall brain function. Even in regard to reducing the frequency of manic episodes, its efficacy is doubtful and it causes manic withdrawal reactions (see following sections).

## Turning Down the Dial of Life

Confirming the brain-disabling principle, lithium has the same subduing effects on psychiatric patients as on normal volunteers. Speaking of individuals successfully treated with lithium, Dyson and Mendelson (1968) observed the following:

> It is as if their "intensity of living" dial had been turned down a few notches. Things do not seem so very important or imperative; there is greater acceptance of everyday life as it is rather than as one might want it to be; and their spouses report a much more peaceful existence.

As a demonstration of the brain-disabling concept of psychiatric treatment, the reference to the spouse's report of a more peaceful existence is reminiscent of Schou et al.'s (1968) observation that one of the children preferred it when Dad's "responsiveness to environmental stimuli was diminished." The comparison to neuroleptic deactivation and to lobotomy again seems apparent.

According to Dyson and Mendelson (1968), even on effective maintenance therapy, the dial of life remains turned down. They quoted some of their patients:

> "I just don't get irritated and upset at things as I used to." "Things that used to bother me don't seem so important anymore." "I don't have any energy, can't accomplish what I used to be able to."

Schlagenhauf et al. (1966) found that "when improvement was first noted the patients complained of feeling internally 'curbed,' a subjective experience that all of them had considerable difficulty in describing very precisely." The patients felt "unable to talk, think or move as fast as they

would like." Again, lithium is obviously and grossly disabling the brain and mind.

Demers and Davis (1971) examined the attitudes of spouses toward patients treated with lithium. Without intending to emphasize the point, the study made clear that there is an overall reduction in all forms of lively expression or vitality:

> An apparent unfavorable result of lithium treatment was a reduction in enthusiastic behavior, as well as sexual responsiveness in the manic-depressive. Hypomanic joviality, enthusiasm, and spontaneity are often regarded as social pluses; and manic-depressives and their spouses complain about the loss of these valued attributes. When pressed to discuss the sexual compatibility of the marriage, frequently they will say it is worse since lithium treatment started, as the lithium-treated spouse has less libidinal strivings.

This excerpt illustrates the brain-disabling principle that the evaluation of treatment success depends upon the observer's attitude toward the drug-induced mental disability. In these instances, the spouses are described as missing their partners' vitality and sexuality. On the other hand, the doctors label these valued attributes "hypomanic" in order to justify the brain-disabling effect of their treatments.

## Crushing Creativity

Ronald Fieve, of the New York State Psychiatric Institute, achieved national attention ("New Old Treatment," 1973) in newspapers and magazines when he presented theatrical producer–director Joshua Logan at the annual meeting of the American Medical Association, where Logan gave a testimonial for lithium.

The entire question of testimonials for various treatments is a difficult and complex one. Quack cures, for example, often have avid supporters. Logan (1976), in his autobiography, described his many contacts with psychiatric treatment over the years, including earlier public testimonials for psychiatry. He expressed surprise that people are critical of electroshock treatment, which he found to be very "benign."

Logan's own psychiatrist, Fieve, coauthored an article (Polatin et al., 1971) describing three individuals (rare cases, in the authors' opinion) who rejected maintenance lithium, two of whom did so specifically on the grounds that it interfered with their creativity as writers of bestsellers: "These patients report that lithium carbonate inhibits creativity so that the individual is unable to express himself, drive is diminished, and there is no incentive."

Despite their claim that lithium does not interfere with creativity, Schou and Baastrup (1973) described its inhibiting, flattening effect:

> It is not always the elation that is missed. An undertaker's customers, mistaking depressive sadness for compassion, complained about his appearance of indifference when he was in lithium treatment. Another patient regretted that in discussions he was unable to attain the level of excitement he considered necessary: "Doctor, I am a communist and I must get excited when I discuss." There are also patients who feel that lithium treatment makes life "flat" and less colorful, "curbs" their activity, and prevents them from going as fast as they would like. In most cases these complaints disappear when the patients become used to the stable life course.

Whether these complaints do in fact disappear in most cases has never been carefully investigated. Even if the complaints become less frequent, there may be many unfortunate reasons for this, including the extremely spellbinding effect of lithium. In my clinical experience, children and adults exposed to any psychiatric drug for a lengthy period of time lose their ability to perceive their emotionally subduing effects; but the spellbinding effect of lithium is especially potent

Jefferson (1993) and Goodwin and Jamison (1990) also confirmed that loss of creativity is experienced by some patients on lithium; but it did not daunt their advocacy for the drug.

## Cade Supports the Brain-Disabling Hypothesis

There is a particular irony in the date of the first publication on the use of lithium in mental patients: Cade's article appeared in 1949, the same year that Corcoran et al. published "Lithium Poisoning From the Use of Salt Substitutes" in the *Journal of the American Medical Association.*

In regard to neuroleptics, we found that pioneers in their use were most straightforward about its brain-disabling effects. We find the same phenomenon with lithium. Cade (1949) indicated that lithium, when used for other medicinal purposes, produced "actual mental depression" in a variety of patients, not just those suffering from mania or manic depression. The drug enforced a so-called quieting effect on persons he considered schizophrenic (*dementia praecox,* in his nosology):

> An important feature was that, although there was no fundamental improvement in any of them, three who were usually restless, noisy and shouting nonsensical abuse…lost their excitement and restlessness and became quiet and amenable for the first time in years.

Cade (1949) preferred lithium to lobotomy on "restless and psychopathic mental defectives" in order "to control their restless impulses and ungovernable tempers."

## SPELLBINDING AND IATROGENIC HELPLESSNESS AND DENIAL

The previously cited research by Judd demonstrates how professionals utterly fail to see lithium-induced disabilities that are obvious to friends and detectable with psychological testing. Due to medication spellbinding, patients themselves have difficulty evaluating their mental status on lithium. Toxicity often creeps up slowly over many days or weeks so that their judgment is impaired in an almost imperceptibly gradual manner. In fact, patients cannot be relied on to notice when they are becoming severely toxic, even though the symptoms include marked gastrointestinal disturbances, tremor, and disturbed mental functions. Instead of relying on the perceptions of patients, blood levels must be carefully monitored and the patients carefully watched.

In keeping with this medication spellbinding effect, normal volunteers on small doses suffer impairments of their reflexes but do not realize or acknowledge the impairment (Linnoila et al., 1974). Lithium patients who report no side effects often have grossly obvious tremors. The failure of patients on maintenance therapy to notice their own neurologic defects clearly demonstrates that long-term treatment with lithium is medication spellbinding.

## TOXICITY TO THE CENTRAL NERVOUS SYSTEM

### The Production of Cognitive Deficits

It is now generally accepted that lithium can impair intellectual function. For example, Shaw et al. (1987) found impairments of memory and hand motor speed on lithium. In *Manic-Depressive Illness,* a book written wholly from a biopsychiatric perspective, Frederick Goodwin and Kay Jamison (1990) nonetheless concluded that lithium does cause serious cognitive impairments. They summarized much of the literature up to that time and declared,

> Since the drug's primary action is mediated through the central nervous system, it is not surprising that lithium can cause cognitive

> impairments of varying types and degrees of severity. Indeed, memory problems are among the side effects of lithium treatment that patients report most frequently. Although affective illness itself contributes both to cognitive deficits and complaints about such deficits, it is important to bear in mind that impairment of intellectual functioning caused by lithium is not uncommon and, in many patients, leads to noncompliance. Creativity can also be affected. (p. 706)

More recently, Stip et al. (2000) summarized the literature on lithium-induced memory problems: "Several studies have shown cognitive impairment in short-term memory, long-term memory and psychomotor speed in bipolar patients taking lithium." Their study aimed at testing the effect of lithium in normal subjects in a double-blind, 3-week study. They found that lithium-treated volunteers had long-term memory deficits on recalling words compared to the placebo group.

## Acute Organic Brain Syndromes

Considering how vigorously lithium is promoted as relatively free of overpowering mental effects, it is surprising how many cases of toxic delirium during routine lithium therapy were reported soon after the drug came into use (Johnson et al., 1968; Mayfield et al., 1966; Prien et al., 1972; Shopsin et al., 1971; Strayhorn et al., 1977). Prien et al. (1972) found that almost one-third of the patients in their highly active category suffered "severe" reactions, including several with toxic confusion described as "disorientation, confusion, lack of continuity of thought, and reduced comprehension." Lithium is highly neurotoxic.

## SILENT: Irreversible Lithium-Induced Neurotoxicity

In 1987, Adityanjee discussed so-called lithium poisoning and made an observation that remains true today: "There is a general lack of awareness about irreversible and untreatable complications of lithium treatment despite evidence to the contrary."

Originally, it was thought that, except in extreme cases, lithium-induced neurotoxicity was reversible. However, it eventually became apparent that many patients develop irreversible brain damage and dysfunction, often involving the cerebellum (Grignon et al., 1996). In the last two decades, researchers have defined a syndrome of irreversible lithium-effectuated neurotoxicity (SILENT). Adityanjee et al. (2005) reviewed the literature from 1965 to 2004 for cases of lithium neurotoxicity with the persistence of sequelae for at least 2 months after cessation of treatment. They found 90 cases of SILENT, with persistent cerebellar dysfunction as the most commonly reported persistent aftereffect. These

chronically disabled patients may need "physical rehabilitation for gait ataxia, speech training for dysarthria, and cognitive training for dementia and memory impairments" (p. 47). The most likely cause, according to the authors, is "demyelination caused by lithium in multiple sites in the nervous system, including the cerebellum." Not surprisingly, lithium toxicity can also cause chronic neuropsychological changes, including impaired memory, attention, executive control functions, and visuospatial deficits (Brumm et al., 1998).

Irreversible neurotoxicity can occur at relatively low serum doses. Lang and Davis (2002) described "the case of a 44 year old man who presented with a two-month history of dysarthria, ataxia and leg weakness whilst on maintenance lithium for bipolar disorder." He had significant cerebellar and pyramidal dysfunction. His serum lithium was 1.5 mmol/L, a moderate elevation for this patient. His recovery was only partial, leaving him mainly with cerebellar ataxia. The authors warned about the insidious onset of persistent neurotoxicity during routine treatment.

## Neurotoxic Effects in Low-Dosage Maintenance Therapy

Branchey et al. (1976) published a follow-up of patients on long-term lithium maintenance (6 months to 7 years). Only 10 of 36 were "free of neurologic symptoms," even with the low maintenance doses employed. Four of 36 patients had parkinsonian symptoms at a "low level of severity."

## Abnormal Brain Waves Produced by Routine Lithium Therapy

From early on, the electroencephalogram (EEG) was found to demonstrate significant pathologic response to lithium therapy, confirming the intoxicating effect of the drug (Baldessarini, 1977; Corcoran et al., 1949; Mayfield et al., 1966; Peach, 1975; Schou, 1957; Small et al., 1972). Consistent with the brain-disabling principle, Mayfield and Brown (1966) correlated EEG abnormalities with the therapeutic response to treatment. Muller-Oerlinghausen et al. (1977) reported grossly abnormal brain wave patterns in patients and normal volunteers. These persisted in the volunteers at the final testing 7 days after the withdrawal of lithium therapy.

Two review articles confirmed reports of persistent brain wave changes in patients treated with lithium (Friedman et al., 1977; Reisberg et al., 1979). Reisberg and Gershon (1979) declared, wholly without proof, that "the evidence is that these effects are benign."

Because some studies had shown changes in functional imaging in patients diagnosed with bipolar disorder during cognitive testing, Bell

et al. (2005) sought to separate out the influence of medication. They conducted a double-blind study of volunteers taking lithium or valproate using functional MRI. Both medication groups showed a significant decrease in the magnitude of the blood-oxygen-level-dependent (BOLD) signal. The authors linked these changes to the cognitive dysfunction measured in many studies of lithium.

### Lithium Disruption of the Compromised Brain

In combination with neuroleptics, especially haloperidol, there is an increased likelihood of severe encephalopathic syndromes that are sometimes irreversible (Baldessarini, 1978; Cohen et al., 1974). There is a case report of a similar reaction from combining lithium with the newer neuroleptic, risperidone (Swanson et al., 1995).

Lithium administered in combination with electroshock produces more severe acute organic brain syndromes (Weiner et al., 1980). Remick (1978) and Hoenig and Chaulk (1977) reported single cases of an acute, severe delirium resulting from this combination. Mandel et al. (1980) reported on two more cases of this nature. In 1980, Small et al. reviewed 25 patients given electroshock while being treated with lithium and found that the patients had more severe memory loss, more severe confusion, and occasional neurologic dysfunctions. The authors recommended against the use of electroconvulsive therapy (ECT) in patients receiving lithium therapy.

The literature concerning lithium administration to individuals with preexisting brain disease is sparse but indicates the expected increase in brain disability, including in the elderly (Baldessarini, 1978).

Beitman (1978) described a case of reactivation of tardive dyskinesia as a result of lithium therapy; the tardive dyskinesia had been quiescent for many years. Crews and Carpenter (1977) also described a case in which lithium aggravated a preexisting tardive dyskinesia.

## BRAIN DAMAGE AS TREATMENT

### General Toxicity to Neurons and Other Cells

Writing from the viewpoint of the pharmacologist, rather than the psychiatrist, Peach (1975) observed:

> The accumulation of lithium in the intracellular environment could be envisioned to perturb any event that is modulated by monovalent cations, e.g., sodium or potassium. These possible interactions signify the

enormous magnitude of the task of determining precise mechanisms of action of the lithium ion.

Lithium disrupts almost every measurable cellular activity pertaining to nerve transmission as well as many other vital functions. In addition, its distribution is fairly uniform throughout the central nervous system, with no known areas of specific concentration. It produces what Wilson et al. (1975) called a *nonselective diminution in neuronal activity.* The neurophysiology of lithium, even without supporting clinical data, renders absurd the notion of a specific biochemical treatment for a specific disease and confirms the brain-disabling effect.

Because of its neurotoxic impact, lithium appears to increase the risk of tardive dyskinesia for patients taking neuroleptics (Ghadirian et al., 1996). Consistent with this, there have been reports of extrapyramidal symptoms in patients taking lithium without neuroleptic exposure, including parkinsonism (Lecamwasam et al., 1994), chorea (Podskalny et al., 1996), tardive parkinsonism (Muthane et al., 2000), tardive dystonia (Chakrabarti et al., 2002), and tardive dyskinesia (Meyer-Lindenberg et al., 1997). The existence of extrapyramidal side effects on maintenance lithium has been found in numerous studies (e.g., Kane et al., 1978; Shopsin et al., 1975). Shopsin and Gershon's (1975) patients, like those of Branchey et al. (1976), did not complain about their neurologic symptoms, suggesting further mental impairment and a profound medication spellbinding effect.

Lithium also impairs the function of the peripheral nervous system, reducing motor nerve conduction velocity (Faravelli et al., 1999). It causes many metabolic adverse effects, resulting in hypothyroidism, hyperthyroidism (rare), hyperparathyroidism, and diabetes insipidus (Livingston et al., 2006).

Psychiatry has gone from denying that lithium causes kidney damage to trying to ignore it. The threat is very real. Lepkifker et al. (2004) reviewed the files of 140 patients exposed to lithium for at least 4 years and found that 20% developed *creeping creatinine* (a laboratory test for kidney malfunction) and renal insufficiency. Overall, lithium is very toxic to cells (Yao et al., 1999).

## The "Protective" and Therapeutic Effects of Poisoning Brain Cells

An increasing number of psychiatric drugs have been shown to cause abnormal proliferations of brain cells. The process is abnormal, first, because it is caused by the toxic impact of a drug; second, because the drugs are already known to cause many clinically obvious toxic effects

on brain cells and many organs of the body; and third because the number and morphology of the cells are abnormal. Yet researchers are so dependent on the psychopharmaceutical complex, both emotionally and economically, that many persist in seeing these abnormalities as evidence of a specific therapeutic mechanism. Lagace and Eisch (2005) reviewed the so-called neuroprotective effects of mood-stabilizing agents, including lithium, valproic acid, carbamazepine, and neuroleptics. Two separate effects were studied: neuroprotective and neurogenic changes caused by mood stabilizers.

First, these drugs exert a so-called protective effect on cell cultures, preventing cell death from occurring in response to certain trauma. For example, a rat is stressed by immobilizing it in a glass tube (Lim et al., 2005). This causes changes to take place in the responsiveness of brain cells to electrical stimulation, as measured in the decapitated animal's postmortem brain. If 1 hour after death, slices of the animal's brain are bathed in lithium, the brain changes in response to stimulation do not occur. Unbelievably, this laboratory finding in animal brain slices has been leaped on by researchers, including Lagace and Eisch (2005), as an indication that this postmortem protection may have something to do with the clinical effect of these drugs in living human beings. Never mind that lithium, for example, is extremely toxic to the human central nervous system and peripheral nervous system, a virtual poison to brain cells; this quirk in a Petri dish may nonetheless show that these drugs protect brain cells.

Second, these drugs produce abnormal cell growth. The researchers call this process *neurogenesis* as if it were benign; but the neurons are not normal in appearance. According to Lagace and Eisch (2005),

> In general, these studies have assessed neuron proliferation, neurite [axonal] outgrowth, regeneration, and differentiation. In sensory neurons, lithium, valproic acid, and carbamazapine have a common effect of increasing growth of cone formation, leading to a spreading of the neuron and a shorter neuronal axon.... Recently, lithium has been shown to induce proliferation and neuronal differentiation of rap hippocampal progenitor cells.... Like lithium, valproic acid treatment has been shown to induce neurogenesis in vitro, specifically inducing neurite growth, cell reemergence, and the formation of mature neurons in embryonic cortical cells.

These authors are a little more skeptical than others; they do not want to make the complete leap to clinical, therapeutic effects. But they are hoping: "To determine if the clinical efficacy of mood-stabilizing drugs is dependent on the neuroprotective or neurogenic properties of these medications, greater strides need to be made in relating findings

from cell culture and animal models to human imaging and pathology." The obvious brain-disabling, mood-flattening effects of lithium are ignored in the interest of promoting a more benign effect based on the most flimsy experimental grounds.

Chen et al. (2000) gave lithium to rats in their chow, achieving blood levels comparable with human treatment, and found a proliferation of brain cells in the hippocampus. They made the leap to claim that this neurotrophic effect may make lithium "of use in long-term treatment of other neuropsychiatric disorders." In other words, stimulating the brain to make abnormal brain cells is likely to be good for a variety of psychiatric disorders. This kind of giant leap, utterly ignoring the obvious toxic effects of lithium, has become common in the literature.

Not all researchers are so quick to assume that any drug-induced abnormal growth in brain cells will be beneficial to human beings. Harada et al. (1996) set out to "understand the mechanism underlying the neurotoxicity of lithium." They found that lithium impaired the function of nerve growth factor in rat cells. In doing so, it caused some of the abnormalities seen in lithium treated cells, including attenuated neurite growth.

Meanwhile, it does not occur to these researchers that lithium causes demonstrable memory dysfunction and that the hippocampus plays a major role in memory processes, suggesting instead that they were looking at how lithium *harms* the brain—and not how it might help it. Indeed, there is research that addresses the effect of lithium on biochemical processes that specifically affect mental functions such as memory and spatial discrimination. Banchaabouchi et al. (2004) gave rats lithium for 4 weeks to reach a typical human therapeutic serum level. This resulted in a suppression of a biochemical factor in the hippocampus associated with cognitive processes (Nurr 1) and also resulted in impairment of spatial discrimination in the animal. (Nurr 1 also plays a role in dopamine cell function and perhaps in the development of parkinsonism, Zetterstrom et al., 1997; lithium-induced dysfunction in Nurr 1 may be associated with the drug's capacity to cause dopamine-related neurological disorders, such as parkinsonism.)

The finding of abnormal cell growth stimulated by mood stabilizers is consistent with research showing that bipolar patients taking lithium and valproic acid have increased hippocampal regions measured on MRI. Beyer et al. (2004) found that this increase in hippocampal size correlated with the use of lithium. They also related it to the laboratory studies of neurogenesis.

There are, of course, many contradictory findings in the literature, but it is apparent that exposure to mood stabilizers, especially lithium,

profoundly impairs the function of the brain, even causing abnormal cell proliferation in some cases, and cell loss in others (Blumberg et al., 2003). The distorted thinking in the psychiatric sciences is so rampant that none of the studies view these recently documented abnormalities in cell growth and brain size as a cause for alarm. Instead, they are automatically promoted as evidence of benefit and cause for hope.

## THE RELATIVE INEFFECTIVENESS OF LITHIUM IN ACUTE MANIA

The myth of lithium specificity is shattered in exactly that arena in which one would expect to find the most support: clinical use as described by its advocates. Early on, it became generally accepted that the neuroleptics, not lithium, are most effective in stopping acute mania (Baldessarini, 1978; Juhl et al., 1977). Even with the development of combined neuroleptic–lithium therapy, some authorities advocate ECT, as well, for the control of especially severe cases (Hollister, 1976).

The clinical preference for the neuroleptics as the treatment for acute mania was based on the single most comprehensive, controlled study, which was conducted by Prien et al. (1972). They specifically contradicted the thesis that lithium has any specificity for mania or the "underlying manic process." They cautioned that "unfortunately, these observations have been all but lost in the vast number of unqualified endorsements of lithium carbonate therapy that have deluged the literature." Alexander et al. (1979) and Growe et al. (1979) also opined that lithium is not disease-specific for mania.

In the past, a great deal was written about the use of lithium for the control of violence (Fieve, 1989; Marini et al., 1977; Micer et al., 1974; Morrison et al., 1973; Sheard et al., 1976, reviewed in Breggin, 1983b). While these claims have not been confirmed, they focus once again on the tendency to use or advocate lithium for a variety of purposes.

## HOW EFFECTIVE IS LITHIUM IN PREVENTING THE RECURRENCE OF MANIC EPISODES?

Lithium has been promoted so strongly within psychiatry and to the public as a method of preventing recurrences of mania that few practitioners or consumers doubt its efficacy. In reality, lithium's effectiveness in this regard remains questionable. At the height of lithium's popularity, Prien et al. (1974) reviewed the literature and found that studies showed a relapse rate as high as 50% over 2 years during lithium prophylactic

treatment. Lithium did reduce the number of manic episodes in patients who had a history of infrequent attacks. But in patients with a high rate of past manic episodes, lithium did no better than placebo, and all patients in this group eventually relapsed. If lithium were a disease-specific treatment, it surely would have performed better than this.

Continuing research has been even more discouraging. Gitlin et al. (1995) conducted a prospective study of patients treated with lithium for bipolar disorder. The patients were carefully monitored for effective drug treatment. Despite this, 73% of the patients relapsed into mania or depression within 5 years. Of those who relapsed, two-thirds had multiple episodes. Even among those patients who did not completely relapse, many suffered serious emotional difficulties. The authors concluded, "even aggressive pharmacological maintenance treatment does not prevent relatively poor outcome in a significant number of bipolar patients" (p. 1635).

## MANIA AND DEPRESSION AS LITHIUM WITHDRAWAL REACTIONS

Although little notice was given of the phenomenon within the profession, I recall my own patients telling me about painful emotional reactions that they suffered during lithium withdrawal. The evidence is now substantial in regard to serious adverse psychiatric effects caused by lithium withdrawal.

Suppes et al. (1991) analyzed 14 studies and found that the rate of relapse into mania increased following the discontinuation of lithium. The patients, who tended to cycle into mania about once a year (mean 11.6 months), developed a new episode less than 2 months (mean 1.7 months) after stopping their medication. In other words, discontinuation of treatment with lithium produced a much more rapid onset of mania than the untreated patients would have endured.

Numerous studies have now confirmed that withdrawal from lithium causes adverse psychiatric reactions. Cavanagh et al. (2004), in a 7-year follow-up, found that lithium withdrawal caused both mania and depression. They concluded, "These results confirm that acute discontinuation of lithium leads to a high immediate relapse rate." However, they did not find that this justified the continuation of lithium. To the contrary, "outcome was not worsened by discontinuation."

Unfortunately, patients who relapse soon after taking lithium are rarely, if ever, told that their relapse was probably caused by lithium withdrawal. Instead, they are told that the new manic episode proves the need to take the medication for the rest of their lives.

Many psychiatrists advise patients who are diagnosed bipolar or manic that they must take lithium for many years, or even for the rest of their lives. They are told that it is irresponsible for them not to do so. Families and psychotherapists are pressured to urge or coerce patients to take their lithium. The data do not confirm this strong advocacy for the drug.

On the basis of the general observation that the brain tends to fight back against psychoactive interferences in the brain, any medication used to control mania should be viewed as having the potential to cause mania during withdrawal. For example, Jess et al. (2004) described a case of rebound mania during withdrawal from carbamazepine.

## OTHER ADVERSE REACTIONS TO LITHIUM WITHDRAWAL

Swartz and Jones (1994) reviewed the literature and presented three cases concerning severe and often persistent adverse reactions to the abrupt withdrawal of lithium in patients suffering from elevated serum levels during routine treatment. One of the patients became severely demented. In their review of 50 cases obtained from the Lithium Information Center of the University of Wisconsin, they found that many patients became demented or otherwise deteriorated severely when abruptly withdrawn from lithium. Patients subjected to kidney dialysis for lithium toxicity often deteriorated mentally with a rapid drop in lithium levels. Neurologic sequelae persisted in 30% of the 50 patients. The authors found substantial neurotoxic risks in rapidly withdrawing patients from high lithium levels.

If rapid withdrawal from high lithium levels can produce mania and disable neurologic reactions, then it is probable that rapid withdrawal from lower levels may produce more subtle adverse reactions.

## LITHIUM IN YOUR DRINKING WATER

In 1970, Dawson et al. tried to support a fantastic thesis: Increased rainfall dilutes certain minerals in reservoirs, including lithium, producing a correlation between areas of lesser rainfall, higher lithium levels in drinking water, and a lower incidence of mental illness as measured by hospital admissions. In *Psychiatric Drugs* (1983b), I examined and debunked the study and its various supporters (see Fieve, 1989; "In Texas," 1971). The researchers recommended putting lithium in the drinking water, much like drinking water has been fluoridated. Perhaps this is

the logical extension of absurd claims that psychiatric treatments correct biochemical imbalances without adversely affecting the brain.

## OTHER SO-CALLED MOOD STABILIZERS

Three antiepileptic drugs have now been FDA approved as mood stabilizers for the prevention of recurring episodes of mania: divalproex sodium (Depakote), extended-release carbamazepine (Equetro), and lamotrigine (Lamictal). Many of these drugs are prescribed to children for the control of epilepsy and, increasingly, for bipolar disorder. A critical question is their effect on the developing mental and emotional function of children, but there is little research on the subject (Loring, 2005).

Valproic acid (Depakene), sodium valproate (Depakene syrup), and divalproex sodium (Depakote, enteric-coated combination of the other two) are forms of an antiepileptic agent that has been approved by the FDA for the treatment of bipolar disorder. The drug can be hepatotoxic, especially in children. From the brain-disabling perspective, it can cause sedation, tremor, and ataxia. More rarely, it can cause adverse changes in mood and behavior, including behavioral automatisms, aggression, and confusion. Somnolence or delirium can develop, especially when combined with other sedatives (Silver et al., 1994). There may be "mild impairment of cognitive function with chronic use" (Hyman et al., 1995, p. 127). Like lithium, valproic acid causes delirium in a significant percentage of older patients (Shulman et al., 2005). It also causes a variety of endocrine disorders and metabolic changes (Verrotti et al., 2005). Clinically, I have seen this drug cause depression and hostility.

Of as yet unknown consequence to the brain and nervous system, there are many studies indicating that valproic acid promotes a variety of potentially dangerous viruses (e.g., Fan et al., 2005). Both valproic acid and carbamazepine cause a small increase in the rate of major congenital malformations in infants (Wide et al., 2004). Acute and potentially fatal pancreatitis has been reported with valproic acid (e.g., Grauso-Eby et al., 2003). Liver failure is a known problem as well. Valproic acid is known to cause hyperammonemia with encephalopathy (e.g., McCall et al., 2004). Severe and even lethal skin disorders can occur with all of the antiseizure medications now used as mood stabilizers. The various adverse effects of valproic acid and other mood stabilizers are not nearly as benign as physicians believe in their eagerness to switch patients from lithium.

Carbamazepine (Tegretol) is closely related to the tricyclic antidepressants. In neurological medicine, its principal uses are as an anticonvulsant for partial complex seizures and in the management of tic

douloureux, a facial pain syndrome. It causes similar brain-disabling effects to the older antidepressants, including sedation, tremor, confusion, depression, psychosis, and memory disturbances (chapter 7). Cognitive disturbances are more common with concomitant use of neuroleptics, with preexisting brain damage, and with aging (Hyman et al., 1995). In addition, it poses the threat of potentially lethal agranulocytosis or aplastic anemia. Carbamazepine can cause *hyponatremia* (low serum sodium), leading to a syndrome that includes lethargy, confusion or hostility, and stupor.

Clonazepam (Klonopin), a benzodiazepine tranquilizer, has been used to treat both acute mania and as prophylaxis. It has all the many, sometimes severe, problems associated with the other benzodiazepines, including sedation, rebound and withdrawal syndromes, addiction, and behavioral abnormalities (chapter 12). Neuroleptics remain the mainstay for controlling acute manic reactions.

Verapamil (Calan and others) is a calcium channel blocker used for the treatment of cardiac disorders that has also been used off-label as a mood leveler. It can produce a variety of cardiovascular side effects.

Clonidine, an antihypertensive drug, also has been used in the treatment of mania. Sudden withdrawal can produce a rebound hypertensive crisis. Consistent with the brain-disabling principles, it can produce a variety of psychiatric symptoms, including sedation, vivid dreams or nightmares, insomnia, restlessness, anxiety, and depression. More rarely, it can cause hallucinations. Unfortunately, this drug is too commonly used as a so-called mood stabilizer in children. When mistakenly prescribed with stimulants, it causes an elevated risk of cardiac arrhythmia and cardiac arrest in children.

Some clinicians will add a variety of antidepressants, including SSRIs like Prozac, to the treatment of patients with bipolar disorder. Nearly all antidepressants can cause or worsen mania (chapter 7). Nonetheless, Eli Lilly managed to obtain FDA approval for Symbyax, a combination of Zyprexa and Prozac, for the treatment of depressive episodes associated with bipolar disorder. In reality, Prozac should not be prescribed to patients with bipolar disorder, given the frequency with which SSRIs cause and exacerbate manic reactions.

The lengthy list of attempts to substitute for lithium suggests, once again, that it is hardly a specific magic bullet for mania or bipolar disorder.

## WHY SO MANY "BIPOLAR" PATIENTS?

When I was in my psychiatric training, we rarely saw a patient undergoing a florid manic episode. When a case was admitted, it would become a subject for grand rounds for everyone to see and evaluate. I can

remember only a handful of such cases during nearly 4 years working in psychiatric hospitals. Nowadays, the diagnosis of bipolar disorder has become a fad, and many patients are given it without meeting the diagnostic criteria. But many other cases do involve patients who have undergone maniclike episodes. Why the increase? As we saw in chapters 6 and 7, the newer antidepressant drugs commonly cause mania.

When a patient develops a maniclike adverse drug reaction, the correct diagnosis, according to the official American Psychiatric Association (2000) diagnostic manual, is substance-induced mood disorder. Yet I cannot recall a single patient who was properly diagnosed in this manner in either my clinical or forensic experience (Breggin, in press). Doctors do not want to admit to their own mistakes, and they do not want to disclose the mistakes of their colleagues, so it is so much easier to diagnose the patient as having a manic episode or bipolar disorder than as having an adverse drug reaction with manic features.

Even when the drug is such an obvious culprit that its role cannot be denied, the typical health care provider is likely to tell the patient and the family that the drug merely unmasked an underlying disorder. Instead of withdrawing the patient from the offending agent, the health care provider is likely to increase the dose or to add another drug, ultimately worsening the patient's condition. But as the research in chapters 6 and 7 shows, many people with no past history of manic episodes are driven into maniclike states by antidepressant medication.

Chapter 10 will examine one of the great shames of my profession of psychiatry: the increasing numbers of children diagnosed with bipolar disorder and medicated with adult mood stabilizers and neuroleptics.

## CONCLUSION

Lithium is a highly neurotoxic substance with a generally suppressive effect on neuronal function and mental function in the commonly prescribed therapeutic range. It is poisonous to brain cells. The much-promoted concept that lithium and other "mood stabilizers" are somehow "protective" of brain cells is fantastical.

Lithium has no specific therapeutic effect on mania or other states of overexcitement. Its brain-disabling effect is not specific for patients diagnosed as manic or bipolar. Lithium will subdue or suppress the mental and physical functioning of animals, newborn infants and nursing infants of mothers who take lithium, and normal volunteers, as well as people diagnosed with psychiatric disorders. Lithium-treated volunteers suffer devastating effects on their ability to relate and to function intellectually. Animals show similar taming effects.

Lithium is highly spellbinding. Normal volunteers fail to perceive how impaired they have become, and patients given therapeutic doses easily become severely toxic without perceiving their deteriorating clinical condition. Patients treated long term with lithium typically fail to perceive how subdued they have become or how impaired their memories have become.

The various alternatives to lithium have their own brain-disabling effects, and none of the drugs is specific for mania.

Although lithium possesses these suppressive properties, it is not as effective in controlling mania as the neuroleptics, especially in acute mania or in severe, recurrent mania. This is partly because lithium is too overwhelming in toxicity in doses sufficient to subdue severely disturbed or rebellious individuals.

The claim that lithium is a disease-specific therapy for mania or manic-depressive (bipolar) disorder has no basis in fact; it is a brain-disabling agent. Its efficacy has been exaggerated, and its adverse effects on the brain and mind, as well as the body as a whole, have been too frequently minimized.

## NOTE

1. I obtained a translation of the original article from one of the authors.

CHAPTER 9

# Electroconvulsive Therapy (ECT) for Depression

ECT is frequently used and retains enormous support within the medical profession. Despite recent scientific blows to their "treatment," electroshock advocates remain determined, powerful, and influential. Anyone who doubts this need only read the September 12, 2007, issue of the *Journal of the American Medication Association (JAMA)* titled "Interest Surging in Electroconvulsive and Other Brain Stimulation Therapies" (Lamberg, 2007). Beneath a photo of health professionals hovering over an unconscious ECT patient, the caption reads, "Although studies have demonstrated that electroconvulsive therapy (ECT) is an effective and safe treatment for severe major depression, inaccurate perceptions of ECT contribute to lingering stigma and fear regarding its use." This positive and even promotional attitude flies in the face of decades of research and heartrending patient testimonials. The publication of this puff piece at this time is probably intended to counter yet one more recently published scientific study that demonstrated the damaging effects of electroshocks to the brain (Sackeim et al., 2007).

Beginning in 1979 with the publication of my book *Electroshock: Its Brain-Disabling Effects,* followed by many other book chapters and scientific reports, I have marshaled innumerable studies, bolstered by my clinical experience, to show that electroconvulsive therapy (ECT) causes permanent brain dysfunction and damage, including widespread memory

and cognitive deficits. I have also evaluated evidence that contrary to claims that ECT prevents suicide, ECT is ineffective and actually causes or contributes to suicide.

Since the 1997 edition of this book, my task has been lightened by research from the heart of the ECT establishment confirming that ECT causes permanent brain damage and dysfunction with widespread cognitive deficits and that ECT greatly elevates the suicide risk, especially in the first week following treatment. In addition, a recent review of controlled clinical trials for ECT demonstrated once again that the so-called treatment is ineffective. And finally, for the first time in history, an ECT malpractice case has been won in court.

Since the ECT literature almost never provides clinical cases that describe the damage caused by the treatment, I will begin with a case from my own clinical practice.

## A LIFE DESTROYED BY ECT

Sarah Williams was 55 years old when her husband died of a sudden heart attack in the early spring. She managed to teach music in high school for the remainder of the year, but by the summer, her "blues" worsened. She lost weight, had difficulty staying asleep at night, and even lost her zest for visiting with her grown children. Her oldest daughter, Jeannette, became concerned and in June took her to a psychiatrist. On the first visit, he put her on a tricyclic antidepressant, doxepin, that made her feel too groggy, so she stopped taking it. Then he put her on Prozac, which made her feel agitated. She was now both depressed and agitated, and her psychiatrist admitted her to a hospital for ECT.

Jeannette was very reluctant to submit her mother to ECT, but she was convinced by the doctor and a video film that shock was the most effective modality for depression. Jeannette and her mother were told that the electrical current and the grand mal convulsion that it produced were virtually harmless. The electrodes would be placed on only one side of the head *(unilateral ECT),* with the latest modifications to prevent injury.

Mrs. Williams herself protested about having electricity passed through her brain, and she wondered why no one seemed to want to talk with her about her feelings. Didn't psychiatrists do talking therapy anymore? But she was willing to accept anything that promised an end to the hopelessness that pervaded her life. She especially wanted to stop being a burden to her daughter Jeannette.

After the first shock treatment, Mrs. Williams developed a headache and stiff neck. She was somewhat nauseated. By the third treatment,

given every other day, she was confused and could not recall her daughter's previous visit. Her daughter was reassured by the doctor that this was "normal" for ECT, that all the effects were temporary, and that it would be best if she did not see her mother until the series of 10 ECTs was completed.

The nurse's notes from the hospitalization showed increasing "complaints" of memory difficulties by Mrs. Williams as the treatments progressed in number. However, after the eighth ECT, she stopped communicating about anything. The doctor's progress note at this point stated, "Improved. No longer complaining of feelings of depression." The nurse's progress note indicated, "No complaints. Sits quietly."

By the 10th treatment, Mrs. Williams could not find her way around the ward. The head of occupational therapy noted that the patient was too "disoriented and confused" to participate in the music and art activities.

When Jeannette visited her mother again at the conclusion of the treatments, she hardly recognized her. The expression on her mother's face was bland and indifferent, rather than pained. Sometimes her mother got a silly, almost goofy look that especially upset Jeannette. Her mother had always been so serious and dignified. To her daughter's dismay, her mother could not remember any of the events of the previous summer, including the visits to the psychiatrist. She could not remember who had come to her husband's funeral the previous April. She could not remember much about teaching for two semesters during the school year.

Mrs. Williams stayed in the hospital for 1 week after the completion of the ECT. At that time, her insurance ran out, and she was discharged home. Her discharged diagnosis was "major depression in remission."

Jeannette could see that her mom looked confused as she drove her home. She did not seem to recognize the neighborhood where she had lived for 30 years and raised her children. At home, her mother could not find the coffee or the sugar. She did not recognize the blender that Jeannette had bought her the previous Christmas.

A week later, Jeannette went to see the psychiatrist with her mother. The psychiatrist reassured her that he had never seen a case of permanent memory loss following electroshock, except for memory blanks for the period immediately around the shock treatment.

In September, 2 months after the ECT, Mrs. Williams tried to return to teaching but quit after 2 weeks. She could not remember the books or teaching materials she had been using for several years. The principal, who had started at the school a year earlier, looked like a stranger to her. She had trouble recognizing most of her previous students, including some who had been in music class with her for several years.

For the first time in her life, Mrs. Williams found she was having difficulty hearing music in her head. She was slow reading music and was

distraught that she could not learn new pieces by heart anymore. She felt like a beginner in music, except she could not learn as well as a beginner. She wanted to die and became suicidal for the first time in her life.

Jeannette took her mother back to the psychiatrist, who insisted that none of these problems could be from the shocks administered to her mother's head. He said that Mrs. Williams was depressed and needed more ECT. Instead, Jeannette took her mother home to live with her.

It was now January, and her mother was not getting any better. Mom was a changed person. Her personality was gone. So was her vitality. She could not remember the simplest things such as a phone call message or a list of three items to get at the grocery store.

Jeannette took her mom to the university medical center for evaluation. Lengthy neuropsychological testing over a 2-day period indicated that her mother had major impairments in anterograde memory (learning and recalling new material) and in retrograde memory (remembering past events). Some of her memory losses extended back several years. She had difficulty concentrating, and there were impairments of abstract reasoning. Formerly very quick mathematically, she was now poor at simple calculating. Her overall IQ had dropped 20 points. She became very fatigued and frustrated from the effort of trying so hard on the tests.

The neuropsychologist described the pattern as typical of traumatic brain injury, but after a consultation with Mrs. Williams's former psychiatrist, he avoided any suggestion that the deficits could have been caused by a series of electroshocks to the brain. Brain wave studies showed that Mrs. Williams had abnormal slow waves on her electroencephalogram (EEG) consistent with brain injury to the right frontal lobe and the anterior portion of the right temporal lobe (the two sites of electrode placement). A brain scan (MRI) showed possible atrophy in the same region.

To this day, Mrs. Williams's psychiatrist states that he has never seen a case of permanent memory loss, or any other permanent neuropsychological deficits, following ECT. He did not report the case in the literature, to the Food and Drug Administration (FDA), or to the manufacturer of the shock machine.

Mrs. Williams remains chronically depressed and refuses to go to any doctors for anything. She lives with her daughter, who supports her financially.

Cases like Mrs. Williams's have become increasingly common as psychiatry relies more and more exclusively on drugs and ECT. The last decade has seen a resurgence in the promotion and use of ECT, also called electroshock, or simply shock treatment. For a brief time before the 1997 edition of this book, the press had taken note of the escalating controversy surrounding its use (Boodman, 1996). A critical article by Cauchon (1995) in *USA Today* was followed up by a remarkable editorial

("Patients, Public Need," 1995), declaring that "the long-term effects can be devastating. They include confusion, memory loss, heart failure, and, in some patients, death." In more recent years, the shock doctors have been working hard to promote this barbaric treatment and have received less criticism from the media.

ECT is a treatment that originated in Italy in 1938 for producing convulsions in psychiatric patients. At the time, it was thought that convulsions induced by a variety of methods, including insulin coma and stimulant medication, were useful in treating psychiatric disorders, especially schizophrenia.

Nowadays, ECT is recommended for major depression, usually when other approaches have failed. However, some doctors quickly resort to it. Probably more than 100,000 patients a year in the United States are shocked. The majority are women, and many are elderly. Advocates of shock have resisted the creation or maintenance of state registers for shock treatment, so most of the data on the frequency of its use are relatively old. In California, for example, two-thirds of shock patients were reported to be women, more than half of whom were 65 or older (Department of Mental Health, 1989). Data (1989–1993) from Vermont concerning ECT showed that 77% of shock patients were female (W. Sullivan, personal communication, 1996). For all sexes, 58% were at least 65 years old, and 20% were at least 80 years old. During this time, one Vermont hospital, Hitchcock Psychiatric, shocked 35 women and 1 man who were 80 and older. Overall, the hospital shocked 112 women and 26 men during those 5 years.

The use of ECT tends to vary from institution to institution. At Johns Hopkins, for example, a biologically oriented center, 20% of the inpatients may be on a regimen of ECT at any one time (Wirth, 1991). The data was obtained under oath in a deposition, and I'm unaware of any more recent data, but shock treatment in general has increased in usage since then.

## BREAKING NEWS IN ECT RESEARCH: SHOCK TREATMENT CAUSES IRREVERSIBLE BRAIN DAMAGE AND DYSFUNCTION

Beginning in 1979, when I published *Electroshock: Its Brain-Disabling Effects,* through the 1997 edition of *Brain-Disabling Treatments in Psychiatry,* and even until 2006, during my most recent trial testimony in an ECT malpractice case, I have had to marshal sophisticated, detailed, scientific arguments to show that shock treatment causes permanent memory loss and cognitive dysfunction. In presenting my evidence and my

conclusions, I had to overcome uniform disapproval and disagreement from the electroshock establishment that dominates the scientific discourse. Even psychiatrists who rejected ECT in their own practices would not risk standing up in opposition to the powerful ECT lobby.

Then something remarkable happened. In 2007, a team led by longtime, staunch electroshock advocate Harold Sackeim et al. published a follow-up study of patients given electroshock. The researchers found that the patients were devastated with widespread losses not only in memory, but also in cognitive functioning—the ability to think and learn.

Sackeim et al. (2007) followed up 347 patients given the range of currently available methods of electroshock, including the supposedly newer and most benign forms, and confirmed that electroshock causes *permanent* brain damage and dysfunction. The patients were selected from the community, that is, from patients in the real world of clinical practice rather than from an experimental study.

When tested 6 months after the last ECT, each form of treatment was found to cause lasting memory and cognitive dysfunction. The losses extended far beyond the erasure of memories surrounding a few months before and after the treatment. Many patients never recovered normal memory function. They described difficulties learning new things and suffered measurable losses on testing in "global cognitive status." Although the authors avoided straightforward language, the patients were suffering from permanent brain damage affecting global mental function.

The results of the Sackeim et al. (2007) study were highly statistically significant ($p < .0001$ on 10 of 11 tests and $p < .003$ on the 11th). Adding to the evidence for permanent brain damage, many of the patients also had persistent EEG abnormalities 6 months after the treatments had ended. Although the older shock techniques were the most damaging, they were also the most commonly used in the community, and the newer technologies also produced significant lasting deficits in memory and cognitive function.

Despite Sackeim's vigorous opposition to my views over the past many years, his study (Sackeim et al., 2007) cited my 1986 scientific article "Neuropathology and Cognitive Dysfunction From ECT" published in the *Psychopharmacology Bulletin,* noting that "critics contend that ECT invariably results in substantial and permanent memory loss."

## STILL AVOIDING THE FACTS

Remarkably, the detailed Sackeim et al. (2007) study leaves out some of the most important details, such as exactly what proportion of patients

suffered from each of the various deficits in memory and overall cognitive functioning. The tone of the article implies that just about everyone suffered from deficits; they are treated as one catastrophic group. But the all-important details were not disclosed. The extraordinarily low *p*-value on the cognitive testing ($p < .0001$) provided a strong indicator that the devastation was widespread, involving the vast majority of patients.

Sackeim et al. (2007) also failed to address the real-life impact of these losses on individual patients and did not provide any clinical vignettes. Stating that shock treatment permanently reduces memory and cognitive function, and describing it statistically, failed to capture the manner in which the "treatment" destroyed the minds of these patients and wrecked their lives. That is why I opened the chapter with the story of Sarah Williams.

Did his own research at last induce Harold Sackeim to make public statements withdrawing his previous wholehearted support for ECT? To the contrary, shortly after the publication of his paper I began to receive calls from the media asking me to respond to promotional claims by Dr. Sackeim in support of a supposedly new and improved form of ECT that sounded very much like the same old thing. One is left to wonder what drives so many mental health professionals in such an unrelenting, remorseless fashion to damage the brains of their patients.

## MORE BREAKING NEWS IN ECT RESEARCH: SHOCK TREATMENT CAUSES SUICIDE

ECT is frequently justified as treatment of last resort in cases at high risk for suicide. But research uniformly shows that ECT has no beneficial effect on the suicide rate. Indeed, the most thorough study available, published in the *British Journal of Psychiatry* in 2007, found an overall *increased* rate of suicide in patients previously given ECT (Munk-Olsen et al., 2007). In addition, "patients treated with ECT in the past week had a *greatly* increased risk of suicide compared with other patients (RR = 4.82, 95% CI 2.22–10.95)" (p. 437, emphasis added).

The authors are proshock and minimized the importance of their results concerning increased suicide, not even mentioning it in the title. Furthermore, they failed to make clear that this data wholly contradicted the main justification for giving shock treatment: that it is supposedly the quickest and most effective way of preventing acute suicidal activity. Instead, without evidence the authors repeated the old saw that "suicidal intent in patients with depression is rapidly relieved by ECT" (p. 438).

Munk-Olsen et al. (2007) based their observation on ECT-induced suicidality on a review of all inpatient admissions to a Danish hospital

from 1976 to 2000 where 95% of the treatments were unilateral, indicating that the more modern techniques were used. Although the total number of patients given ECT was not provided, the numbers were considerable, given that 149 patients died by suicide during the study period.

All ECT studies involving larger numbers of patients are conducted by doctors who favor the treatment and therefore have access to the data, and invariably they minimize or misrepresent negative results. Munk-Olsen et al. (2007) are typical in this regard, not including any research critical of ECT in their bibliography. The study found that mortality from natural causes was also elevated during the first 7 days after ECT but that overall, it was decreased, especially for respiratory diseases. However, there is no discussion of death due to ECT treatment itself, including anesthesia, which in itself poses a significant risk (Lagasse, 2002).

In a blatantly misleading fashion, a series of negative studies were cited by the American Psychiatric Association (APA; 1990b) task force report as showing a positive effect. For example, a retrospective study by Avery and Winokur (1976) found no improvement in the suicide rate compared to matched controls who had no shock treatment: "In the present study, treatment was not shown to affect the suicide rate" (p. 1033). Yet it was presented in the 1990 task force report as supporting the position that ECT results in "a lower incidence of suicide" (p. 53). The task force also mentioned three other studies as supporting a beneficial effect on suicide. However, two of them (Avery et al., 1977; Milstein et al., 1986) specifically found no such beneficial effect, and the third (McCabe, 1977) did not even deal with suicide. Meanwhile, unmentioned were two retrospective studies of relatively large populations of ECT patients and matched controls in which ECT had no effect on the suicide rate (Babigian et al., 1984; Black et al., 1989).

I have rarely seen so much outright fabrication in the psychiatric literature as I have seen in regard to ECT and lobotomy (for more details, see Breggin, 1979, 1981a&b, 1982). Perhaps because these treatments are so violent and devastating, the doctors who perpetrate them, much like other perpetrators of violence (Breggin, 1992a), are especially prone to hide or to lie about the harmful effects of what they are doing.

Overall, there is little or nothing in the literature to suggest that ECT ameliorates suicide, whereas a significant body of literature confirms that it does not, and the most thorough study shows that it increases the overall suicide rate, including a major increase within the week after the last ECT. Once again, treatment opinions are not driven by empirical data. Instead, empirical data is ignored, distorted, or misrepresented to confirm treatment opinions.

My own clinical impression also confirms that ECT increases the suicide risk for many patients. After ECT many patients profoundly miss

memories of significant past events in their lives and feel overwhelmed by their inability to learn and to remember as well as they once did. Many feel as if their personalities and identities have been destroyed. As a result, they often feel deeply betrayed by their doctors. Inevitably some grow increasingly hopeless and suicidal. It is well known, for example, that Ernest Hemingway attributed his suicide to despair over ECT ruining his memory and rendering him unable to write (Hotchner, 1966).

As they attempt to recover from the treatment, ECT patients frequently find that their prior emotional problems have now been complicated by brain damage and dysfunction that will not go away. If their doctors tell them that ECT never causes any permanent difficulties, they become further confused and isolated, creating conditions for suicide.

Many shock survivors have told me that reading my articles and books about ECT was a life-affirming experience for them. Instead of reacting with more despair to the confirmation of their ECT-induced brain damage and disability, they have felt understood and empowered for the first time. Mental health professionals should be advised that it is both ethical and beneficial to acknowledge to patients in a supportive, empathic manner that they have been injured by the treatment.

## ADDITIONAL BREAKING NEWS: ECT IS INEFFECTIVE

Ross (2006) recently reviewed the sham ECT literature: "The author reviewed the placebo-controlled literature on electroconvulsive therapy (ECT) for depression. No study demonstrated a significant difference between real and placebo (sham) ECT at 1 month posttreatment." This was the crowning summary of considerable prior research confirming that ECT is ineffective.

Rifkin (1988) noted that the claim is frequently made that ECT is more effective and works more rapidly than drugs in the treatment of depression. He found nine controlled studies comparing the two treatments, but they were badly flawed. He could find no conclusive evidence that ECT was better than antidepressant treatment.

Crow and Johnstone (1986), in a review of controlled studies of ECT efficacy, found that both ECT and sham ECT were associated with "substantial improvements" and that there was little or no difference between the two. Crow and Johnstone concluded, "Whether electrically induced convulsions exert therapeutic effects in certain types of depression that cannot be achieved by other means has yet to be clearly established" (p. 27).

Crow and Johnstone's (1986) critical review, which was presented at a large conference of shock advocates, is not cited in the APA report

on ECT. Instead, the APA (1990b) task force's proposal for a "sample patient information sheet" declared that "ECT is an extremely effective form of treatment" (p. 160).

At the June 1985 Consensus Conference on ECT, critics and advocates of ECT debated the issue of efficacy. The advocates were unable to come forth with a single study showing that ECT had a positive effect beyond 4 weeks. Many studies showed no effect, and in the positive studies, the improvements were not dramatic. That the treatment had no positive effect after 4 weeks confirmed the brain-disabling principle since 4 weeks is the approximate time for recovery from the most mind-numbing effects of the ECT-induced acute organic brain syndrome or delirium.

The Consensus Conference panel concluded in its report that ECT had no documented positive effect beyond 4 weeks. Acute brain damage and dysfunction, with a high probability of permanent adverse effects, are inflicted upon the patient in order to achieve a brief period of traumatically induced emotional blunting or euphoria. ECT is a wholly irrational, unjustifiable treatment.

## ANOTHER DRAMATIC EVENT IN THE WORLD OF SHOCK TREATMENT

For several decades, I have been a medical expert in lawsuits against doctors and hospitals for causing permanent brain damage with electroshock treatment. I have also been an expert in product liability suits against the manufacturers of the machines. A number of the suits against doctors, hospitals, and shock manufacturing companies were resolved, often with substantial settlements for the victims. But on several occasions, when cases against doctors went to trial, they were lost. The cases in which I testified were not the only ones that failed to win a jury verdict. Until 2006, not a single electroshock malpractice case had ever been won in court anywhere in the world.

Why were the cases lost in trial? There are no easy answers. In several of the cases in which I was involved, our side presented two, three, and even four medical experts who confirmed that shock causes brain damage. At the same time, the defendants could always find well-known professors of psychiatry to defend the treatment as essentially harmless and enormously beneficial. Probably it has been hard for juries to disentangle totally conflicting evidence from critics and advocates of the treatment. In addition, critics like me refuse to send patients for shock treatment, and of course, we do not administer it to patients, so the advocates can present themselves as the only experts with the "clinical experience." In addition, it must be hard for juries to believe that so many doctors and so

many medical groups would support a treatment that routinely damages the brain. They must find it hard to believe that doctors would simply lie about the damaging effects of their treatments. Finally, victims of shock treatment often remain irritable and angry for the rest of their lives, suffering from the emotional instability and poor impulse control associated with brain damage and dysfunction. As a result, they sometimes present unsympathetically when they testify before juries.

Finally, in 2006, an electroshock case was won against a physician. But even then, the verdict was quirky. The jury found the prescribing physician negligent. He was the one who initially recommended the treatment. But it exonerated the physicians who administered the treatment, even though they broke numerous standards, including giving the treatment on an outpatient basis on a much more frequent basis than is usually done in the hospital. I thought the doctors who carried out the treatment in such an excessive and cavalier manner were far more to blame than the doctor who recommended it.

The case involved a nurse who believed she had previously benefited from the treatment. This time, the series of closely packed treatments obliterated her nursing training and her personal memories extending back years and caused continued memory and cognitive dysfunction. I cannot explain why this case was won, while so many others have been lost. In most of the prior ECT trials, I was one among several experts testifying on behalf of the victim; but this time I was by myself. However, the patient's psychotherapist, an empathic and courageous woman, described the devastating effects of the treatment on her client. The attorney was excellent; but I have worked with good attorneys on earlier shock suits. A key defense expert in many cases, Max Fink (see subsequent discussion), was not called to the witness stand, and this probably hampered the doctors' case. Fink had admitted in deposition that he had not read the victim's medical record but that he had already decided to testify on behalf of the doctors that they had done nothing wrong. It seemed to compromise his credibility and perhaps kept the defense from calling him to the stand. Whatever the reasons for this victory, in the future, medical experts who are critical of shock treatment will now be armed with Sackeim et al.'s (2007) research, creating a major breach in the professional wall of silence about shock's damaging effects.

## THE FOOD AND DRUG ADMINISTRATION AND ECT

In 1979, the FDA classified shock devices as demonstrating "an unreasonable risk of illness or injury" (see Food and Drug Administration [FDA], 1990). This would have required animal testing for safety. However, under

pressure from the APA, the FDA gave notice of its intent to reconsider its original decision and to reclassify ECT machines as safe. The APA's (1990b) task force report was timed to come out in the midst of the FDA's political squirming over ECT.

The FDA's (1990) final report reads remarkably like the APA's (1990b) report, including the mistaken or false citations mentioned earlier in this chapter. Although no large animal studies have been done with shock devices since the 1950s (some have been done with rats) and although those earlier large animal studies consistently demonstrated brain damage (see subsequent discussion), the FDA panel recommended defining ECT devices as safe for depressed patients. It did so ambivalently, recommending that the approval be delayed until the establishment of engineering safety standards for the machines. The approval process continues to be delayed by the lack of approved standards, and ECT exists in a kind of FDA limbo, which has not discouraged psychiatrists from using it.

I have reviewed what the FDA has made available through the Freedom of Information Act as its complete file on ECT. There are dozens of recommendations from state-funded and private patient rights and advocacy groups to ban ECT, and hundreds more from patients who feel that they have been permanently damaged by the treatment. It is astonishing that the FDA has ignored or rejected such an avalanche of official recommendations and personal reports and protests.

In recommending the approval of ECT as safe and effective, the FDA ignored a most remarkable situation. Before being put on the market, the ECT machines, such as the commonly used MECTA, were not tested for safety on animals or humans. There were no systematic or controlled studies to evaluate their impact on the living brains of animals or humans. The FDA simply took the word of organized psychiatry and ECT advocates that the treatment is safe and effective. Once again I am left to wonder if we are dealing with a treatment that is so egregiously abusive that the perpetrators, including the APA and the FDA, feel compelled to hide the facts from the public.

## THE POLITICS OF THE 1990 AMERICAN PSYCHIATRIC ASSOCIATION REPORT

The political nature of the APA (1990b) task force report is reflected in the membership of the panel that wrote it. The chairperson, Richard Weiner, was APA's official representative in defense of ECT at the FDA hearings and has for some time been APA's chief spokesperson on the subject. Two of the other six members are psychiatrist Max Fink and psychologist Harold Sackeim, whom we have already met as among the

nation's most zealous promoters of the treatment. Fink (1994, 1995) has actively pressed for the increased use of shock treatment for children and adolescents. Sackeim et al. (1993) wrote an article calling for a return to much higher electrical doses, given the "old-fashioned way," with bilateral electrode placement (see subsequent discussion) to increase the intensity of the shocks.

By contrast, the task force (APA, 1990b) sought no input from the several patient organizations that oppose the treatment, and none from psychologists, psychiatrists, neurologists, and other professionals who are critical of it.

The APA (1990b) task force report, in its acknowledgments, thanked the manufacturers of electroshock machines for their contributions; company advertising handouts are listed as useful sources of public information; and the names, addresses, and phone numbers of these companies are provided in the report. The task force is particularly positive toward Somatics Inc., whose sole function is to manufacture the electroshock machine Thymatron. Somatics Inc. is acknowledged for providing "input into the guidelines." Under the heading "Materials for Patients and Their Families," the task force cited a pamphlet by Richard Abrams and Conrad Swartz and a videotape by Max Fink, both of which are advertising materials for Thymatron and can only be obtained by writing to the manufacturer.

The report (APA, 1990b) nowhere mentions any link between Thymatron and Richard Abrams, who would appear to be the task force's most valued expert. One of Abrams's articles is recommended under "Materials for Patients and Their Families" and another under "Materials for Professionals." Nine of his publications are cited in the report's general bibliography, making him by far the most heavily represented author. Abrams is also listed among those individuals who "provided comment on the draft of the ECT Task Force Report." However, his most interesting affiliation is unmentioned: Abrams owns Somatics Inc. In a deposition in which he was a medical expert (*DeToma v. Brohamer,* 1991), as a result of my prompting the defense attorney to ask the question, Abrams had to acknowledge under questioning that Somatics Inc. is the source of 50% of his income.

## ECT, WOMEN, AND MEMORY LOSS

Women have always been the main victims of the most destructive psychiatric treatments, including lobotomy. In recent decades, older women have become the major population for ECT, despite the absence of controlled studies on safety or efficacy in the elderly.

One of the most remarkable reports in the ECT literature was published by Warren (1988), who studied 10 women post-ECT, including their family relationships. Many of the women thought that the purpose of the treatment was to erase their memory. While some felt it was helpful to forget painful memories, they "uniformly disliked the loss of everyday memory, as well as associated effects such as losing one's train of thought, incoherent speech, or slowness of affect. What specifically was forgotten varied from matters of everyday routine to the existence of one or more of one's children." Warren is not a physician and perhaps without knowing about the specific clinical syndrome, she described mild to moderate dementia caused by closed-head injury in the form of ECT.

According to Warren, family members sometimes approved of the memory loss. One husband said, "They did a good job there," referring to his wife's loss of memory concerning their past marital conflicts. A patient who had been molested by her mother's brother believed that her mother wanted her to have "the full treatment" to "make me forget all those things that happened."

Three of the 10 women lived in dread of ECT for years afterward but were afraid to express their angry feelings for fear of being sent back to the hospital for involuntary shock treatment. In my clinical experience, this is a realistic fear. Doctors frequently respond to complaints about the treatment by deciding that the patient is in need of more treatment. Repeated "treatment" can usually be relied on to put an end to all protests.

Shock treatment has been used even more blatantly to erase the memories and even the personalities of patients, usually women. H. C. Tien, in the early 1970s, described the use of unmodified ECT to erase the personalities of women, then to "reprogram" them as more suitable wives—with their husbands' help ("Electroshock," 1972; "From Couch to Coffee Shop," 1972). World-renowned Canadian psychiatrist D. Ewen Cameron at McGill University, in part utilizing secret funds from the Central Intelligence Agency, used multiple ECTs to obliterate the minds of his patients and then to reprogram them (Cameron et al., 1962; for more details on the Tien and Cameron controversies, see also Breggin, 1979, 1991b).

## ECT AND THE ELDERLY

As already noted, elderly women have become the most frequent target of ECT. The elderly, of course, have more fragile brains and are especially sensitive to biopsychiatric interventions, even relatively mild doses of drugs. In addition, many elderly already suffer from memory dysfunction

due to a variety of causes, making them especially vulnerable to the worst effects of ECT.

Against all common sense, the APA (1990b) task force advised that ECT can be used "regardless of age" (p. 15) and cited the successful treatment of a patient aged 102 (pp. 71–72). It did warn, however, that "some elderly patients may have an increased likelihood of appreciable memory deficits and confusion during the course of treatment" (p. 72).

The aged are, in fact, gravely at risk when exposed to any form of head trauma, including electrically induced, closed-head injury from ECT. There are a growing number of reports of special dangers to the elderly that were not mentioned in the APA (1990b) or FDA (1990) reviews (Figiel et al., 1990; Pettinati et al., 1984). In a curious twist, an article by Burke et al. (1987) was listed in the bibliography of the APA report but not cited in the actual discussions of the elderly. Burke et al. found a high rate (35%) of complications among the elderly. They noted, "Common complications in the elderly include severe confusion, falls, and cardiorespiratory problems" (p. 516).

In a study involving 3 times as many women as men, Kroessler and Fogel (1993) produced data indicating that ECT can cause a devastating decline in longevity:

> This is a longitudinal study of 65 patients who were 80 years old or older at the time they were hospitalized for depression. Thirty-seven were treated with ECT and 28 with medication. Survival after 1, 2, and 3 years in the ECT group was 73.0%, 54.1%, and 51.4% respectively. Survival after 1, 2, and 3 years in the non-ECT group was 96.4%, 90.5%, and 75.0% respectively. (p. 30)

These are extraordinary findings, indicating a very high increase in mortality in the elderly who received ECT. The authors, however, argued that the patients receiving ECT were more physically ill and hence at greater risk of dying. They provided no data to justify this speculation or to otherwise explain such a vast difference in mortality.

In the Kroessler and Fogel (1993) study, the tragic lethality of ECT was compounded by its lack of efficacy. ECT patients were much more frequently rehospitalized for depression than non-ECT patients (41% vs. 15%). The recurrence rate of depression was more than twice as high among the ECT patients compared to the non-ECT patients (54.1% vs. 25%). Lasting recovery from depression was much lower in ECT patients (22% vs. 71%). If psychiatry were practiced in a rational manner, a study like this would have brought a halt to giving ECT to the elderly.

Elderly women are particularly vulnerable to being diagnosed with depression, with the associated risk of having ECT imposed upon them.

Older women often have many reasons—psychosocial and economic, some of them rooted in the ageist and sexist attitudes of our society—for feeling depressed. Often, these women need improved medical care, social services, family involvement, and loving care from friends and volunteers. Too often, their depression is being caused or aggravated by multiple medications for elevated hypertension or elevated cholesterol that can cause feelings of fatigue and depression. Even the so-called antidepressants that have been given to them prior to ECT can cause suicidal depression and an overall worsening of their mental state. Instead of ECT, they need their medications and their overall health care reevaluated, along with all of their basic needs. Meanwhile, they typically do not have the strength to resist a doctor's proposal that they undergo electroshock. There may be no family members available or willing to protect them. One thing the elderly do not need is more brain cell death, mental dysfunction, and memory deficits.

I have been a consultant or a medical expert in several suits in which psychiatrists have tried to administer electroshock against the will of elderly women who had no family to defend them. Each time, the doctors have backed down or, as in the case of Lucille Austwick, they have lost in court (Boodman, 1996). However, many other elderly women are probably getting shocked involuntarily without their situation gaining public attention. In addition, in my experience, many seemingly voluntary patients are badgered or misled into taking the treatment.

## BRAIN INJURY BY ELECTROSHOCK

### The Production of Delirium (Acute Organic Brain Syndrome)

After one or more shock treatments, ECT routinely produces delirium or an acute organic brain syndrome. Abrams (1988), although an advocate of the treatment, has himself observed that

> a patient recovering consciousness from ECT understandably exhibits multiform abnormalities of all aspects of thinking, feeling, and behaving, including disturbed memory, impaired comprehension, automatic movements, a dazed facial expression, and motor restlessness. (pp. 130–131)

At times, patients are so organically impaired following ECT that they will sit around apathetically on the ward, unable to engage in any activities. On occasion, the patients' neurological dilapidation from routine ECT will reduce them to lying in a fetal position for many hours. In malpractice suits in which I have been a medical expert for plaintiffs,

psychiatrists for the defense have claimed that this kind of neurological collapse following ECT is normal and harmless.

Given that ECT routinely produces acute, marked brain dysfunction, there can be no real disagreement about its damaging effects. The only legitimate question is, "How complete is recovery?" Even without all the confirmatory evidence presented in this chapter, basic neurology warns that it will frequently be incomplete.

## ECT As Closed-Head Electrical Injury

Neurology recognizes that relatively minor head trauma—even without the delirium, loss of consciousness, and seizures associated with ECT—frequently produces chronic mental dysfunction and personality deterioration (Bernat et al., 1987). If a woman came to an emergency room in a confusional state from an accidental electrical shock to the head, perhaps from a short circuit in her kitchen, she would be treated as an acute medical emergency. If the electrical trauma had caused a convulsion, she might be placed on anticonvulsants to prevent a recurrence of seizures. If she developed a headache, stiff neck, and nausea—a triad of symptoms typical of post-ECT patients—she would probably be admitted for observation to the intensive care unit. Yet ECT delivers the same electrical closed-head injury, repeated several times a week, as an alleged means of improving mental function. ECT is electrically induced closed-head injury.

The symptoms of mild to severe closed-head injury were listed in detail by Fisher (1985). They include impairment of every area of mental, emotional, and behavioral function, and confirm that the multiple adverse effects of ECT on the mind and brain are classic symptoms of closed head injury. McClelland et al. (1994) described the postconcussive syndrome in terms of

> the emergence and variable persistence of a cluster of symptoms following mild head injury. Common to most descriptions are somatic symptoms (headache, dizziness, fatiguability) accompanied by psychological symptoms (memory and concentration difficulties, irritability, emotional lability, depression and anxiety).

The authors observed that between one-third and one-half of head injury victims experience this symptom cluster over the first few weeks and a "substantial minority" continue to experience it for months or a year or more.

Head injury victims, including post-ECT patients, frequently develop an organic personality syndrome with shallow affect, poor judgment,

irritability, and impulsivity. They seem "changed" or "different" to people around them, much as lobotomy patients often seem to their families. Sometimes they become slightly clumsy, moving awkwardly or dropping things. Often they have "lapses" where they cannot think or cannot voice their thoughts. Sometimes their handwriting deteriorates. Headaches frequently begin with the traumatic treatment and may recur indefinitely.

Many post-ECT patients suffer from irreversible generalized mental dysfunction with apathy, deterioration of social skills, trouble focusing attention, and difficulties in remembering new things. I have worked with a number of them who suffer from dementia, confirmed by neuropsychological testing. Several have developed partial complex seizures or psychomotor epilepsy, permanently abnormal EEGs, and atrophy on brain scans. Many have been deprived of the experience of years of their lives, their professional careers, and their mental ability following ECT (Breggin, 1979, 1981a).

## Death, Suicide, and Autopsy Findings

Many deaths were reported in association with ECT in the first few decades of use. An extensive autopsy series indicated that many suffered from trauma to the brain resulting in visible pathology (Impastato, 1957). Advocates for ECT have claimed the death rate is very small or nearly nonexistent; but I have suspected that deaths are simply no longer reported. For example, I know of deaths of ECT recipients in the Baltimore–Washington, DC, area that have gone unreported.

There has been some epidemiological confirmation of the probability of a significant death rate. A law passed in Texas in the early 1990s required the reporting of death within 2 weeks after ECT. From June 1993 through August 1994, 8 deaths were reported among nearly 1,700 patients subjected to shock treatment. Controversy surrounds causation, and critics of ECT attempted without success to obtain more autopsy details (Smith, 1995).

## Memory Deficits

Electroshock specialists almost never seriously consider the memory deficits of their patients. In case after case that I have evaluated for clinical or forensic purposes, I have been the first doctor to take the symptoms seriously, let alone to take a complete inventory of memory losses and ongoing mental difficulties. I have previously outlined a method for evaluating memory deficits from ECT (Breggin, 1979).

The recent study by Sackeim et al. (2007) described earlier in the chapter should put to rest the question of whether or not ECT causes

permanent cognitive dysfunction and memory loss. However, psychiatry has a long history of ignoring negative research about its treatments.

For example, the APA (1990b) task force report, like the FDA (1990) report, disregarded all of the relevant research on memory loss, except for Freeman and Kendell's (1986) study, which the task force mentions and then grossly misrepresents. That study asked patients to assess their memory function a year or more after electroshock treatment. The authors themselves remarked that the study was biased toward a low reporting of memory dysfunction because the patients were interviewed by the same doctor who had treated them. Nonetheless, 74% mentioned "memory impairment" as a continuing problem, and "a striking 30% felt that their memory had been permanently affected." In defiance of the facts, the APA (1990b) task force cited Freeman and Kendell (1986) as indicating that "a small minority of patients, however, report persistent deficits."

Squire and Slater's (1983) study, also omitted by the APA (1990b) task force, found that 7 months after treatment, patients reported an average loss of memory spanning 27 months. Squire, in a personal communication to me at the June 1985 Consensus Conference on ECT, explained that one patient lost the recollection of 10 years of her life. He told me that he felt it was not necessary to report this in his actual publication.

The Consensus Conference on ECT (1985) used Squire and Slater's (1983) results to conclude that "on average, patients endure memory loss extending from 6 months prior to the treatment to 3 months afterward." These data, while serious enough in themselves, are misleading. The data reported at 7 months following treatment, cited in the above paragraph, are more likely to be accurate. The brain cannot regenerate lost brain cells or lost memories. With the passage of more time, there is little likelihood of increased improvement, but much likelihood of a growing tendency to deny the losses.

The APA (1990b) task force also ignored older controlled clinical studies by Janis (1948, 1950; Janis et al., 1951) showing extensive, permanent loss of important personal memories and life history following routine ECT. Janis (1948, 1950; Janis & Astrachan, 1951) interviewed 19 patients before and after routine ECT, and 11 control patients with similar diagnoses in the same hospitals. The results 1 month postshock were striking: Every shock patient had significant memory losses. Many patients were unable to recall 10–20 life experiences which had been available to recall prior to electroshock treatment.

Janis (1950) followed up five of the patients at 2.5–3.5 months later. Most of the lost memories remained lost. Another follow-up 1 year later showed continuing losses (see review in Breggin, 1979).

The data generated by Janis (1948) confirmed the importance of ECT spellbinding with denial and anosognosia. Patients tended to minimize or even confabulate to cover up their memory losses, rather than to exaggerate them. One patient, for example, in his pre-ECT interview, reported that he had been unable to work for several months prior to coming to the hospital. The historical facts were confirmed by the family. But after 12 ECTs, he was unable to recall the period of unemployment. Instead, he claimed that he worked right up to his hospitalization. As Janis confirmed, patients often do not complain spontaneously to doctors about their memory loss; they tend to deny it.

Not only was Janis's research left out of the 1990 APA report, but over the years, his work has been wholly misrepresented by shock advocates. Two of the more important reviews commonly read during my psychiatric training actually cited Janis as evidence that ECT did not harm memory (reviewed in Breggin, 1979).

In 1986, Weiner et al. attempted to measure the loss of personal subjective recollections following ECT because these are "most consistent with the nature of memory complaints by ECT patients themselves." The memory inventory in the study spanned several years prior to the shock treatment. The group found "objective personal memory losses" that lasted through the 6-month duration of the study.

In an earlier article by a team that also included Weiner (Daniel et al., 1982), there was emphasis on the potentially injurious effect on the patient and the patient's family of losing autobiographical memories. The authors observed that "autobiographical memory failures, if added across a course of ECT, may produce gross autobiographical memory gaps that may be disconcerting to a patient and a patient's family, because the patient's sense of continuity with his or her own past may be disrupted" (p. 923).Yet their subsequent study, in which they demonstrated the existence of the autobiographical memory losses, failed to mention how distressing they can be (Weiner et al., 1986).

One of the newer techniques of shock treatment—multiple monitored electroconvulsive therapy (MMECT)—employs four electroshocks in one session, while recording EEG, electrocardiogram, and vital signs. Barry Maletzky, an advocate of the treatment, is one of the few who have asked patients in detail about their memory function following ECT. After pointing out that psychological testing has sometimes failed to confirm cognitive deterioration (Maletzky, 1981), he observed,

> However, if one listens to what patients say who are treated with either conventional ECT or MMECT, subtle cognitive deficits, not easily tested, are discussed. Some patients will mention deficits only if careful inquiry is pursued. Most will not identify these problems even if asked,

> thus indicating that either they are absent or so subtle as to be imperceivable to the patient. (p. 180)

Maletzky (1981) then goes on to describe a series of 47 MMECT patients who were interviewed 3–6 months after ECT treatment. Thirty-six percent identified a cognitive problem, including difficulty finding their way around, recalling past events in sequence, and understanding TV shows. In another ECT follow-up study by Maletzky (1981) reported in the same book, patients were given a questionnaire and interviews and 23% reported "long-term memory deficits." The problems described by Maletzky's patients extend beyond memory dysfunction to substantial cognitive deficits such as a math student's loss of his ability to do computations in his head.

Devanand et al. (1994), in their review, skated over the surface of the many cognitive studies, dismissing most of them, failing to mention any of the Janis studies, ignoring follow-up studies indicating that patients frequently experience permanent memory loss, and raising no issues about the improbability of full recovery from traumatic acute organic brain syndromes. Appearing in the *American Journal of Psychiatry* amid growing controversy surrounding ECT, Devanand et al.'s (1994) review was seemingly intended as an establishment response to criticism. For this reason, I shall examine its conclusions at relevant points in this chapter.

## STUDIES OF BRAIN DAMAGE FROM ECT

The recent study by Sackeim et al. (2007) that found widespread, persisting generalized cognitive dysfunction provides proof that ECT causes brain damage. There is also an extensive literature confirming brain damage from ECT. The damage is demonstrated in many large animal studies, human autopsy studies, brain wave studies, and an occasional CT scan study.

Animal and human autopsy studies show that shock routinely causes widespread pinpoint hemorrhages and scattered cell death. While the damage can be found throughout the brain, it is often worst beneath the electrodes. Since at least one electrode always lies over the frontal lobe, it is no exaggeration to call electroshock an electrical lobotomy.

In 1976, Friedberg published the first review of brain damage from ECT. This was followed by my own detailed critiques (Breggin, 1979, 1981a, 1986). None of these studies and none of the reviews on brain damage were mentioned in the 1990 APA task force report.

The original animal studies are from the 1940s and 1950s, but they are still valid. Several of them were elegant by any scientific standard.

The model for these studies was conducted by Hans Hartelius on cats and published in 1952 in a book-length publication titled "Cerebral Changes Following Electrically Induced Convulsions."

In the double-blind microscopic pathology examination, Hartelius (1952) was able to discriminate between the eight shocked animals and the eight nonshocked animals with remarkable accuracy. The experimental animals showed vessel wall changes, gliosis, and nerve cell changes:

> The *vessel wall changes* found more frequently and more distinctly in the animals subjected to ECT consist of characteristic sac-like dilatations of the perivascular spaces, which in some cases contain histiocytic elements. The *glial reaction,* of the progressive type, consists of an increase in the number of the small glial elements in the parenchyma and satellitosis beside the nerve cells. The *nerve cell changes* observed are in the form of various stages of chromophobia, frequently with coincident nuclear hyperchromatism. The arrangement of such cells is mainly focal.

The changes were statistically significant. Confirming their basis in sound pathology, the abnormalities were found most heavily in the animals given the greater numbers of ECTs, were most dense in the frontal lobe, and were correlated with increased age of the animal (implying increased vulnerability).

Hartelius (1952) was cautious in his determination of irreversibility. He required the detection of shadow cells and neuronophagia (the removal of dead or diseased nerve cells by phagocytes). On the basis of these findings, he concluded, "The question whether or not irreversible damage to the nerve cells may occur in association with ECT must therefore be answered in the affirmative."

Hartelius (1952) used relatively small doses of ECT. In fact, the amount of electrical energy he used was a fraction of that currently applied to the heads of shock patients. In general, however, animals are less susceptible to electroshock trauma to the head than humans and require more intensive electrical currents to achieve the same degree of damage. If given the doses used in clinical practice, the damage to the cats would almost certainly have been even greater.

Ferraro et al. (1946, 1949), of Columbia University and the New York State Psychiatric Institute, conducted controlled studies involving clinical doses of ECT on rhesus monkeys. The researchers used regular ECT machines, smaller-sized electrodes to fit the monkey heads, restraint to keep the heads from banging, and the minimally necessary dose of electricity to cause a convulsion, thereby approximating the intensity of current and voltage used to treat human beings (Ferraro and Roizen, 1949). The total energy dose was less than that routinely used in modern ECT.

In the 1946 study, Ferraro and Helfand administered ECT three times per week to the monkeys in relatively short courses of 4 to 18 in number. As a result of only 4 ECT, one animal had microscopic findings: "Here and there in the cerebral cortex there were some areas of rarefaction [cell loss]." After 12 ECT, another showed "small areas of rarefaction" as well as other evidence of cell deterioration and death. Another, again after 12 ECT, displayed "slight rarefaction of nerve cells and a few acellular areas in the front lobes." In addition to areas of cell death, they also found cells in various states of degeneration, loss of myelin sheaths, glial proliferation, dilated blood vessels, microscopic effusions of blood, petechial hemorrhages, and other neuropathology that they associated with the ECT. The pathological findings were roughly proportional to the numbers of ECTs. Their overall findings were very consistent with, although more severe than, those reported by Hartelius in cats.

In their 1949 study, Ferraro and Roizin. used larger numbers of ECTs (32–100). Although excessive by some standards in psychiatry, many patients in fact receive such larger numbers of shock treatments, usually spread over a number of years. After the fewest electroshocks, the researchers found evidence of cell death in the form of "moderate nerve cell rarefaction" and "acellular areas, again proportionate to the current intensity and the number of ECT." Photographs of the microscopic findings were reproduced in both papers.

Alpers and Hughes (1942a) studied the effects of ECT on cats and found evidence of subarachnoid hemorrhages and scattered punctate hemorrhages in the brain. They correlated this damage with autopsy findings in two human cases (Alpers and Hughes, 1942b). Alpers (1946) reviewed the literature on ECT experiments involving animals, including additional studies of cell death in dogs (Neuberger et al., 1942) and rabbits (Heilbrunn et al., 1942). Alpers noted that even studies that claimed to show little or no effects from ECT in fact often provided evidence of cellular abnormalities and even cell death in the brain.

Neither the Hartelius (1952) study nor any of the other studies using large animals cited in this section were included in the 1990 APA task force report on ECT. An oversight such as that cannot occur by chance but instead must have reflected a conscious attempt to withhold vital information about the dangerousness of ECT.

The Russians carried out a variety of neuropathology studies on animals subjected to clinical ECT to determine if there is permanent brain damage. Babayan called for a ban on the treatment in 1985, citing work at the USSR Academy of Medical Sciences as "convincing proof . . . pointing to grave changes in the central nervous system, the nerve cells, the glial-tissue apparatus" (p. 37). At another institute, studies of the brains of animals led to a "drastic reduction in the use of electroshock

therapy in clinical practice" (p. 134). Babayan compared the treatment to lobotomy.

There have been no studies of large animals using modified ECT under clinical conditions, even though this so-called new form of ECT was developed in the 1960s. Meldrum and Brierley (1973) studied *drug-induced* (bicuculline) lengthy seizures in baboons and found widespread ischemic (due to lack of blood flow) changes. Meldrum et al. (1973) repeated their earlier experiment, now employing modified ECT, and found similar but lesser ischemic changes in neurons. They concluded that modifying the ECT gave some incomplete protection. However, the seizures were very long. Meldrum et al. (1974) once again studied the impact of drug-induced (allylglycine) seizures in baboons under modified conditions. They used 13 animals, and in 8, the seizures were brief, recurring 6–63 times in 2–11 hours, followed by recovery. The short-duration seizures produced no detectable pathology.

Templer (1992) reviewed the question of ECT and permanent brain damage. In regard to animal studies, he focused on Hartelius (1952) and also pointed out that animals given artificial ventilation (modified ECT) in other studies also had "brain damage of somewhat lesser magnitude."

While few psychiatrists are willing to admit in public that ECT causes brain damage, a large survey of the APA membership, conducted with anonymity in the 1970s, showed that 41% of the respondents agreed with the statement "It is likely that ECT produces slight or subtle brain damage." Only 26% responded that it did not (APA, 1978).

As noted previously, Devanand et al. (1994) published an article titled "Does ECT Alter Brain Structure?"[1] They concluded that animal studies do not show brain damage. They did this by dismissing the best studies. Hartelius (1952), for example, was criticized for applying a series of four ECTs, with each one spaced at 2 hours. But there is no reason to assume that this method is more damaging than larger numbers of shocks spaced over longer intervals. As currently used, multiple-monitored ECT inflicts four shocks within the space of an hour or so. In addition, it is extremely misleading of Devanand et al. (1994) to focus on that one group of animals. Some of Hartelius's animals, for example, were given one ECT per day for 4 days, others were treated "with clinical frequency" (three per week), and many showed evidence of brain damage.

Devanand et al. (1994) dismissed Ferraro and Roizen (1949) for using a "large number of ECSs [electroconvulsive shocks] relative to clinical practice," but in fact, many patients are given 32 or more treatments, sometimes in one series, more often in several. Ferraro et al. (1946), utilizing fewer shocks, were dismissed on the speculation that the current went through the brain stem.

Devanand et al. (1994) did not deal with the fact that almost every study using large animals, by their own table, showed damage. My review indicated that even purportedly negative studies, on actual reading, indicated harmful effects (Breggin, 1979). For example, Devanand et al. (1994) described Lidbeck's (1944) three dogs as developing "minimal perivascular and ischemic changes." They left out that in two of the four animals, "nerve cells were shrunken and there was a decrease in the number of stainable granules" (Lidbeck, 1944). Nor did they mention that one of the animals developed blood clots in its brain.

Even if Devanand et al. (1994) had valid points to make, criticizing a raft of animal studies that show damage cannot be used as a method for proving the safety of ECT. To be ethical and scientific, shock advocates would have to produce carefully conducted, large-animal studies that show no damage. In fact, the only studies that Devanand et al. (1994) found acceptable were performed on rats, rather than dogs, cats, and primates, whose brains are more akin to humans and more sensitive to damage. In comparison to monkeys, cats, and dogs, rats, with their smaller brains and thick skulls, are notoriously resistant to head trauma.

The prospects of more modern ECT being safe are nil. The newer methods add the risk of anesthesia, often complicated by multiple psychiatric drugs administered simultaneously. The electrical trauma must be sufficient to cause a grand mal seizure. Grand mal seizures, when repeated and especially when as severe as those caused by ECT, are in themselves harmful to the brain. Nor are modern variations in current intensity necessarily more benign because, in order to cause a seizure with the weaker currents, exposure time is often increased by 10-fold or more over earlier ECT methods. Also, in order to overcome the anticonvulsive effects of the sedatives administered to put the patients to sleep, modern ECT often inflicts more intense electrical energy on the brain than the older animal studies and older forms of ECT (see the section "Modified ECT"). Perhaps most obvious and important, the study by Sackeim et al. (2007) shows that the effects of modern ECT continue to be devastating.

In addition to demonstrating safety, shock advocates would also have to prove efficacy through double-blind clinical trials comparing ECT to sham or placebo in which the subject is put to sleep without the actually administering the shock. Thus far, placebo-controlled trials have failed to show any significant superiority of ECT over sham ECT.

## Brain Scans

There has been contradictory evidence of ECT damage in brain scan studies, most of which have been carried out by staunch advocates of the

treatment. Using CT scans, Weinberger et al. (1979) found that chronic patients with schizophrenia who had ECT had more enlargement of their ventricles (cerebral atrophy) than those who had no ECT. Stretching to exonerate ECT, they declared, "Either ECT further enlarged the ventricles of the patients treated with it, or it was used with greater frequency in patients who tended to have larger ventricles." In another CT study, Calloway et al. (1981) found a correlation between frontal lobe atrophy and ECT in 41 "elderly depressives."

Coffey et al. (1991), using MRI, studied 35 patients before and after ECT. The follow-ups were 2 or 3 days after and 6 months after. In five subjects, they found "an apparent increase in subcortical hyperintensity." Coffey, a strong ECT advocate who has performed shock on many patients, dismissed his own finding as "most likely secondary to progression of ongoing cerebrovascular disease during follow up." I have seen several other patients with very similar post-ECT MRI findings.

Pande et al. (1990) found no MRI pathology in seven ECT patients. However, the studies were performed 1 week after the last ECT so that late-maturing pathology would not have been discovered. Bergsholm et al. (1989) found no pathology on MRI in 40 patients, with the exception of a 69-year-old man, who suffered a dilatation of the left temporal horn, which the authors dismissed as unrelated to ECT.

Devanand et al. (1994) reviewed the brain scan literature and found the evidence for brain damage unconvincing. They accepted Coffey et al.'s (1991) unsubstantiated claim that the four damaged patients had progressive cerebral vascular disease, rather than ECT pathology. They dismissed studies showing damage.

In reality, brain scans are not an appropriate instrument for measuring ECT brain damage. None of the damage found in the large-animal studies—such as small areas of dead and dying cells and small pinpoint hemorrhages scattered throughout the brain—would show up on brain scans, which cannot detect damage at a microscopic level until it is massive enough to result in gross atrophy or tissue shrinkage. To use brain scans to show that ECT is harmless is a scientific scam. On the other hand, in my medical-legal work I have on occasion seen patients whose before-and-after brains scans did detect atrophy following ECT.

## MODIFIED ECT

For the past 40 and more years, a modified form of ECT has been standard, involving sedation with a short-acting barbiturate, muscle paralysis with a curare derivative or similar drugs that prevent activation of the muscles of the body, and artificial respiration with oxygen. The purpose

of these modifications was not, as some advocates claim, to reduce memory loss and brain damage. Muscle paralysis was intended to prevent fractures from severe muscle spasms, while the artificial respiration kept the paralyzed patient breathing.

The modifications used in contemporary ECT make it clear that ECT-induced convulsions are far more severe than the spontaneous convulsions in grand mal epilepsy. Patients with spontaneous seizures of unknown origin, or with seizures due to brain injury, rarely break their limbs or their vertebrae during the convulsion. The muscle spasms are not intense enough to produce these dramatic effects. Yet these fractures were common with unmodified ECT.

Shock advocates claim that newer modifications have made the treatment much safer and that its negative public image is unfairly based on the older methods. However, the most basic modifications—anesthesia, paralysis, and artificial respiration—are not new at all. I prescribed and administered this kind of modified treatment more than four decades ago (1963–1964) as a resident at Harvard Medical School's main psychiatric teaching facility, the Massachusetts Mental Health Center.

The public's so-called "mistaken" image of ECT is, in reality, based on modern modified ECT, which has been around for a long time. As mentioned earlier, it is actually more dangerous than the older forms. The electrical currents must be more intense to overcome the anticonvulsant effects of the sedatives that are given during modified ECT (Breggin, 1979). Too frequently, the patient is routinely given a sleeping medication or tranquilizer the night before, further increasing the brain's resistance to having a seizure. Although ECT experts recommend against it, commonly patients are prescribed multiple psychiatric drugs at the same time. In addition, patients are exposed to the added risk of anesthesia. Other modifications include changes in the type of electrical energy employed and the use of unilateral shocks applied to the nondominant (nonverbal) side of the brain. However, the efficacy of these modifications remains controversial among shock advocates and, as a result, older methods continue to be used much or even most of the time (Sackeim et al., 2007).

Since the APA (1990b) task force does not exclusively endorse the modified forms of ECT, the claim that modern ECT is somehow much safer is again undercut. Besides, as already emphasized, some ECT advocates give excessive doses—beyond the dose required to produce a convulsion. Sackeim has advocated using electrical doses so large that the safety controls on the machines have to be disabled (Sackeim et al., 1993).

There is no reason to believe that shocking the nonverbal side of the brain is less harmful. As Blakeslie (1983) confirmed, damage and

dysfunction on the nonverbal side are more difficult for the individual to recognize or describe (see discussion of anosognosia in chapter 1). But the defects are no less devastating. Injury to the nonverbal side impairs visual memory, spatial relations, musical and artistic abilities, judgment, insight, intuition, and personality. Because of the victim's difficulty in perceiving damage to the nondominant side of the brain, and because it impairs judgment and insight, modified nondominant ECT is probably more spellbinding. Meanwhile, it is ironic that biopsychiatry promotes sacrificing the nonverbal side of the brain, while humanistic psychology is emphasizing its importance to the full development of human potential.

## The Brain-Disabling Principle

Beginning with Cerletti and Bini, who introduced electroshock in 1938 in Italy, many advocates of the treatment have *not* wanted to make the treatment less harmful to the brain. They have considered brain damage necessary for the cure and often spoke openly about it (Cerletti, 1940; reviewed in Breggin, 1979).

Fink, himself a member of the 1978 and 1990 APA ECT task forces, for decades argued and demonstrated scientifically that ECT's "therapeutic" effect is produced by brain dysfunction and damage. He pointed out in his 1979 textbook that "patients become more compliant and acquiescent with treatment" (p. 139). He connected the so-called improvement with "denial," "disorientation" (p. 165), and other signs of traumatic brain injury and an organic brain syndrome. This is a direct confirmation of the brain-disabling treatment and the use of iatrogenic denial in authoritarian psychiatry.

Fink was even more explicit in earlier studies. In 1957, he stated that the basis for improvement from ECT is "craniocerebral trauma." In 1966, Fink cited research indicating that after ECT, "the behavioral changes related to the degree of induced trauma" (p. 475). Referring to the multiple abnormalities produced in the brain following ECT, he wrote, "In these regards, induced convulsions in man are more similar to cerebral trauma than to spontaneous seizures" (p. 481). He stated that improvement depends on the development of an abnormal EEG and other changes in the brain and spinal fluid typical of trauma and compared ECT to "cerebral trauma" (p. 48). Fink (1966) cited Tower and McEachern (1949), correctly stating that they "concluded that spinal fluid changes in induced convulsions were more like those of craniocerebral trauma than those of spontaneous epilepsy." He then gave further evidence for this comparison between ECT and traumatic brain injury.

Up to at least 1974, Fink continued to propose that ECT has its effect by traumatizing or damaging the brain. He began his discussion by

noting that psychiatric treatments have often been "drastic" and then cited, among other examples, heat and burning, bleeding, water immersion, and craniotomy. He then went on to present several axioms of ECT, including the connection between the supposed therapeutic effect and traumatic changes in the brain. He spoke directly of the producing "cerebral 'trauma'" (p. 9) reflected in EEG slow wave activity. He compared induced convulsions to "craniocerebral trauma" (p. 10). He attributed improvement to the increased use of "denial" by the patient and to the development of "hypomania" (p. 14)—both clinical signs of profound irrationality caused by brain damage and dysfunction.

Psychiatry's more recent emphasis on proving that ECT is harmless has developed in response to scientific criticism of the damaging effects made by me and by others, such as neurologist John Friedberg (1976, 1977) and shock survivor Leonard Frank (1979, 1980, 1990, 1991, 2001). Thus, the APA (1990b) task force report, despite Fink's participation, made no such comparisons between head injury and ECT; instead, the report dismissed any suggestion that the treatment is severely traumatic. In depositions and trial testimony in defense of doctors who give ECT, Fink now takes the position that ECT causes no brain damage.

The 1990 APA task force report noted that low-dose unilateral ECT is often less effective than forms of ECT that deliver more electrical energy. This observation tends to confirm the brain-disabling principle that so-called therapeutic efficacy is a function of the degree of treatment-induced damage.

Sackeim et al. (1993) covertly revived the concept promoted by ECT pioneers that a therapeutic response depends on inflicting brain damage and dysfunction. They advocated bilateral ECT—the most obviously damaging method—using a dose of electricity 2.5 times that required to induce a convulsion in the patient. I evaluated a case in which a doctor followed Sackeim et al.'s published recommendation and gave his patient the increased dosage. The patient suffered severe, irreversible memory loss and chronic mental dysfunction, rendering her permanently unable to work at her previously high intellectual level.

Psychiatric drugs are nowadays frequently justified on the grounds that they correct biochemical imbalances. Like Prozac, shock treatment is said to work by enhancing serotonin (e.g., Abrams, 1988). Accepting this rationale requires ignoring the more gross damage being done: The shocked brain is so traumatized that the patient is rendered too confused and blunted to feel any subtle emotions. Even psychosurgery is nowadays sometimes justified on the grounds that it corrects biochemical imbalances. One advocate looks forward to delivering serotonin "psychosurgically" to "serotonin-depleted sites" in the brain (Rodgers, 1992, p. 106).

### Iatrogenic Helplessness and Denial, and Spellbinding

ECT provides a prototype for the concept of iatrogenic helplessness and denial, and spellbinding (chapter 1). Controlled studies of ECT show that any therapeutic effect evaporates after 4 weeks—the approximate time it takes to recover from the most severe symptoms of organic brain syndrome or delirium. Except for psychosurgery, ECT provides the most extreme example in which the psychiatrist denies the damage he is doing to the patient, and then utilizes the effects of that damage to produce a less emotionally aware, less autonomous, and more manageable patient. As Max Fink's earlier work openly described, through brain damage and the exercise of medical authority, patients are pushed deep into denial about the harm done to them as well as about their still unresolved personal problems. This is an example of profound spellbinding intentionally inflicted on the patient under the guise of treatment.

Consistent with other victims of central nervous system damage, most ECT patients minimize or deny their real losses of mental function. This denial of mental dysfunction in brain-damaged patients is called anosognosia (discussed in chapter 1). While damage to either side of the brain can produce anosognosia, it seems more common following damage to the nondominant side (in right-handed individuals, the right is usually nondominant). In electroshock treatment, at least one electrode lies over the nondominant side. In contemporary ECT, both electrodes are frequently placed over the nondominant side. As already noted, damage to the nondominant side of the brain impairs judgment and insight without the patient realizing it, making the treatment very spellbinding.

Nondominant shock starkly illustrates the principle of iatrogenic helplessness and denial: The doctor damages the brain in such a way as to confound the patient's ability to perceive the resulting dysfunction.

Advocates of ECT are well aware that shock patients suffer from anosognosia and denial and therefore cannot fully report the extent of their memory losses and mental dysfunction. Yet these same advocates claim that patients exaggerate their post-ECT problems.

Interviews with family and friends of patients often disclose that they are painfully aware of the damage done to their loved ones. Often, the psychiatrist is the only one who consistently and unequivocally denies the patient's damaged state.

## A LONG CONTROVERSY SURROUNDING ECT

The 1978 APA task force report labeled electroshock treatment as controversial. The 1985 Consensus Conference on ECT report stated,

"Electroconvulsive therapy is the most controversial treatment in psychiatry" and referred to 45 years of dispute surrounding issues such as efficacy and "possible complications." In the opening sentence of the introduction to Abrams's (1988) book, Fink referred to the "more than 50 years of controversy" surrounding ECT.

Since my 1979 book, I have hammered at the right of patients to know that ECT is a controversial treatment, and I have cited the previous quotations in medical-legal reports and testimony. Many survivors of shock treatment, such as David Oaks of MindFreedom and Leonard Frank, have made similar points. Perhaps as a result, the 1990 APA task force report said not a word about controversy. ECT is presented as if no one in the profession has ever criticized it. Psychosurgery remains the only treatment surrounded by more controversy than ECT, but it is used much less frequently (Breggin et al., 1994b). The two treatments are closely related in many ways. Electroshock can be understood as "closed-head electrical lobotomy."

The most significant challenge to ECT within the medical profession was launched by neurologist John Friedberg (1976), whose book for laypersons was followed by a journal review (Friedberg, 1977). Friedberg's publications were quickly followed by a volume edited by Leonard Frank (1978) and a book by this writer (Breggin, 1979). Reviews of ECT-induced damage to the brain and mind have continued to be published in professional journals (Cameron, 1994; Frank, 1990; Templer, 1992). Templer and Veleber (1982), for example, summarized their review of the literature:

> Some human and animal autopsies reveal permanent brain pathology. Some patients have persisting spontaneous seizures after having received ECT. Patients having received many ECTs score lower than control patients on psychological tests of organicity, even when degree of psychosis is controlled for.
>
> A convergence of evidence indicates the importance of the number of ECTs.... Our position remains that ECT has caused and can cause permanent brain pathology.

Boyle (1986) reviewed the literature and stated,

> In conclusion, there is considerable empirical evidence that ECT induces significant and to some extent lasting brain impairment. The studies cited above are but a few which suggest that ECT is potentially a harmful procedure, as indeed are most naturally occurring episodes of brain trauma resulting in concussion, unconsciousness and grand mal epileptic seizures. Accordingly, the continued use of ECT in psychiatry must be questioned very seriously. (p. 23)

After hearing evidence presented to the Food and Drug Administration's Respiratory and Nervous System Device Panel, consumer representative Susan Bartlett Foote (1983) reported back to the FDA that

> evidence of the safety and efficacy of ECT devices remains controversial and conflicting. The "new evidence" submitted [by the American Psychiatric Association] petition did not, by any means, eliminate the unanswered or troubling questions surrounding safety and efficacy of the machines. (p. 2)

Consider that all of this was published before Sackeim et al.'s (2007) study showing permanent harm to the brain and mind caused by ECT. Psychiatry has ignored the decades of research that long ago should have brought the treatment to a halt.

Survivors of shock treatment have become an increasingly active force. In addition to writing and appearing in the media, many who have undergone ECT continue to protest at national psychiatric conventions and shock symposia and even chain themselves to the gates and doors of so-called "shock mills."

More than 30 states have passed legislation to monitor ECT, set limits on the number of treatments or the age at which it can be given, and require second opinions and informed consent. Four states have banned its use on children, most recently Texas. While efforts to require informed consent have proved almost impossible to enforce in the face of psychiatric resistance, they have raised further questions about the use of shock treatment. However, critics of shock have relatively little clout or funding compared with the American Psychiatric Association and organized shock advocates, who have fought continuously against any monitoring or any restraint of ECT; little progress in reform has been made in recent years.

The most dramatic threat to shock treatment became known as the "Berkeley ban." Ted Chabasinski, who had been subjected to electroshock as a child, organized a grassroots citizens' movement in support of a referendum to ban ECT in Berkeley, California. After the proposition was overwhelmingly approved by the electorate, the psychiatric establishment, led by the APA, intervened and had the ban overturned in court. But the survivors could claim a partial victory—a so-called "power outage" of 41 days at Herrick Hospital, the city's only ECT facility, in the winter of 1982.

California again became the center of public criticism of electroshock. Inspired by a coalition of former patients and concerned professionals, Angela Alioto, a member of the San Francisco Board of Supervisors, held hearings on ECT. About two dozen "shock survivors" testified about

permanent damage to their brains and minds. Although both sides had ample time to organize, no shock patients showed up to offer testimonials in favor of the treatment (Breggin, 1991b, 1991c; Frank, 1991).

The recommendations of Alioto's committee were adopted by the city's governing body and signed by Mayor Art Agnos on February 20, 1990. The resolution declared the opposition of the Board of Supervisors to the "use and financing" of ECT in San Francisco (Figueroa, 1991). It also called for the state legislature to develop more strict requirements for informed consent, including the exposure of potential patients to live or videotaped presentations by critics of the treatment. The resolution, which followed the recommendations made in my testimony at the Alioto hearings, was not legally binding. While the resolution has been an important moral and educational victory for electroshock opponents, its actual impact was negligible.

David Oaks is the executive director of MindFreedom (http://www.mindfreedom.org), the leading survivor organization in the world fighting for psychiatric patient rights and resisting psychiatric abuses. He edits the group's magazine, organizes protests against psychiatric abuses like electroshock treatment, and in general inspires reform-minded professionals and victims alike.

## THE NEED TO BAN ECT

The 1990 APA task force report represented a disillusioning and disappointing watershed for my own reform activities around ECT. I had long argued that ECT was an ineffective, dangerous, anachronistic treatment that should be abandoned by modern psychiatry. Yet, despite the urging of many victims of ECT, I refused for many years to endorse public or legislative efforts to ban it. It was my position that the practice of medicine and the rights of patients were better served by insisting on informed consent—and by holding liable those psychiatrists who fail to convey to their patients the controversial nature of ECT and its potentially damaging effects. Unfortunately, the 1990 APA report and the APA's political pressuring of the FDA demonstrated that organized psychiatry was determined not to inform professionals or patients about the risk of ECT. Despite the disclaimer tucked away on its copyright page, the APA report provided a shield for those who recommend and administer ECT—an "official" conclusion that there is no serious risk of harm. Doctors who prescribe or recommend ECT can try to hide behind this report when their injured patients protest to them or bring legal actions.

In the environment created by the APA, informed consent for ECT became a mirage. Therefore, after much initial hesitation, I decided to

endorse public efforts to ban ECT. I believe that all concerned mental health professionals should support the banning of ECT.

Given that even the APA and the FDA published fraudulent claims about the harmlessness of ECT, it is fair to conclude that patients are rarely if ever going to be given informed consent by doctors who advocate the treatment. Because ECT promoters like Max Fink, Richard Abrams, and Harold Sackeim are considered believable authorities by their colleagues, practicing psychiatrists feel safe in telling their patients that ECT is relatively harmless and very effective.

I have read sworn testimony by many shock doctors, reviewed the medical charts of their patients, and seen the "consent" forms that they give to their patients—and I have never seen a case in which a patient was given adequate information about the treatment's brain-damaging effects. If they were informed about the results of animal experiments or the results of Sackeim et al.'s (2007) recent research, all but the most self-destructive patients would refuse the treatment. Because ECT patients will never be given informed consent, the only alternative is a ban on the treatment. Some patients do feel "helped" by ECT. Often, they have been so damaged that they cannot judge their own conditions. They suffer from ECT spellbinding, as well as iatrogenic denial and helplessness. But should a treatment be banned when some people believe they are helped by it? In fact, it is commonplace in medicine and psychiatry to withdraw treatments and devices that have caused serious harm to a small percentage of people, even though they may have helped a very large percentage. The risk of serious injury to a few outweighs helping many. In the case of ECT, a large percentage of people are being harmed, and there is little evidence that any are being helped.

## CONCLUSION

Based on the original large-animal studies that demonstrated ECT-induced brain damage, organized psychiatry should have banned the "treatment" decades ago. Even without the animal studies, Sackeim et al.'s (2007) demonstration of permanent ECT-induced memory loss and other cognitive deficits consistent with dementia should have been sufficient to stop all use of the treatment. This chapter has also reviewed a mountain of additional research confirming that ECT damages both the brain and the mind.

There is no need to advocate for additional research. Why damage the brains of more animals and more people? The facts have been conclusively established. Shock treatment physically damages the brain, irreversibly impairs mental function, and ruins the lives of many if not most

patients who are subjected to it. On top of that, controlled clinical trials comparing ECT to sham ECT show no advantage to the treatment. ECT should be utterly discarded as a useless, damaging relic from psychiatry's more violent past.

Unfortunately, psychiatry shows not the slightest inclination to rein in its compulsion to damage the brains of its patients in the name of "treatment." Sackeim et al.'s (2007) study aroused no concern whatsoever within the profession. Psychiatry's more abusive treatments, such as ECT, will never be stopped by psychiatry itself. ECT will have to be stopped by forces outside the profession including public outrage, court decisions prohibiting its use, and legislation banning it.

## NOTE

1. Devanand is one of the authors in Sackeim et al. (1993) calling for the use of intensive electroshock using 2.5 times the electrical current required to produce a convulsion.

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CHAPTER 10

# From Attention-Deficit/ Hyperactivity Disorder (ADHD) to Bipolar Disorder

## *Diagnosing America's Children*

The Web site sounds innocent enough: ADHDinfo.com. But it is sponsored by Novartis, the manufacturer of Ritalin. It opens with the question, What causes attention-deficit/hyperactivity disorder (ADHD) in school-age children? It answers, "The exact cause of ADHD is not known. Scientists think that ADHD may be caused by an imbalance of chemicals in the brain that help to control behavior." So your hyperactive child does not need better discipline; he needs a corrected biochemical imbalance. So your inattentive daughter does not need a more interesting classroom; she, too, just needs to get those pesky chemicals corrected.

Beneath the suggestion that biochemicals are the culprits, the drug company continues with seemingly wonderful news for overburdened parents, stressed schoolteachers, or rotten schools: Researchers have confirmed that ADHD is *not* caused by

- poor parenting
- family problems
- bad teachers
- ineffective schools

Is it any wonder that the drugging of the nation's children is escalating? The drug companies are teaching society that no one is to blame and

that no one needs to take responsibility for improving the behavior of our children. Hardly anyone realizes that this constitutes a virtual abandonment of our children to the medical authorities and their drugs. Hardly anyone realizes that this disempowers the very people who are best positioned to save our children, both individually and collectively: their parents and teachers.

The Novartis Web site goes on to deny basic facts about stimulants, claiming, for example, that they do not stunt growth. They paint a picture of an enormous market for their products:

> An estimated 3% to 5% of school-age children and 2% to 4% of adults have ADHD. As many as 2 million American children may have the disorder. It is estimated that every classroom in the United States has 1 to 3 children with ADHD.

No wonder teachers have gone into the business of diagnosing children. Every one of them has diagnosable kids in his or her classroom. The front page of Novartis's ADHDinfo.com has a headline and section titled "School Personnel: Do You Have a Child With ADHD in Your Class?" If you click on it, you will get information like the following: "Find out what you need to know about your role in helping children taking medication for ADHD."

But even though ADHD is a biochemical disorder, you can have ADHD and yet become a household name, indeed, one of the world's greatest people. According to Novartis,

> you might be surprised to learn of some very famous people who had the disorder. All of the following are believed to have had ADHD:
>
> - Thomas Edison
> - Babe Ruth
> - Eleanor Roosevelt
> - Albert Einstein
> - Alexander Graham Bell
> - Walt Disney
> - Ludwig van Beethoven
> - Winston Churchill
> - Agatha Christie

Led by drug company public relations campaigns and advertising, over the last few years, there has been a massive increase in the prescription of stimulant drugs to children for the treatment of ADHD. Meanwhile, the controversy surrounding them has never been resolved and, if anything, continues to heat up. Perhaps in response to the efforts of

reformers, the public is becoming more skeptical of medicating children. A recent survey found (Pescosolido et al., 2007) that

> most respondents believed that psychiatric medications affect development (68%), give children a flat, "zombie"-like affect (53%), and delay solving "real" behavior-related problems (66%). Most (86%) believe that physicians overmedicate children for common problems.

I have been documenting and publicizing these unfortunate realities for decades, and the American public is catching on. But to the authors of the survey study, these are false and stigmatizing attitudes. The authors come from the heart of the psychopharmaceutical complex, with the study receiving funding from as seemingly diverse entities as the National Institute of Mental Health (NIMH) and Eli Lilly and Company. Ironically, drug promoter Peter Jensen (1989), one of the authors of the report, has himself written about how stimulants can cause zombielike behavior in children (see subsequent discussion).

Meanwhile, the number of children involved is staggering. According to the Centers for Disease Control (CDC), estimates for the number of children afflicted with ADHD vary widely from 2% to 18%, with considerable variation in the numbers treated in different parts of the nation (Visser et al., 2005). On the basis of 2003 data, the CDC found that 11% of children had been diagnosed with ADHD at some time in their lives, including 6% of 4- to 8-year-olds, 13.5% of 9- to 12-year-olds, and 13.9% of 13- to 17-year-olds. The CDC further determined that 6.2% of boys and 2.4% of girls were currently being treated with medication for ADHD. Overall, 4.3% of children were being medicated.

One particular study in the *American Journal of Psychiatry* made an unusually low estimate for stimulant prescriptions to children and claimed, against all other estimates, that there had been no increase in rates over the past decade (Zuvekas et al., 2006). I puzzled over what had motivated publication of the study. Then, some time later, I came on an unashamed, boastful explanation by editor Robert Freedman (2006) about how the Zuvekas article was rushed to print to discourage the Food and Drug Administration from placing additional warnings on stimulant labels. The following is taken from an annual review by the editors of especially memorable events and achievements (Zuvekas et al., 2006):

> This study, which was scheduled for publication several months later, showed that the prescription of stimulants to children had been remarkably stable over the past decade and that, if anything, too few children are treated. The final version of the April issue had already gone to our printer the morning that we decided this article needed to be published

> sooner than its scheduled time. Fortunately, because the printers were out to lunch and work had not yet started we could hold the issue for this article. . . . The only article we could displace immediately was a review article by Kenneth Kendler, M.D., who told us that the needs of children should come first. The article appeared while the FDA hearings were ongoing, and the FDA decided not to issue a more severe warning about the safety and use of drugs that have a unique value in the treatment of childhood mental disorder.

How driven are the leaders in psychiatry to defend their drugs? Driven enough to stop the presses in their rush to publish an article, however idiosyncratic in its conclusions, to influence the FDA. The editors were driven enough to bump an article that instead urged that the needs of children should come first. They seem to have no idea how bad their confessions make them look.

In a letter to the acting commissioner of the FDA in 2006, U.S. senator Charles E. Grassley, head of the Senate Finance Committee, expressed concern about new data highlighting psychiatric and cardiovascular risks associated with stimulant drugs for the treatment of ADHD and about the lack of assessment of long-term risks in general for these drugs.

Grassley (2006) cited reports that ADHD drug sales had skyrocketed with a threefold increase in sales between 2000 and 2004, from a total of $759 million to $3.1 billion, and that more than 2.5 million children under age 17 were taking the drugs. He demanded to know why the FDA was so lax in evaluating the risks of these drugs. It is not just the FDA; it is the entire psychopharmaceutical complex, including the scientific journal of the American Psychiatric Association.

## THE ADHD/STIMULANT MARKET

### Shifting Patterns of Use in the United States

Boys have always been the most frequently medicated with stimulant drugs. In 2002, an estimated 14% of U.S. boys were on stimulants (Vedantam, 2004), a figure that has probably grown considerably since then. The *Pharmaceutical Business Review* noted that the United States had become a so-called mature market for ADHD drugs, with relatively little room for expansion. In reality, the drug companies hit up a whole new market within the United States—adults with ADHD.

The use of prescription medication for ADHD doubled between 2000 and 2004 (Hitti, 2005; Elias, 2005), according to data compiled by Medco Health Solutions, one of the nation's largest prescription benefit managers. The increases were largest among adults age 20–44, especially

women, but a 56% increase was also seen among children. According to Medco, nearly 1.5 million Americans age 20 and older (about 1% of the adult population) were using drugs for ADHD.

Advertising plays a role in increased use of ADHD drugs, with the manufactures of Adderall XR (Shire) and Concerta (McNeil) advertising in magazines geared to parents and the maker of Strattera (Eli Lilly) advertising on television to promote the drug for adults. But the overall push to medicate America and the world comes from all the components of the psychopharmaceutical complex—drug companies and those in their financial thrall, including physicians, medical organizations, medical journals, medical schools, and also health insurers, who prefer the costs of drugs to the higher costs of psychosocial and educational interventions. On the other hand, drug advocates, who see these trends as good, declared that the diagnosis of ADHD was missed in little girls due to the lack of hyperactivity but was showing itself among women as they grew older in the form of concentration deficits.

The convenience of once-a-day dosing for some drugs may also help increase sales. To make it even easier for parents to administer drugs to their children, on April 6, 2006, the FDA approved a skin patch for the delivery of methylphenidate (Ritalin) to children. A patch sounds a lot less ominous than a drug. Called Daytrana, the patch can be slapped on the child's hip for up to 9 hours at a time. When taken orally, methylphenidate has a shorter duration of action (3–6 hours), typically requiring a second dose handed out by the school nurse during the school day.

## The Worldwide Market

The concept of ADHD and the use of stimulants to control the behavior of schoolchildren is beginning to spread from America across the world as drug companies vigorously seek new markets for their products (Kean, 2005, 2006).

Here is how the online *Pharmaceutical Business Review* saw the growing ADHD market and its future as of September 2005 (Focusing attention on ADHD, 2005):

> In April, the World Federation for Mental Health launched an international campaign to improve the diagnosis and treatment of children with ADHD. While awareness of ADHD is increasing, the condition is still associated with significant social stigma, especially in conservative societies like Japan. Meanwhile, research shows that the American ADHD market dwarfs all others in terms of revenues.
>
> While over 20 million children globally have been diagnosed with ADHD, it is estimated that only 5–10% of children suffering are ever actually diagnosed. . . . Datamonitor research reveals that the American

> ADHD market overshadows all others, with 2004 revenues of over $2.5 billion—97% of ADHD drug revenues.

The *Pharmaceutical Business Review* goes on to say in a subhead, "Not Just an American Problem," but that some conservative societies are more reluctant to drug their children. It laments, "Unlike the US, there is some reluctance to prescribe drugs to children in the EU." That is an important concept: Pharmaceutical marketing specialists see no reluctance in the United States on the part of parents to drug their children. "There is definitely a higher willingness to prescribe drugs and acceptance by families to have their children on drugs in the US, where parents in the EU generally prefer to try other non-drug interventions first."

The business review concludes on an upbeat note and an exhortation for everyone—parents, teachers, doctors, parents' groups, and the media—to get behind the drugging of children:

> Despite the low rate of diagnosis, Datamonitor forecasts the global ADHD market to grow from $2.7 billion in 2005 to $3.3 billion in 2015. However, it is the success of awareness campaigns to encourage physicians, teachers, the media and parent support organizations to work together to ensure the proper treatment and management of children with ADHD and to reduce the public stigma of the disease and its treatment that will be a more telling statistic.

Can anyone doubt that the spreading of the ADHD diagnosis across America—and soon the world—has more to do with marketing than with treating a genuine disease?

## THE ADHD DIAGNOSIS

Seemingly reputable sources like the *New England Journal of Medicine* bandy about statistics such as "ADHD is the most common childhood psychiatric disorder, affecting 4 to 10 percent of young people in the United States, with as many as half of them continuing to have symptoms into adulthood" (Kadison, 2005).

ADHD is the diagnostic justification for the often cavalier prescription of stimulants to young people and, increasingly, to older people as well. Although few professionals can recite the American Psychiatric Association (APA; 2000) diagnostic criteria as delineated in the *Diagnostic and Statistical Manual of Mental Disorders (DSM–IV–TR),* their existence creates a strong, albeit misleading, impression of validity for the diagnosis of ADHD.

## DIAGNOSING BIPOLAR DISORDER IN CHILDREN

In the last decade and especially in the past few years, prodrug interests have rallied behind the diagnosis of childhood bipolar disorder to justify prescribing adult mood stabilizers and even the highly toxic neuroleptic drugs to children. Between 1994 and 2003, there was a 40-fold increase in diagnosing bipolar disorder in children (Moreno et al., 2007), and the trend has been escalating since then (Carey, 2007). Before the mid-1990s, doctors hardly ever diagnosed bipolar disorder in young children and only rarely in adolescents; now they do it on a routine basis. The increase in the diagnosis of bipolar disorder has gone hand-in-hand with an equally huge increase in prescribing adult antipsychotic and mood-stabilizing drugs to children. Moreno et al. (2007) found 90.6% of the children received psychiatric medications, including 60.3% on mood stabilizers and 47.7% on antipsychotics, with most on combinations.

### How Doctors Learn to Diagnose and Medicate So-Called Bipolar Children

At the annual meeting of the APA in Atlanta, Georgia, in 2005, a symposium was presented on Bipolar Disorder Management: A New Edition ("Bipolar Disorder," 2005). Physicians attending this particular seminar could get free credits toward maintaining their medical licenses and professional organization memberships. The program overview stated, "One of the most significant gaps in our knowledge of how to diagnose and treat bipolar disorder relates to children and new findings will be presented." Even the psychological issues will be geared to drugs, according to the program overview: "Psychological factors with an emphasis on reasons for non-compliance will be reviewed." *Noncompliance* refers to children or their parents refusing to take the drugs.

The program is straightforward in its call to start drugging children in the absence of any scientific basis: "In the absence of treatment data, treatment of childhood bipolar illness is modeled on that of adults." Even if the child shows no signs of psychosis, the most toxic adult drugs are recommended: "For non-psychotic children, in descending order, treatment should be tried with lithium, divalproex, atypical antipsychotic, combining any of these approaches, and other anticonvulsants plus atypical antipsychotics or conventional antipsychotic."

The reference to "combining any of these approaches" indicates why so many children are now being treated with cocktails of several toxic chemicals at once; the drug company–paid "experts" at professional seminars are encouraging them. In my clinical practice, I am frequently faced with having to withdraw preadolescent and adolescent

children from combinations of four or five medications, all of which are causing them adverse mental and emotional reactions and doing much more harm than good.

In regard to bipolar disorder in children, the program booklet was summarizing the views of Gabrielle A. Carlson, Director, Division of Child and Adolescent Psychiatry, and Professor of Psychiatry and Pediatrics, Stony Brook University of Medicine, Stony Brook, New York. But Dr. Carlson has some other credentials that come out in the Disclosure Information section of the booklet. She is on the Speakers' Bureau of Abbot Laboratories and Eli Lilly and Company, and she gets research grants from Janssen Pharmaceutica Johnson & Johnson, Otsuka, and Shire Pharmaceuticals. The number of drugs she advocates for children reflects the numbers of drug companies that sponsor her efforts.

But Carlson's list of drug company affiliations is hardly the longest among the other speakers. Frederick Goodwin—who lost his job as director of NIMH when my wife and I criticized his racist biopsychiatric initiatives in America's inner cities (Breggin et al., 1994b)—lists himself as a consultant to six drug companies, a research grant recipient from nine drug companies, and a Speakers' Bureau member for seven drug companies. But even Fred Goodwin is not the record holder for pharmaceutical corporation affiliations. Another speaker, Terence Ketter, has an even longer list. He is also a professor of psychiatry at Stanford University School of Medicine and an example of how drug company tentacles have a stranglehold on academic medicine.

Who is paying for the seminar itself and the glossy 12-page booklet—this free opportunity for psychiatrists to get CME (Continuing Medical Education) credits? It was sponsored by an educational grant from GlaxoSmithKline. But the booklet appears to be distributed by the APA, whose seal, name, and address appear on the back cover, along with the statement "Commercially Supported Activities." The seminar is part of a concerted effort by the pharmaceutical complex, including APA, to push more drugs on America's children, in this case by first diagnosing them with bipolar disorder.

## Developing Guidelines for Medicating Children

In 2005, the pharmaceutically oriented *Journal of the American Academy of Child and Adolescent Psychiatry* published guidelines for the diagnosis and treatment of bipolar disorder (Kowatch et al., 2005). Martha Hellander, a coauthor of the guidelines, declared, "These kids suffer so badly, and deserve to have evidence-based treatment as early in life as possible. Many respond quickly to mood stabilizing medication."

The phrase *evidence based* in psychiatry means nothing more nor less than "dictated by the psychopharmaceutical complex." There is no substantial evidence on which to base diagnosing children with bipolar disorder and drugging them with adult medications. In the vast majority of cases, the practice involves "off label" prescribing, that is, using medications outside the guidelines provided by the FDA drug approval process. Often it involves what can be called "off label diagnosing," that is, diagnosing outside the guidelines of the *DSM*. These supposedly evidence-based treatment guidelines are typically written by authors with strong vested interests in drug companies (Taylor et al., 2005). These authors see bipolar disorder in children as lifelong, meaning that the youngsters will become lifetime consumers of drugs.

Abboud (2005b) of *The Wall Street Journal* did a good job exposing the rush to diagnose more and more children with bipolar disorder and to treat them with drugs. She pointed out that a small group of doctors are pushing the diagnosis to as early as age 4, when they begin prescribing adult mood stabilizers and neuroleptics such as Risperdal and Seroquel. On the basis of a huge health care information database, the number of children diagnosed with bipolar disorder rose 26% from 2002 to 2004. As noted earlier, a more recent study (Moreno et al., 2007) found a 40-fold increase in the diagnosis from 1994–2003. This irrational exuberance about diagnosing children with bipolar disorder is the direct result of a drug company–inspired promotional campaign

According to Abboud (2005b), Joseph Biederman, a Harvard psychiatrist, believes that displaying violent outbursts and rages is likely bipolar, even in the absence of more classic symptoms. Biederman has long been a drug company henchman, coming to the fore whenever needed, for example, to produce research aimed at minimizing adverse effects of stimulants such as growth suppression and drug dependence. As Abboud noted, Biederman's group receives research funds from the makers of atypical neuroleptics, and Biederman is also a consultant to these companies, which manufacture the drugs being prescribed off label to these children.

Encouraged by the Biedermans of the psychiatric world, healthcare providers often diagnose bipolar disorder in children on the flimsy grounds of temper tantrums, irritability, or hyperactivity. In my practice, I have evaluated children who have been diagnosed bipolar when in fact they were normal children responding with typical childhood exuberance to a lack of parental control. In numerous cases, children have been continued on mood stabilizers and neuroleptics for a number of years by several consecutive doctors until coming to see me. After helping their parents learn and apply a program of consistent, rational discipline combined with unconditional love, most of the children have been

easily withdrawn from the drugs, and they have gone on to live normal childhoods.

In my training and psychiatric practice spanning several decades, I rarely if ever saw a child who had been diagnosed bipolar. All that changed in the 1990s. Now I see them on a regular basis. In many cases, the diagnosis simply has no basis. In a number of cases, however, the children have undergone maniclike episodes; but in every single case, the episode could be traced to either antidepressant or stimulant toxicity. Although stimulants can cause psychosis and mania (Ross, 2006), by far, the major cause of these drug-induced maniclike reactions have been the SSRIs and Effexor (reviewed in chapter 7).

Instead of being diagnosed with bipolar disorder, these children should have been diagnosed with antidepressant-induced mood disorder and easily treated by removing the causative agent. Instead, without removing the offending agent, these children are almost invariably also treated with mood stabilizers and neuroleptics. By the time I see them, they have lived on a drug-induced roller-coaster ride, driven up and down by competing toxicities.

At the same time, false claims are being made that these children have biological disorders. However, as Foltz (2006) astutely concluded,

> Finally, at a fundamental level, there is no doubt that the brain is continually involved in our emotional and behavioral experience in every instant. Just as we cannot identify the neurological or neurochemical basis of resiliency, courage, love, or honesty in the brain, we cannot identify mania, delusion, anger, or oppositionality. (p. 154)

The ADHD and bipolar diagnoses also influence how millions of parents and teachers view the children in their care. Nowadays, nearly all parents and teachers have heard of hyperactivity and, more specifically, ADHD. Many teachers believe that they can diagnose it. To my increasing dismay, teachers have now begun to diagnose bipolar disorder in children.

## Public Backlash

Meanwhile, as noted earlier in the book, there is the beginning of a backlash, with a recent survey finding that 85% of those interviewed believe that doctors overmedicate children with depression and ADHD and that drugs are harmful to a child's development (Pescosolido et al., 2007). More than half believe that psychiatric medications "turn children into zombies." One developmental pediatrician complained about the public's growing skepticism, instead proposing, "We need to view

depression and ADHD like we do allergies. They are very treatable" (Marcus, 2007). In contrast, I am pleased that Americans are finally catching on, and hope I have made some contribution to that newfound enlightenment.

Unfortunately, frontline professionals are not catching up to public opinion. A 2004 survey demonstrated that school psychologists, who literally hold children at their mercy, continue to believe that ADHD has a proven "neurological/genetic, or otherwise, biological basis" (Cushman et al., 2004, p. 187). They are not catching up, in part, because leaders in the field of psychopharmacology, in cooperation with their pharmaceutical industry patrons, continue to push medications, seemingly oblivious to their harmful effects (Leo, 2005).

Also along the bittersweet continuum, a *New York Times* article in December 2006 was titled "Parenting As Therapy for Child's Mental Disorders," in which doctors were advising that parents of children diagnosed with ADHD receive help with their parenting skills (Carey, 2006). Should it be news that parenting has something to do with whether or not a child behaves in an undisciplined fashion? But the doctors are not really recommending improved parenting; they are recommending artificial regimens of reward and punishment called *behavior modification*. Children, of course, see through these manipulations as more adult tactics to control them. As I describe in *Talking Back to Ritalin* (2001c) and *The Ritalin Fact Book* (2002b), children respond quickly to a combination of meaningful direction and explanation from a caring therapist and, most important, a consistent parental plan for unconditional love and rational discipline.

## Growing Concerns About Adverse Effects

The drug companies have had a few scares about their stimulant drugs in the past few years but seem to have weathered them easily. In Canada, Adderall XR, a once-a-day formulation, was temporarily removed from the market in February 2005 (Branswell, 2005). The Canadian regulatory agency made the decision based on reports of sudden death and stroke in the United States, where 37 million prescriptions of Adderall and Adderall XR had been written since 1994. In response to the withdrawal of the drug, there was uproar from physicians and lobbying groups, leading to its reinstatement in August 2005. Canadian psychiatrist Umesh Jain, who condemned the removal of Adderall XR from the market, inadvertently testified to its addictive nature when he brought forward one of his patients to say, "I had a panic the way I would imagine a crack addict would have a panic if he just heard his dealer had gotten busted" (Branswell, 2005).

## RAMIFICATIONS OF THE ADHD DIAGNOSIS

### Destructive Behavior Disorders

Along with conduct disorder and oppositional defiant disorder, ADHD was originally considered one of the "disruptive behavior disorders" in the *DSM–III–R* (APA, 1987). In the *DSM–IV,* an attempt is made to separate ADHD from the other two disruptive disorders, at least when ADHD manifests itself primarily as inattention, rather than hyperactivity. The DSM committee found that while disruptive behavior and attention problems often occur together, some ADHD children are not hyperactive and disruptive (Fasnacht, 1993).

Despite any attempt to separate them, the three diagnoses often overlap each other, and research projects often refer to them as one group: the DBDs. The *DSM–IV* observed that "a substantial portion of children referred to clinics with Attention-Deficit/Hyperactivity Disorder also have Oppositional Defiant Disorder or Conduct Disorder." An NIMH study similarly concluded that pure conduct disorder or pure oppositional disorder are "relatively rare" (Kruesi et al., 1992), with most cases also qualifying for an attention-deficit disorder diagnosis. All this casts doubt on the meaningful existence of any one of the diagnoses. It adds up to saying that a kid in trouble is a kid in trouble or that a kid in conflict with adults is a kid in conflict with adults, regardless of how you list and categorize the problems or behaviors.

The *DSM–IV* does not discuss the definition of disruptive behavior disorder. The *DSM–III–R* stated that DBD children are "characterized by behavior that is socially disruptive and is often more distressing to others than to the people with the disorders." The so-called illness consists of being disruptive to the lives of adults—a definition tailored for controlling children, while exonerating adults.

### ADD Criteria

The *DSM–IV* (1994, 2000) distinguishes between two types of ADHD: one marked by inattention and the other by hyperactivity–impulsivity. The official standard for ADHD requires any six of nine items under each category. For hyperactivity–impulsivity, the first four items, in descending order, include the following:

1. often fidgets with hands or feet or squirms in seat
2. often leaves seat in classroom or in other situations in which remaining seated is expected

3. often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
4. often has difficulty playing or engaging in leisure activities quietly

The first four items in the list for diagnosing the inattention form of the disorder include the following:

1. often fails to give close attention to details or makes mistakes in schoolwork, work, or other activities
2. often has difficulty sustaining attention in tasks or play activities
3. often does not seem to listen when spoken to directly
4. often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)

The list appeals to teachers, containing virtually every behavior that annoys them or demands their attention. Its marketing success is based on this redefinition of relatively normal classroom behaviors, especially among bored or poorly managed children, into a disorder treatable by drugs. The same list of behaviors in children could be used to identify, not a disease in the children, but incompetent or overstressed teachers, boring classes, and poor classroom discipline.

## Russell Barkley: Rationalizing Oppressive Control

Barkley (1981), a man who has done more to suppress America's children than perhaps any other psychologist, stated, "Although inattention, overactivity, and poor impulse control are the most common symptoms cited by others as primary in hyperactive children, my own work with these children suggests that noncompliance is also a primary problem" (p. 13). In other words, an underlying "primary" problem with these children is their refusal to comply with adult authority. They are disobedient!

What does Barkley suggest as his approach to disobedience? Not improved disciplinary practices and unconditional love to guide the children and to win their cooperation. Barkley uses his observation as an authoritarian justification for oppressing and controlling children with drugs.

It is not surprising that many children are "noncompliant" with Barkley. Although not a medical doctor, he has been a leader among those who minimize adverse drug effects while exaggerating their benefits. He not only pushes medication; he exclusively blames the children for conflicts they are having with family and school. As he put it, "There is, in

fact, something 'wrong' with these children" (p. 4). In his written words, one can hear echoes of confused, frustrated, potentially abusive parents yelling at their children, "There is something wrong with you!"

By indicting the children as having "something wrong" with them, Barkley deflects parents and teachers from the need to examine and improve their own attitudes and behavior toward the children in their care. Although the behavior of children is enormously responsive to adult interventions and although the distress of children often results directly from the actions of adults in their lives, in Barkley's mind the role of the adults can be ignored. The adults, in effect, get a free pass. They have little or no role in *causing* or *ameliorating* the emotional suffering and disturbing conduct of the children in their care.

While this "free pass" may relieve some parents and teachers of feeling guilty, it undermines their sense of responsibility and efficacy in the lives of the children. By making parents and teachers believe that they have no control over the lives of the children in their care, drug advocates like Barkley disempower them. Mistakenly convinced that they cannot exert influence over the children in their care, parents and teachers more readily abandon them to authoritarian diagnosticians and drug pushers like Barkley.

To the contrary of Barkley's oppressive attitudes toward children, any adequate, rational, and caring approach to helping children must view them in the context of the family and the school. Only by looking at the whole picture of the children's lives can we understand why they are distressed or distressing and how we, as responsible and caring adults, can better meet their needs.

## A Disease That Goes Away With Attention

The symptoms or manifestations of ADHD often disappear when the children have something interesting to do or when they receive a little adult attention. This is agreed on by most or all observers and indirectly finds its way into the *DSM–IV,* where it is specified that the symptoms may become apparent when the child is in settings "that lack intrinsic appeal or novelty." The so-called disorder may also be minimal or absent when "the person is under very strict control, is in a novel setting, is engaged in especially interesting activities, is in a one-to-one situation," including being examined by the doctor. Most advocates of ADHD as a diagnosis also note that it tends to go away during summer vacation.

If the list of criteria for ADHD has any use, it identifies children who are bored, anxious, or angry around some of the adults in their lives or in some adult-run institutions such as a particular classroom or family setting. These so-called symptoms should not red flag the children as

suffering from psychiatric disorders. They should signal to adults that renewed efforts are required to attend to the child's basic needs (for a discussion of basic needs, see Breggin, 1992a).

When a small child, perhaps 5 or 6 years old, is persistently disrespectful or angry, there is always a stressor in that child's life—something over which the child has little or no control. Sometimes the child is not being respected. When treated with respect, children tend to respond respectfully. When loved, they tend to become loving.

While the source of the child's upset may ultimately be more complicated, often, its roots are observable in the first family session with the child and parents. Commonly the parents are too fearful or distracted to apply rational discipline and let the child run wild. They have lost all sense of their own moral authority, and consequently, the child no longer treats them with respect. Often the parents cannot agree on a rational plan, subjecting the child to contradictory commands. Sometimes the child is being abused outside the home or is simply unable to fit into the highly structured, boring environment typical of many classrooms. Too often, psychiatrists have instructed the parents that the problem lies in the child and therefore they should not bother to examine how they relate to their offspring or what may be happening to their child in the outside world.

Small children do not, on their own, create severe emotional conflicts within themselves and with the adults around them. When older children end up generating severe conflict, it usually comes from a long history of prior conflicts with adults. Children are not born bored, inattentive, undisciplined, resentful, or violent, but the stigmatizing psychiatric labels imply that they are. Indeed, fabricated theories about the genetic origin of so-called ADHD are created for the purpose of proving the argument that children are born with problems that, in reality, they develop in response to their environments.

In my experience, children labeled ADHD are usually more energetic and more spirited, or more in need of an interesting environment, than their parents and teachers can handle. One of the early advocates of hyperactivity as a diagnosis describes them as unusually dynamic bundles of energy (Wender, 1973). They sound like prototypes of health, vigor, and youth. Yet they are being diagnosed with a psychiatric disorder—a label that will follow them into adulthood, forever stigmatizing them in their own eyes and in the eyes of others.

## ADD and TADD

Many and probably most so-called ADHD children are receiving insufficient attention from their fathers, who may be separated from the family, too preoccupied with work and other things, or otherwise impaired

in their ability to parent. In many cases the appropriate diagnosis is dad attention–deficit disorder (DADD; Breggin, 1991b; Breggin et al., 1994b). A 2007 study in the journal of the Canadian Medical Association confirms what I have written about for years. Strohschein (2007) analyzed data from Canada's National Longitudinal Survey of Children and Youth from 1994 to 2000. Among those children whose parents remained married, 3.3% received Ritalin at some time during the 7-year period. Among those whose parents divorced, 6.1% (almost double) were placed on Ritalin during the period. In partial confirmation of her findings, Strohschein cited several other studies indicating that single-parent households have a higher rate of children on stimulant medication. In my clinical experience, conflict associated with divorce, both before and after the actual separation, invariably causes severe stress in children. The children's distress is a normal reaction; but if brought to a health-care provider, the children are almost always given a psychiatric diagnosis, anything from ADHD or oppositional defiant disorder to an anxiety or mood disorder. Usually, the source of the problem—parental conflict and suffering—is largely or completely ignored, and instead the child is diagnosed and medicated. Sadly, this misguided psychiatric response reinforces the belief commonly held by children that they are somehow at fault, and even to blame, for the fighting among their parents.

After the divorce, when living in a single-parent home, usually under the care of the mother, boys in particular become difficult to handle. They suffer from acute and then chronic DADD. Many of these children are in such great need of male attention that even a once-a-week counseling session with a fatherly therapist is very helpful to them. However, the therapist becomes far more effective if able to increase the involvement of the real father in the child's life and to help both parents reconcile their differences sufficiently to develop a consistent and loving plan for raising their children. The therapist can also help the mother identify other males in the child's life who may wish to take a more active role. In my practice, if the father is not participating in the child's life, I work with the mother and the children as a family, helping to provide support for her parenting decisions.

Young people are nowadays so hungry for the attention of a father that it can come from any male adult. Seemingly impulsive, hostile groups of children will calm down when a caring, relaxed, and firm adult male is around. Arlington High School in Indianapolis was canceling many of its after-school events because of unruliness, when a father happened to attend one of them (Smith, 1993):

> That evening there was an odd quietness on [the father's] side of the auditorium. It turned out that when he would tell his group to settle down, some students would second him. One said: "That's Lena's father. You heard him. Be quiet; act right." (p. 5)

Since then, the school has begun to enlist volunteer dads to help supervise after-school events.

At other times, the so-called disorder should be called TADD: teacher attention–deficit disorder. Owing more to problems in our educational system than to the teachers themselves, few students get the individualized educational programs that they need.

Overall, in our society, parents and teachers receive too little support for their tasks, which are among the most difficult in society. The average parents receive more training in how to breathe during the delivery of their children than they will receive in how to relate to their offspring over the ensuing 18 years. The average teacher has difficulty keeping himself or herself afloat amid the pressures of teaching poorly disciplined children in overcrowded classes. The teacher has little time to individualize his or her instruction to particular educational needs and even less to develop relationships with students. Nevertheless, as burdened as parents and teachers may feel, they should not try to escape their responsibilities by drugging children. Instead, they should find the support they need to continue improving their skills, while also working toward improving their schools and families.

## CRITIQUES OF ADHD

In 1993, neurologist Fred Baughman Jr. noted that studies have failed to confirm any definite improvement from the drug treatment of ADHD-labeled children. Baughman cited estimates of the frequency of ADHD, which varies from 1 in 3 to 1 in 1,000. He therefore asked, Is attention-deficit hyperactivity disorder, after all, in the eye of the beholder?

The eye of the beholder theme echoes Diane McGuinness (1989), who has systematically debunked ADHD as the emperor's new clothes. In a chapter in *The Limits of Biological Treatments for Psychological Distress,* she observed,

> The past 25 years has led to a phenomenon almost unique in history. Methodologically rigorous research…indicates that ADD [attention deficit disorder] and hyperactivity as "syndromes" simply do not exist. We have invented a disease, given it medical sanction, and now must disown it. The major question is how we go about destroying the monster we have created. It is not easy to do this and still save face. (p. 155)

According to Vatz (1993), "attention-deficit disorder (ADD) is no more a disease than is 'excitability.' It is a psychiatric, pseudomedical term."

Frank Putnam (1990), a director of one of NIMH's research units, applauded "the growing number of clinicians and researchers condemning

the tyranny of our psychiatric and educational classification systems." Putnam found that it is "exceedingly difficult to assign valid classifications [to children, and yet] children are by far the most classified and labeled group in our society." He warned against "the institutional prescriptions of a system that seeks to pigeonhole them."

In recent years, the "inattention" aspect of the ADHD diagnosis has received increasing emphasis in an effort to spread the net wider to include girls who display no hyperactivity. Educators Thomas Cushman and Thomas Johnson (2001) have examined the multiple causes of inattention in children including stress, feelings of sadness, temperament, nutrition, and genuine medical disorders. They examine sources of so-called inattention in the ecological environment of the school. Finally, they challenge the basic concept of "inattention." In my own clinical experience, children who display "inattention" on academic tests or in school may have a marvelous capacity to involve themselves wholeheartedly in projects they enjoy and have learned how to master.

## Comorbidity and Misguided Diagnoses

The notion of a specific ADHD syndrome is further undermined by the tendency to give the same child a combination of several diagnoses. This reality appears throughout the psychiatric literature. Dulcan and Popper (1991) observed that multiple diagnoses for a single child are common and that hospitalized children average four diagnoses at once. Like the proverbial cookie cutter, the diagnoses chop the child into various predesigned shapes that bear little or no resemblance to the child's underlying psychosocial problems, family or school conflicts, and unmet needs.

Without fully exploring the implications, Dulcan and Popper (1991) also pointed out that the diagnosed behaviors may turn out to be assets in adulthood:

> Certain individuals may even learn to turn childhood deficits such as excessive sensitivity (separation anxiety), unrelenting stubbornness (oppositional defiant disorder), or uncontrolled activity and enthusiasm (attention deficit hyperactivity disorder) into strengths in adulthood. (p. 2)

Unfortunately, Dulcan and Popper (1991) missed the point. The child does not have deficits to begin with. The deficits lie within the inability of the adults and their institutions to meet the child's needs and to guide his or her energies into positive forms of expression. Indeed, the requirements we place on children for conformity and docility in the classroom are antithetical to success in a competitive, mentally demanding adult world. Furthermore, once the child is labeled as having a disorder or

deficit, the view of the child's behavior becomes entirely negative. Instead of channeling the energy, it is viewed as an illness to be eliminated. Time after time, parents come to me preoccupied with their child's supposed deficits, such as ADD and dyslexia, without any corresponding focus on the child's assets, such as computer skills, social abilities, and imagination. Worse yet, when the child is drugged, the potentially positive traits are driven underground and potentially destroyed by a combination of drug toxicity and stigmatization.

## The Supposed Physical Basis for ADHD

A study led by NIMH's Alan Zametkin et al. (1990) received a great deal of publicity for finding increased brain metabolism in PET scans of adults with a history of ADHD in childhood. However, when the sexes were compared separately, there was no statistically significant difference between the controls and ADHD adults. To achieve significance, the data were lumped together to include a disproportionate number of women in the controls. In addition, when individual areas of the brain were compared between controls and ADHD adults, no differences were found. It is usually possible to massage data to produce some sort of statistical result, and Zametkin et al.'s study is a classic illustration.

Since the behaviors associated with ADHD do not constitute an organic disorder but, in most cases, a manifestation of conflict between children and adults, it is unreasonable to expect that a biological cause will ever be found. Put another way, since the adults have more influence over the origins and resolutions of the problem, it is irrational to seek a biological defect in the child. Golden (1991) put it simply:

> Attempts to define a biological basis for ADHD have been consistently unsuccessful. The neuroanatomy of the brain, as demonstrated by neuroimaging studies, is normal. No neuropathologic substrate has been demonstrated. (p. 36)

Meanwhile, the emphasis on possible genetic and biological causes of upset behaviors in children ignores research confirming their psychosocial origins (see earlier in the chapter and Breggin, 1992a; Green, 1989).

The neurobiological basis for ADHD remains a cornerstone of the argument for diagnosing and drugging children, even as the search for scientific evidence continues to flounder (Seitler, 2006; Stolzer, 2007). The search for a genetic and biological cause of ADHD can never succeed because the biopsychiatric researchers are looking in the wrong place. When a child lacks self-discipline or feels bored and frustrated by school tasks, the fault does not lie in the child's biology but in the adult world's

failure to discipline and to engage the child. There are an infinite number of psychosocial and educational approaches to helping the kind of children who get falsely labeled with ADHD, but these better methods will never be fully implemented until the diagnosis of ADHD and the use of toxic chemicals have been abandoned by the psychiatric and educational establishment (Timimi, 2004).

### ADHD: An American Disease? A Boy's Disease

Through the 1990s, the United States used 90% or more of the world's Ritalin. The pattern is changing now, however, as drug companies seek new markets. Drug company marketing has led to increasing worldwide use of the ADHD diagnosis with the prescription of stimulants (Kean, 2005, 2006).

Similarly, males used to be given 90% of the Ritalin in the United States, but drug company promotion of stimulants for inattention has led to more and more girls being diagnosed and prescribed medication. Nonetheless, boys still remain the main target of psychiatric drugs that aim at eliminating or subduing their more rambunctious or difficult behaviors. Aside from feeling bored or in conflict with adults, why would boys ordinarily tend to act resentfully and rebelliously toward the authority of their mothers and female teachers? The simplest answer is that the culture trains them to be disrespectful toward women in general. In fact, many grown men continue to resent "being told what to do" by women. In some authoritarian societies, the adult male continues to demand unquestioned authority over women.

A multiplicity of factors contribute to the conflicts and confusion in little boys. Respect for authority in general is on the decline in society. Boys are culturally encouraged, and even trained, to suppress their tender ("feminine") sides. Meanwhile, the culture too often encourages them to feel and to act domineering and hostile toward girls and women. These lessons are imprinted through TV and other entertainment media and reinforced in sports and on the playground as well as in some families.

In our modern society, girls also receive increasingly confusing messages about assertiveness, and more and more of them are being diagnosed with one or another DBD. Often, they are children with special enterprise and boldness.

## CHADD: A DRUG COMPANY ADVOCATE

Founded in 1987, Children and Adults with Attention Deficit Disorders (CHADD) has now expanded its horizons to include adults, as well, with

ADHD.[1] Founded and led by parents who have children labeled with attention deficit disorders, from the beginning, its unofficial policy has been "we are not to blame." CHADD's official policy views these children as suffering from genetic and biological problems. In the words of CHADD president Sandra F. Thomas (1990), "Our kids have a neurological impairment that is pervasive and affects every area of their life, day and night."

CHADD leaders claim that their children's emotional upset and anger is in no way caused by family conflicts, poor parenting, inadequate schools, or broad social stressors. In a CHADD brochure titled *Hyperactive? Inattentive? Impulsive?,* a headline announced, "Dealing with parental guilt. No, it's not all your fault" (CHADD, n.d.). After stating that ADHD is a neurological disorder, the brochure went on to explain,

> Frustrated, upset, and anxious parents do not cause their children to have ADD. On the contrary, ADD children usually cause their parents to be frustrated, upset, and anxious. (p. 1)

There could be no more blatant example of child blaming and parental exoneration.

CHADD has followed the model of its adult counterpart, the National Alliance for the Mentally Ill (NAMI; Breggin, 1991b). Parents who belong to NAMI usually have grown offspring who are severely emotionally disabled, and they promote biochemical and genetic explanations, drugs, electroshock, psychosurgery, and involuntary treatment. The organization also tries to suppress dissenting views by harassing professionals who disagree with them (Breggin, 1991b). NAMI has developed an affiliate, NAMI-CAN—the National Alliance for the Mentally Ill, Child and Adolescent Network (Armstrong, 1993). Both NAMI-CAN and CHADD believe in what they call *BBBD*—biologically based brain diseases.

## The Power Base of the Parent Groups

Parent members of CHADD and NAMI have developed enormous influence by joining forces with biologically oriented professionals, national mental health organizations, and the drug industry. But where is the money coming from to support high-pressure lobbying, media campaigns, and upscale national conventions at hotels like the Chicago Hyatt Regency? *Pathways to Progress,* CHADD's (1992) convention program, stated,

> CHADD appreciates the generous contribution of an educational grant in support of our projects by CIBA-Geigy Corporation.

CIBA-Geigy (now Novartis) manufactures Ritalin, the stimulant that, at the time, held the lion's share of the ADHD market.

I have been able to obtain a complete list of contributions to CHADD by CIBA-Geigy. The escalating totals are as follows:

| | |
|---|---|
| 1989 to year ending June 30, 1992 | $170,000 |
| Year ending June 30, 1993 | $50,000 |
| Year ending June 30, 1994 | $200,000 |
| Year ending June 30, 1995 | $398,000 |

In 1995, CHADD also had smaller grants from Abbott Laboratories ($37,000) and Burroughs Wellcome ($18,000). Abbott is the manufacturer of the stimulant pemoline (Cylert), used to treat ADHD. Burroughs Wellcome makes several medications used in pediatric medicine, including well-known antibiotics and cold medications. They also make the highly stimulating antidepressant Wellbutrin.

CHADD's dependence on drug companies continues unabated. According to CHADD (2007), obtained from its Web site, "total pharmaceutical donation support of CHADD as of June 30, 2006 was 28% of CHADD's budget ($1,401,000)." Not included in this total are contributions from foundations influenced by the drug companies such as Eli Lilly. The complete list of pharmaceutical supporters includes the manufacturers of most stimulants: Cephalon (Provigil, not approved for treating ADHD), Lilly (Strattera), McNeil (Concerta), New River (lisdexamfetamine dimesylate, a newly approved drug marketed in collaboration with Shire), Novartis (Ritalin in various forms), Shire (Adderall; Daytrana), and UBC (Metadate). Except for corporations making stimulants, CHADD received no other pharmaceutical industry support. CHADD is a committed group.

Does all this money influence CHADD to defend drug company interests, rather than the genuine interest of parents and their children? When the FDA served notice that it might put a new warning onto the label of stimulant drugs concerning cardiac risks in children, CHADD responded with a February 2006 press release warning that the decision was "premature" and calling for the usual "further research" (Goodman, 2006). CHADD concluded, "For many persons, ADHD medications are an important part of a comprehensive treatment program." In the press release, did CHADD describe itself as a drug company–funded advocacy group? No, it called itself "the nation's leading advocacy and family support organization representing people with attention-deficit/hyperactivity disorder (ADHD)."

The adult counterpart of CHADD, NAMI (National Alliance on Mental Illness), has had equal success in its political efforts. It, too, is closely aligned with biological psychiatry and accepts money from the

drug companies. Eli Lilly recently disclosed the recipients of $11.8 million in largesse for the first *quarter* of 2007 (Johnson, 2007). NAMI alone received a whopping $544,500.

In November 2005, the medical director and CEO of the APA wrote a letter to all members, including this author, urging us to become "professional supporters" of NAMI for the price of $75 per year (Scully, 2005). When one organization sends out a mailing urging you to join another organization, you know they are partners. NAMI is an extraordinarily influential member of the psychopharmaceutical complex.

### On-the-Spot Diagnosis

A CHADD *Educator's Manual* was written with the collaboration of professionals, including Russell Barkley (Fowler, 1992), the psychologist whose aim is to crush "noncompliance." It makes clear the intention to diagnose (and subsequently drug) children who fail to conform to strict discipline:

> Attention Deficit Disorder is a hidden disability. No physical marker exists to identify its presence, yet ADD is not very hard to spot. Just look with your eyes and listen with your ears when you walk through places where children are—particularly those places where children are expected to behave in a quiet, orderly, and productive fashion. In such places, children with ADD will identify themselves quite readily. They will be doing or not doing something which frequently results in their receiving a barrage of comments and criticisms such as "Why don't you ever listen?" "Think before you act." "Pay attention."

Note that "children are *expected* to behave in a quiet, orderly and productive fashion." There is no hint that adults should be expected to teach children discipline and to provide them with places in which they are motivated and enabled to behave in a quiet, orderly, and productive manner.

## MENTAL HEALTH SCREENING IN SCHOOLS: THE LATEST THREAT

I have documented cases of parents who were forced to medicate their children by their spouses, the state, or their public school (Breggin, in press). By far the greatest threat to children and their parents lies within the public schools. They are being turned into triage centers to select out children for medication treatment. Parental consent will be steamrollered (Jackson, 2006b). The system is euphemistically called *mental health*

*screening*. In some states, there are proposals to begin with preschoolers and infants.

The impetus is the federal government's New Freedom Commission, which supports both early mental health screening in the schools and the Texas Medical Algorithm Project, a pharmaceutical company attempt to enforce guidelines necessitating the use of its products. Minnesota pediatrician Karen Effrem (2005, 2006) is leading the fight against proposed TeenScreening in our schools. Meanwhile, Effrem's state is moving toward toddler screening, and even infant screening, where legislation has been introduced calling for the "socioemotional" screening of toddlers before admission to kindergarten.

Columbia University is the strongest force in promoting TeenScreen around the nation. Evelyn Pringle (2007), writing for *Independent Media TV,* reported on how Columbia's TeenScreen program is run by Lauri Flynn, the former executive director of NAMI, the drug company–sponsored organization that has led the push for drugging adults and children. Flynn distinguished herself in the late 1980s by leading personal attacks against me because of my criticism of psychiatric medication. Over the years, NAMI has received multimillions from donors like Janssen, Novartis, Pfizer, Abbott Labs, Wyeth-Ayerst, Bristol-Myers, and its largest benefactor, Eli Lilly, which for years has given at a clip of over $1 million a year. The Columbia TeenScreen program was developed in collaboration with NAMI and therefore with America's pharmaceutical industry. TeenScreen is a pharmaceutical marketing program aimed at compelling unlimited numbers of children and youth to take psychiatric drugs.

If these screening programs become fully implemented, "millions more children will be pushed into becoming lifetime consumers of psychiatric drugs. The engorged psycho-pharmaceutical complex will spread its tentacles over family and school alike. Meanwhile, the whole process will gradually become increasingly involuntary. Given that our children need attention to their real educational and family needs, and not diagnosing and drugging, these mental health screening programs are worth fighting against!" (Breggin, in press).

## MORAL, PSYCHOLOGICAL, AND SOCIAL HARM

Children are given stimulant drugs for ADHD during a period of time in which they are developing their psychological and social skills, and, indeed, their very identity. What does it mean to a child, and later to the grown adult, to be told that his or her brain has crossed wires or a biochemical imbalance? What are the repercussions of children hearing that

medication is necessary for them before they can behave in a "normal" manner that conforms to the standards of their family or school?

In my clinical work, it is enormously satisfying to see the reactions of children when I tell them, "I know you've been told by other doctors that you have ADHD and bipolar disorder, and that you need drugs; but none of it's true. Like any kid, you need help in learning to control your behavior. You're a wonderful child and you're going to be fine. We're all going to work together to help you grow up." Parents describe seeing their children look happy for the first time in years on the way home in the car after the first session. Some have told me that within hours their children have started singing or joking for the first time in years as a result of my reassuring them that there's nothing wrong with them and that, with the help of their parents, they can learn to control their own behavior.

It is far more demoralizing for a child to be told that his or her brain is defective than to be called bad. This is because the diagnosed child gets the same message—"you are bad"—plus a message that he or she is a hopeless freak, a person with an abnormal brain and mind. I never tell children they are bad, but they often find relief in hearing, "You don't have anything wrong with your brain; your parents haven't until now figured out how to help you stop behaving so badly. But you can see just from today in our family session how easy it is for you to calm yourself down with only a little help from me. You and your parents will soon be able to do that without my help."

As the list of criteria demonstrates, ADHD is one more DBD—another way a child gets labeled as a source of frustration or disruption. This is true even in regard to some of the criteria for the inattention aspect of the disorder. As Golden (1991) observed, "The behavior is seen as being disruptive and unacceptable by parents and teachers, and the child is socially handicapped as a result."

Dulcan (1994; see also Whalen et al., 1991) summarized some of the harmful moral, psychological, and social effects on children who are prescribed stimulant medications such as Ritalin and Adderall:

> indirect and inadvertent cognitive and social consequences, such as lower self-esteem and self-efficacy; attribution by child, parents, and teachers of both success and failure to medication, rather than to the child's effort; stigmatization by peers; and dependence by parents and teachers on medication rather than making needed changes in the environment. (p. 1218)

An unpublished report (Jensen et al., n.d.), circa 1989, "Why Johnny Can't Sit Still: Kids' Ideas on Why They Take Stimulants," was based on research conducted by physicians Peter Jensen, Michael Bain, and Allen

Josephson. Jensen is an experienced researcher from the Division of Neuropsychiatry at Walter Reed Army Institute of Research. Using interviews, child psychiatric rating scales, and a projective test titled Draw a Person Taking the Pill, the authors systematically evaluated 20 children given Ritalin by their primary care physicians. The researchers concluded that taking the drugs produced (a) "defective superego formation" manifested by "disowning responsibility for their provocative behavior"; (b) "impaired self-esteem development"; (c) "lack of resolution of critical family events which preceded the emergence of the child's hyperactive behavior," and (d) displacement of "family difficulties onto the child."

Many of the children thought they were bad and were taking the pill to control themselves. They often attributed their conduct to outside forces, such as eating sugar or not taking their pill, rather than to themselves. Jensen et al. (n.d.) warned that the use of stimulant medication "has significant effects on the psychological development of the child" and distracts parents, teachers, and doctors from solving important problems in the child's environment.

Jensen et al. (n.d.) concluded, "Research investigating children's perceptions of the meanings of stimulant medication, as mediated by the family context, adult and child attributions, and the child's developmental level, are long overdue." Unfortunately, Jensen never published the paper and instead went on to a lucrative and influential career as one of the nation's most uncompromising advocates of drugs for children.

## Like Shining Stars

Our children relate to us mostly through home and school and, in some families, through church, scouts, and other community organizations. In each place, we need a new dedication to their basic needs, rather than to treating presumed psychiatric disorders. Above all else, our children need a more caring connection with us, the adults in their lives. This link is now being forged in some school systems that have begun to abandon the large, factorylike facilities of the past in favor of a "small is beautiful" philosophy.

There are many advantages to smaller schools, but perhaps the most significant one is this: They allow teachers to get to know their students well enough to understand them personally and to meet their basic educational and emotional needs. At the same time, small schools and classes meet the teachers' basic needs for a satisfying, effective professional identity. Conflict can be more readily resolved as ideally it should be—through mutually satisfying solutions—rather than suppressed through medical diagnosis and pharmacological behavior modification.

Some smaller, more child-oriented schools have shown that the DBDs can virtually disappear. There is no better evidence for how the environment powerfully shapes the behavior that results in children being psychiatrically diagnosed.

In a July 14, 1993, *New York Times* front-page report titled "Is Small Better? Educators Now Say Yes for High School," Susan Chira reported,

> Students in schools limited to about 400 students have fewer behavior problems, better attendance and graduation rates, and sometimes higher grades and scores. At a time when more children have less support from their families, students in small schools can form close relationships with teachers.

Chira (1993) suggests that teachers in these schools have the opportunity for "building bonds that are particularly vital during the troubled years of adolescence." Even students from troubled homes respond to smaller, more caring schools. "They are shining stars you thought were dull," said a New York City teacher. "If you're under a lot of pressure and stress, they help you through that," said a student. "They won't put you down or put you on hold" (Chira, 1993).

Leila Abboud (2005a), the *Wall Street Journal* writer who disclosed the facts behind the diagnosis of childhood bipolar disorder, also examined nondrug approaches to helping children. Abboud opened by pointing out, "With persistent concerns about using powerful psychiatric drugs in children, there is growing interest in counseling techniques for troubled kids that aim to change destructive behavior." The successful, tested methods she described always started with the adults in the child's life. Parent management training, developed by Yale child psychologist Alan Kazdin, involves 5–15 weeks of teaching parents how to manage their child's behavior through role-playing and a disciplined system of rewards and punishments. The Incredible Years, developed by psychologist Carolyn Webster-Stratton, has a database of over 8,000 professionals trained in the program. Parents usually attend 3 months of group sessions structured around videos of how to deal with difficult children. There is a module for teachers as well. Multisystem therapy, developed at the Medical University of South Carolina, centers around intense interventions in the families of high-risk juveniles in trouble with the law who might otherwise be sent to residential facilities. In addition, I have described a variety of approaches to helping children through their families and schools in my books *Reclaiming Our Children* (2000b), *Talking Back to Ritalin* (2001c), and *The Ritalin Fact Book* (2002b).

Children respond so quickly to improvements in the way that adults relate to them that most children can be helped without being seen by a mental health consultant or therapist. Instead, the therapist can consult with the parents, teachers, and other concerned adults. In my clinical practice, I often see children only once or twice with the parents. After that, I work with the parents by themselves to help them to develop more consistent, rational methods of disciplining the child, along with unconditional love and attention to educational needs. If the parents are willing and able to learn new ways of approaching their children's needs, obvious positive changes in the children become apparent within a few days and weeks.

Many psychotherapists routinely help children without actually seeing them in their offices. As "adult therapists," they help their adult patients become more loving or disciplined parents through the routine work of psychotherapy, indirectly transforming the lives of their children. The children get better sight unseen. These therapists may not identify themselves professionally as child psychiatrists or child therapists; but they are doing far more good for children than those professionals who diagnose and medicate them.

Children are not born with emotional disorders; they are born into emotionally disturbing living conditions. I have reviewed some of the research literature linking disturbed home environments, child abuse, and other factors to emotional disturbances in children (Breggin, 1991b, 1992a). A study by Biederman et al. (1995) confirmed that there is a correlation between adversity in the child's life and a diagnosis of ADHD. *Adversity* includes such things as severe marital discord, low social class, large family size, foster parent placement, and mental illness or criminality in the family.

Salyer et al. (1991) provided a discussion with citations to the literature concerning the role of environment in causing a variety of childhood disorders. The focus of their article is learning disability (LD). They pointed out that families with children labeled LD are less cohesive and more chaotic, with less educational stimulation and more economic difficulty. Families with so-called LD children tend to provide less support and less independence, while emphasizing control. In the same vein, they pointed out that even with known biological and genetic disorders, such as brain damage, "the psychosocial environment was found to be the most important predictor of the child's later level of functioning" (p. 238).

Green (1989) provided a comprehensive review showing that virtually every childhood disorder can be produced by environmental trauma and stress. The whole range of childhood disorders, from autistic behavior

to hyperactivity and violence, can be caused by the environment. The message from this seems clear-cut: Adults, through their control over the environment, are in a position to provide harmful or healing alternatives to children.

When adults provide them a better environment, children tend to quickly improve their outlook and behavior. Sometimes children can benefit from learning how to help to ease the conflicted situation, but it is futile to ask young children to contribute in a positive fashion to resolving family problems unless the adults are simultaneously learning the same conflict resolution skills.

By the time children reach adolescence, self-destructive patterns can become so internalized or entrenched that their parents may be unable to reach them. In addition, rebellious teens may be unwilling or unable to respond to positive changes in their parents. As a result, some teenagers can benefit from individual counseling, especially if their parents are also getting help. But for the overwhelming majority of preadolescent children, therapeutic interventions can be directed almost exclusively at the adults in their lives, including the parents and teachers.

If children are brought into a therapy setting, they should *never* be given the idea that they are diseased or defective. They should never be told that they are the original cause of the conflicts they are having with their schools and families. The focus of child psychiatry should not be children, but parents, families, schools, religious institutions, and the wider society. What is most needed is greater adult responsibility for children in all spheres of life, from the personal attention of a parent or teacher to the social reform of our family, school, religious, and social life.

Children can benefit from guidance in learning to be responsible for their own conduct, but they do not gain from being blamed for the trauma and stress that they are exposed to in the environment around them. They need empowerment, not humiliating diagnoses and mind-disabling drugs. Most of all, they thrive when adults show concern and attention to their basic needs as children. These needs include self-esteem, love, discipline, and education. These needs cannot be filled by adults who want to diagnose and drug the children. They can only be fulfilled by adults who are willing to open their hearts to children and to learn new and better ways to approach troubled and troubling young people as individuals.

We have lost sight of these truths in America and have become all too willing to hand over our so-called problem children to experts with credentials that permit them to recommend or prescribe drugs. Our problem children reflect our problems as adults; in each and every case, it is up

to us to find ways to provide what our children need in order to become responsible, self-disciplined, successful adults.

## NOTE

1. At the time of the first edition of this book in 1983, the organization called itself CH.A.D.D. That has been simplified to CHADD. Its official name has been expanded into Children and Adults with Attention Deficit Hyperactivity Disorders.

CHAPTER 11

# Stimulant-Induced Brain Damage, Brain Dysfunction, and Psychiatric Adverse Reactions

Even *Newsweek,* for whom psychiatry is usually sacrosanct, has begun to wonder if too many "quirky" and otherwise normal kids are being stigmatized with psychiatric labels (Ali, 2007). The massive increase in diagnosing children with ADHD, bipolar disorder, and autism spectrum disorders such as Asperger's can lead to only one outcome—more psychiatric drugging of America's children . . . more drugs and less attention to their genuine needs for caring adult role models, improved family life, better schools, and economic opportunity.

Many of the drugs prescribed to children are FDA-approved exclusively or largely for adults and have been discussed in earlier chapters. All of them, including the neuroleptics, mood stabilizers, and antidepressants, cause basically the same adverse effects in children as adults, although they may vary in frequency and intensity. Children are especially vulnerable to developing brain-disabling, spellbinding adverse reactions to psychiatric drugs. For example, antidepressant-induced suicidality was first demonstrated in controlled clinical trials of children and teenagers (chapter 6).

This chapter will focus on the drugs most commonly and specifically prescribed to children: stimulants such as Ritalin, Concerta, Dexedrine, Adderall, and Strattera. A list can be found in the appendix.

## AN INEFFECTIVE TREATMENT

Over the last several years, NIMH has funded a cohort of dedicated stimulant/ADHD advocates to conduct an expensive, nationwide, long-term study under naturalistic conditions in the community to prove the effectiveness of stimulants in treating so-called ADHD (Jensen et al., 2001). The list of authors includes Peter Jensen, Stephen Hinshaw, James Swanson, Larry Greenhill, and even Keith Conners. It was as if the aging Stimulant Club had gone on government relief to produce the NIMH Multimodal Treatment Study of ADHD (MTA), whose results continue to be published.

The MTA researchers led by Swanson were already touting the unpublished results in advance at the 1998 Consensus Development Conference on the Diagnosis and Treatment of ADHD. It seemed to be a foregone conclusion that the upcoming series of publications would be mightily skewed in the direction of proving drug efficacy. Nonetheless, as the various publications began to come out over the ensuing years, the study failed to prove the hoped-for results and began to provide indirect indicators of the superiority of educational and psychosocial interventions (Breggin, 2000a, 2001b; Kean, 2004; Leo, 2004).

Finally, in 2007 the MTA authors published their evaluation of long-term effectiveness. At the 36-month assessment, stimulant medication was no better than any of several other behavioral and educational approaches (Swanson et al., 2007b). Basically, with or without systematic treatment of any kind, all the children ended up the same. Thus, the best, most experienced minds in the ADHD/stimulant lobby could not put together a study to demonstrate any long-term usefulness for the medications. Meanwhile, they did confirm that the medication stunts growth (Swanson et al., 2007a; see following discussion). As always, these negative results did not cause any of the many investigators to call for more caution in prescribing stimulants to children.

In defense of their drugs, the MTA authors argued that perhaps all of the children simply got better over 36 months; that is, their ADHD went away. First of all, this is contrary to the persistent argument made by drug advocates that ADHD is a real biological disease that does not go away and that requires long-term, even lifetime, treatment. Second, if it is true that so-called ADHD clears up on its own, that makes a good argument for never giving toxic drugs to children.

Ritalin and other stimulants are typically prescribed for months and years at a time. Nonetheless, despite decades of effort, biopsychiatry and the drug companies have not been able to demonstrate any long-term gain for children from taking stimulants. Going back many years to the present day, the FDA-approved labels for Ritalin as found in the *Physicians'*

*Desk Reference* (2007) have stated, "Long term effects of Ritalin in children have not been well established" (p. 2273, under "Pediatric Use"). This caveat applies to all of the stimulant drugs. As the National Institute of Mental Health (NIMH) succinctly stated, "The long-term effects of stimulants remain in doubt" (Regier et al., 1992). NIMH had hoped to correct this negative conclusion by paying millions of dollars to drug advocates to conduct the multicenter MTA study that once again failed to prove any long-term effectiveness. NIMH further stated that studies have demonstrated short-term effects such as reducing "class room disturbance" and improving "compliance and sustained attention" (Regier et al., 1992). But it recognized that the drugs seem "less reliable in bringing about associated improvements, at least of an enduring nature, in social-emotional and academic problems, such as antisocial behavior, poor peer and teacher relationships, and school failure." Meanwhile, the short-term impacts of reducing disturbance and improving compliance, as well as improving attention, are brain-disabling effects that last only for a few weeks until the brain manages to compensate for the drug toxicity (see following discussion).

Dulcan (1994) reviewed stimulant treatment for ADHD children. In regard to long-term control, she found that "stimulants have not yet been demonstrated to have long-term therapeutic effects." The *not yet,* it should be emphasized, referred to three decades of trying to prove its effectiveness.

After decades of research, there is still no evidence for efficacy beyond a few weeks' exposure, and that so-called efficacy is based on the capacity of stimulants to suppress all spontaneous behavior and to enforce obsessive behavior (Breggin, 1999a, 2001c; see subsequent discussion). Solanto and Wender (1989) showed that single clinical doses of methylphenidate caused a constriction of cognitive processes and overfocusing on tasks. In the classroom, this is mistaken for an improvement, when in fact it is a drug-induced disorder—a classic example of the brain-disabling principles of psychiatric treatment.

In regard to improvement in learning or educational performance, the record is even worse. There is no convincing evidence for either short- or long-term improvement in cognitive ability or academic performance (reviewed by Breggin, 1991b; Coles, 1987; McGuinness, 1989; Swanson et al., 1992).

Dulcan (1994) also made clear that for the drug to be effective, an array of other interventions are required:

> Specific learning disabilities and gaps in knowledge and skills due to inattention require educational remediation. Social skills deficit and family pathology may need specific treatment. Parent education and

> training in techniques of behavior management are virtually always indicated. (p. 1214)

A program such as Dulcan suggested would in reality do away with the need for drugging children. As a consultant to state programs and clinics, I have found that such a comprehensive program can help the most disturbed and disabled children, including those with more severe diagnoses than ADHD. Such programs are offered to very few children, and even fewer once the decision to medicate has been made.

In May 2006, the Oregon Health and Science University, Oregon Evidence-Based Practice Center issued its final report, "Drug Class Review on Pharmacological Treatments for ADHD" (McDonagh et al., 2006). On the basis of a review of all available research, the 113-page report continued to confirm the shortcomings of the stimulant drugs and, in particular, research surrounding these medications. After reviewing the available literature, the report concluded, "Good quality evidence on the use of drugs to affect outcomes relating to global academic performance, consequences of risky behaviors, social achievements, etc. is lacking." The report also found that safety evidence was of "poor quality" and that evidence of the drugs helping adults was "not compelling."

Concerning effectiveness for reducing ADHD behaviors, the report divided its conclusions into age brackets. For *preschoolers* (age 3–5 years), it found evidence "seriously lacking." The authors could find only five placebo-controlled trials, and only one was of "fair quality." They also found "no evidence of long-term safety" for drugs in this age group. For *elementary school children* (age 6–12 years), some studies supported short-term effectiveness but were generally inadequate. For *adolescents* (age 13–17), McDonagh and Peterson (2006) concluded, "Evidence on the effectiveness of pharmacotherapy for ADHD in adolescence is very limited."

The study seemed to avoid making definitive comments, but the overall impression was captured in the headline "Are ADHD Drugs Safe? Report Finds Little Proof" (Otto, 2005).

## A WIDE VARIETY OF ADVERSE EFFECTS

The stimulant drugs, including all methylphenidate and amphetamine products, produce a wide array of adverse effects on the brain and mind as well as the overall body. Strattera, marketed by Eli Lilly as a nonstimulant, shares most of these adverse effects. Table 11.1 summarizes the adverse drug reaction data from eight controlled clinic trials. Table 11.2

**TABLE 11.1 Methylphenidate (MPH) and D-Amphetamine (AMPH) Adverse Drug Reactions (ADRs) in 8 Double-Blind Placebo-Controlled Studies of Children Diagnosed With ADHD**

| Study | Group[a] | Dose mg/kg | Duration | Salient ADRs |
|---|---|---|---|---|
| 1. Firestone et al. (1998) | 41, age 4–6 | MPH 0.3 and 0.5 BID | 7–10 days | Marked deterioration from placebo to 0.5 mg in Sad/unhappy (69% of children), Drowsiness (62%), Uninterested in others (62%). Loss of appetite (75%). Severe symptoms increased 12% for "Uninterested in others" (0–12%) and 28% for "Talks less with others" (22%–50%). Nightmares increased 35% (28%–62%); tics or nervous movements increased 9% (3% to 12%). |
| 2. Mayes et al. (1994)[b] | 69, age 2–13 | MPH most commonly 0.3 TID | mean 8 days | 6 discontinued because of ADRs. 13 "significantly worse" on drug. 5.8% increase or emergence of "stereotypical behaviors, including hand-wringing, arm-waving, teeth-grinding and foot-tapping." 7% severe reactions with one maniclike. 18.8% experience lethargy: "Children with lethargy were variously described by raters as tired, withdrawn, listless, depressed, dopey, dazed, subdued and inactive." 26% "irritability." |

*(Continued)*

**TABLE 11.1 Methylphenidate (MPH) and D-Amphetamine (AMPH) Adverse Drug Reactions (ADRs) in 8 Double-Blind Placebo-Controlled Studies of Children Diagnosed With ADHD** *(Continued)*

| Study | Group[a] | Dose mg/kg | Duration | Salient ADRs |
|---|---|---|---|---|
| 3. Barkley et al. (1990) | 83, age 5–13 | MPH 0.3 and 0.5 BID | 14–20 days | Decreased appetite, insomnia, stomachaches, and headaches. Proneness to crying increased at least 10% during low dose. Tics/nervous movements increased 10% at the high dose. Decreased appetite and insomnia "serious" in 13% and 18% at both doses compared to 1% and 7% on placebo. 3.6% dropped out due to "serious" ADRs. One case of "excessive speech and disjointed thinking." |
| 4. Schachar et al. (1997) | 46, age 6–12 | MPH approximately 0.5–0.6 ǀ BID | 4 months | 10% drop out due to ADRs, 3 due to "sadness and behavioral deterioration, irritability, withdrawal, lethargy, violent behavior, or rash"; 1 due to "withdrawal and mild mania"; 1 due to "withdrawal and dysphoria." 45% experienced an increase in at least 1 ADR ($p < .005$). Increased severity of affective ADRs (mostly withdrawal, sadness, crying) ($p < .01$). Increased severity of physiological ADRs (mostly anorexia and stomachaches) ($p < .005$). |

| | | | | |
|---|---|---|---|---|
| 5. Gillberg et al. (1997) | 62, age 6–11 | AMPH varying doses | 4–15 months | 3 cases of hallucination, 1 with severe tics. 32% abdominal pain occasionally or often. 56% poor appetite. |
| 6. Borcherding et al. (1990) | 46 boys, age 6–12 | Average weekly dose: MPH 0.5, 0.8, and 1.3 BID. AMPH 0.2, 0.5, and 0.7 BID | 3 weeks | Studied compulsive and tic ADRs. 58% develop abnormal movements. 51% develop obsessive/compulsive or perseverative ADRs. 1 persistent tic. Many severe OCD ADRs. See Table 11.6. |
| 7. Solanto and Wender (1989) | 19, age 6–10 | MPH 0.3, 0.6 and 1.0 QD | 3 separate days | Studied cognitive functions. 42% "overaroused" with "cognitive perseveration" (overfocused, OCD reaction). |
| 8. Castellanos et al. (1997) | 20, age 6–13; all comorbid for Tourette's | AMPH means 0.2, 0.41, 0.64 BID. MPH means 0.43, 0,67, and 1.20 BID | 3 weeks | 25% develop obsessive ADRs on MPH. 3 stopped medication at completion due to increased tics. One-third experienced worsened tics. |

*Note*. QD = once daily; BID = 2×daily; TID = 3×daily.

[a]Placebo subjects were not included in totals. [b]Only the preschoolers were double-blind placebo-controlled.

**TABLE 11.2 Harmful Effects Caused by Ritalin, Concerta, Dexedrine, Adderall, and Similar Stimulants**

| Brain and Mind Function | Cardiovascular Function | Gastrointestinal Function | Endocrine and Metabolic Function | Other Functions | Withdrawal and Rebound Reactions |
|---|---|---|---|---|---|
| Mania, psychosis, hallucinations | Palpitations | Anorexia | Pituitary dysfunction, including growth hormone and prolactin disruption | Blurred vision | Insomnia |
| Agitation, anxiety, nervousness | Tachycardia | Nausea, vomiting, bad taste | Weight loss | Headache | Evening crash |
| Insomnia | Hypertension | Stomachache | Growth suppression | Dizziness | Depression |
| Irritability, hostility, aggression | Cardiac arrhythmia | Cramps | Growth retardation | Hypersensitivity reaction with rash, conjunctivitis, or hives | Hyperactivity |
| Depression, suicide, emotional sensitivity, easy crying, social withdrawal | Chest pain | Dry mouth | Sexual dysfunction | | Irritability |
| Drowsiness, dopey, reduced alertness | Cardiac arrest | Constipation, diarrhea | | | Rebound worsening of ADHD-like symptoms |
| | | Abnormal liver function tests | | | |

| |
|---|
| Confusion, mental impairment (cognition and learning) |
| Zombielike (robotic) behavior with loss of emotional spontaneity |
| Obsessive–compulsive behavior |
| Convulsions |
| Dyskinesias, tics, Tourette's |
| Nervous habits (e.g., picking at skin, pulling hair) |

*Note*. Modified from "Psychostimulants in the Treatment of Children Diagnosed With ADHD, Part I: Acute Risks and Psychological Effects," by P. Breggin, 1999, *Ethical Human Sciences and Services, 1,* and "Psychostimulants in the Treatment of Children Diagnosed With ADHD: Risks and Mechanism of Action," by P. Breggin, 1999, *International Journal of Risk and Safety in Medicine, 12*. Reprinted with permission of Springer Publishing Company. The information is compiled from Arnold and Jensen (1995, p. 2306, Table 38-5, p. 2307, Table 38-7), Drug Enforcement Administration (1995b, p. 23), Dulcan (1994, p. 1217, Table 35-6), and Maxmen and Ward (1995, pp. 365–366). Citations in Breggin (1999a, 1999c).

compiles many of the stimulant adverse effects. I developed this chart for presentation at the 1998 National Institutes of Health (NIH) Consensus Development Conference on the Diagnosis and Treatment of ADHD to confirm the high frequency and the pattern of adverse stimulant effects.

The high rates of psychiatric adverse effects in controlled clinical trials have been largely ignored by the medical profession. However, they have not gone entirely unacknowledged. Table 11.3 is excerpted from a handbook of psychiatric medications (Maxmen et al., 1995).

The Drug Enforcement Administration (DEA, 1995b) provided a summary comparing the adverse effects of methylphenidate and amphetamine. For the central nervous system (CNS), it found excessive CNS stimulation, psychosis, dizziness, headache, insomnia, irritability, and attacks of Tourette's or other tic syndromes. It also listed for both drugs a variety of cardiovascular symptoms, including increased blood pressure and heart rate; various gastrointestinal symptoms, including vomiting, stomach pain, and anorexia; and weight loss and growth suppression. For methylphenidate alone, it listed leukopenia (abnormally low white cells in the blood), anemia, hypersensitivity reaction, and blurred vision. For amphetamine, it lists skin rash or hives.

The DEA (1995b) also observed that adverse effects of irritability or sadness have not been well studied but have been reported in up to 22% of children on stimulant medication. Elsewhere in the same document, the DEA noted that with both Ritalin and amphetamine, "psychotic episodes, violent behavior and bizarre mannerisms have been reported" (p. 16). Emotionally disturbing adverse effects are even more common with the youngest children. Dulcan and Popper (1991) noted that in preschool children, there is a greater risk of side effects, "especially sadness, irritability, clinging, insomnia, and anorexia" (p. 188).

**TABLE 11.3 Rates of Adverse Mental Effects Reported in Stimulant Clinical Trials**

| Adverse Reaction | Methylphenidate | Amphetamine |
|---|---|---|
| Drowsiness, less alert | 5.5% | 5.7% |
| Confused, dopey | 10.3% (8% to 12%) | 3.9% (2% to 10%) |
| Depression | 39% | 8.7% |
| Agitation, restlessness | >10% | 6.7% (3.3% to >10%) |
| Irritability, stimulation | 25% (17% to 29%) | 17.3% (11% to 19%) |

*Note*. The data are from Maxmen and Ward (1995, p. 366). The numbers are percentages of patients reported in studies to suffer from the adverse effect. Numbers in parentheses represent the range reported in studies.

Given the high rates of adverse effects caused by stimulants, it is a wonder that doctors tend to see these drugs in such a benign light, cavalierly prescribing them to children for the control of their behavior.

## MORE EXTREME INTOXICATION REACTIONS

One way to understand the routine effect of any psychiatric drug is to look at its more extreme or toxic effects (Breggin, 1991b). According to the brain-disabling principles described in chapter 1, the clinical or therapeutic effect will be nothing more than a less intense expression of the toxic effect. In discussing methylphenidate's so-called cognitive toxicity, Swanson et al. (1992) summarized the literature:

> In some disruptive children, drug-induced compliant behavior may be accompanied by isolated, withdrawn, and overfocused behavior. Some medicated children may seem "zombie-like" and high doses which make ADHD children more "somber," "quiet," and "still" may produce social isolation by increasing "time spent alone" and decreasing "time spent in positive interaction" on the playground.

These findings are very similar to even more extreme reactions with larger, chronic doses. Schiorring (as cited by Spotts et al., 1980) studied amphetamine intoxication in monkeys and in humans. In monkeys, mothers on amphetamine lost contact with their infants and became obsessed in a stereotypical fashion:

> In mother-infant dyadic relationships, amphetamine eliminated the eye contact, the specific gaze that is an important cue for contact in these animals. In addition, the parental care behavior pattern was disrupted. The mother lost her interest in the infant. She did not react to the calling signals of the infant, spent most of the time away from the infant and was preoccupied with stereotyped self-grooming behavior.

In amphetamine addicts, similar behaviors were observed, including stereotypical, bizarre movements, repetition of single words or phrases, stereotyped writing or drawing, talking without listening, and social withdrawal and isolation (see also Schiorring, 1981).

In discussing amphetamine abuse, Kramer (1970) again compared the stereotypical behavior of animals to some of the reactions in human beings:

> Perhaps the most curious effect of amphetamines is their capacity to induce behavior which is persisted in or repeated for prolonged periods.

> If the issue is not too disorganized the activity may, on the surface at least, be useful. Dwellings may be cleaned, automobiles polished, or items arranged to an inhuman degree of perfection. . . . Analogous to this compulsive behavior in man is what has been termed *stereotypy* in animals. Rats, mice, guinea pigs, cats, and squirrel monkeys, almost without exception, perform repetitive acts.

Notice the author's remark that the behavior may "on the surface at least, be useful." In treating children with Ritalin, Concerta, Adderall, and other stimulant medications, we settle for a surface or cosmetic change in behavior without dealing with the underlying problems in the family, school, and elsewhere. We do so at grave risk to the child's physical and mental integrity.

The label for Ritalin lists the symptoms associated with severe intoxications, while noting that these reactions can also occur at lower doses. Table 11.4 summarizes this information, providing another window into the primary effect of the drug.

**TABLE 11.4 Toxic Reactions to Stimulants: Usually in Overdose and Occasionally at Low Doses**

| | |
|---|---|
| *Psychiatric manifestations* | Sweating |
| Agitation | Flushing |
| Euphoria | Headache |
| Confusion | High fever |
| Hallucinations | Elevated heart rate |
| Delirium | Palpitations |
| Panic states[a] | Cardiac arrhythmias |
| Assaultiveness[a] | Hypertension |
| | Enlarged pupils |
| *Nonpsychiatric manifestations* | Dry mouth, nose, and eyes |
| Tremors | Increased respiration[a] |
| Increases neurologic reflexes | Nausea, vomiting, diarrhea, and cramps[a] |
| Muscle twitching | Muscle breakdown[a] |
| Convulsions | Hypotension, shock, and circulatory collapse[a] |
| Coma | |

[a]Item taken from the 2002 FDA-approved overdose section of the labels for Dexedrine, Adderall, and Adderall XR, but not Ritalin. The remainder was taken from the Ritalin label with some overlap. The Dexedrine and Adderall labels both state that "individual patient responses to amphetamines vary widely" and "toxic symptoms occasionally occur as an idiosyncrasy at doses as low as 2 mg." The Adderall XR label also states that patient responses "vary widely" and "toxic symptoms" may occur "at low doses." Any of the symptoms can occur with any of the stimulants at routine clinical doses.

## ATOMOXETINE (STRATTERA)

Eli Lilly promoted and continues to promote Strattera as the nonstimulant drug to treat ADHD (Eli Lilly and Company, 2006). While the company maintains this position, the drug is nonetheless listed under "Central Nervous System Stimulants" in the *Physicians' Desk Reference* (2007, p. 208). Lilly's extremely shrewd marketing ploy of promoting Strattera as a nonstimulant is meant to allay the concerns of parents and doctors about their children taking stimulants for ADHD.

It is true that Strattera has not been demonstrated to cause dependence and abuse like Ritalin, Adderall, and the other stimulant drugs used to treat ADHD and therefore has not been placed in Schedule II by the DEA. But Strattera is a highly stimulating drug. According to the label for Strattera, as found in the *Physicians' Desk Reference* (2007, p. 1817, Table 1), in the clinical trials used for FDA approval, *irritability* was reported in 8% of subjects, *crying* in 2%, and *mood swings* in 2%.

The real-world effects of Strattera are even more ominous in regard to overstimulation. Henderson and Hartman (2004) examined data from 153 sequential patients at two clinics: "We have observed extreme irritability, aggression, mania, or hypomania induction in 51 cases (33%)." Of the 51 cases, 88% displayed verbal aggression; 49%, physical aggression; 96%, irritability; 96%, mood swings; 69%, grandiosity; 18%, decreased sleep; 14%, hyperactivity; 10%, increased goal behavior; and 6%, hypersexuality. They diagnosed 10 of the 51 patients with mania, and 3 were hospitalized.

Henderson and Hartman (2004) reported dramatic examples of the symptoms as described by parents, including "blows up at everything"; "huge tantrums"; "yelling threats, 'I'm going to get a gun and shoot you,' 'I'll kill you'"; and "physical aggression, physical attacks on another, punching a female peer in the face, strangling a peer, attacking parents, brandishing a weapon." The onset of the symptoms covered a broad range, with an average of 6.39 weeks.

In overdose, like any stimulant, Strattera can cause severe seizures (Sawant et al., 2004).

### Strattera-Induced Suicidality

Strattera is the one ADHD treatment that has received a black-box warning concerning increased suicidality. After a review and analysis of 13 clinical trials conducted with children, all but one for the treatment of ADHD, the FDA (2005c) "identified an increased risk of suicidal thinking for Strattera." The bold black-box warning included in the label can be found in the 2007 *Physicians' Desk Reference:*

> Suicidal ideation in Child and Adolescents—STRATTERA (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit Hyperactivity Disorder (ADHD). Anyone considering the use of STRATTERA in a child or adolescent must balance this risk with the clinical needs. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior.

Once again, Eli Lilly has managed to promote one of its drugs as especially safe, when it is in fact especially dangerous.

## THE FOOD AND DRUG ADMINISTRATION CONTINUES TO MINIMIZE THE RISKS OF STIMULANTS

For many years, I have criticized the FDA-approved labels for stimulant drugs, including amphetamine products such as Adderall and Dexedrine and methylphenidate products such as Ritalin and Concerta. The labels have been especially weak in warning about addiction and serious psychiatric side effects such as psychosis, mania, aggression, and suicide. The FDA (2006b) recently admitted, "Current approved labeling for drug treatments of ADHD does not clearly address the risk of drug-induced signs of symptoms of psychosis and mania (such as hallucinations) in patients without identifiable risk factors, and occurring at the usual doses"—a point I had been making for nearly a decade.

The process of beginning to reassess the risks of stimulants began in June 2005, when the FDA (2005d) first gave notice that it was receiving a large number of reports of adverse psychiatric reactions, including suicidality, for methylphenidate products such as Concerta and Ritalin:

> Post-marketing reports received by FDA regarding Concerta and other methylphenidate products [e.g., Ritalin] include *psychiatric events such as visual hallucinations, suicidal ideation, psychotic behavior, as well as aggression or violent behavior.*
>
> We intend to make labeling changes describing these events.

The FDA provided a summary of 52 adverse psychiatric reactions reported over the prior year for Concerta and Ritalin, including cases of overstimulation (agitation and mania), depression, psychosis, aggression and violence, and suicidal behavior (FDA, 2006b). Notice the similarity to the dangerous effects that the FDA previously recognized as associated with the newer antidepressants. The similarity between stimulant and antidepressant adverse effects is probably due to the stimulating effects of the newer antidepressants.

The FDA announced plans for a September 2006 hearing focused on revising the stimulant labels in regard to cardiovascular and psychiatric adverse effects. The agency's Division of Drug Risk Evaluation (Gelperin et al., 2006) published an extensive memorandum reviewing reports received concerning "Psychiatric Adverse Events Associated With Drug Treatment of ADHD":

> The most important finding of this review is that signs and symptoms of psychosis or mania, particularly hallucinations, can occur in some patients with no identifiable risk factors, at usual doses of any of the drugs currently used to treat ADHD. Current labeling for drug treatments of ADHD does not clearly address the risk of drug-induced signs or symptoms of psychosis or mania (such as hallucinations)…A substantial proportion of psychosis related cases were reported to occur in children age ten years or less, a population in which hallucinations are not common. (pp. 3–4)

According to the March FDA (2006b) report, every type of stimulant drug had caused psychosis, and for each type of drug, there had been reports of rechallenge, where the drug, when administered a second time, once again caused psychosis. The drugs shown to cause psychosis with positive rechallenge reports included all those involved in treating ADHD: various preparations of amphetamine (Adderall and Dexedrine), various preparations of methylphenidate (Focalin, Concerta, Metadate, Methylin, Ritalin), methylphenidate transdermal systems (skin patches), Strattera, and Provigil.

The FDA's (2006b) report also cited reports of stimulant-induced aggression:

> Numerous postmarketing reports of aggression or violent behavior during therapy of ADHD have been received, most of which were classified as non-serious, although approximately 20% of cases overall were considered life-threatening or required hospital admission. In addition, a few cases resulted in incarceration of juveniles.

Once again, positive rechallenge reports were found for each drug.

Finally, suicide also appeared as a risk. However, except for Strattera, there was less demonstrable causality:

> Suicidality has been identified as a safety issue for STRATTERA (atomoxetine), and this information is clearly conveyed in current labeling. A causal association between other drug therapies of ADHD and suicidality cannot be ruled out on the basis of this review. Further evaluation of this issue is recommended. (FDA, 2006b)

## ONCE AGAIN, TOO LITTLE, TOO LATE

In publishing these observations in March 2006, the FDA finally caught up with strong warnings I had issued 8 years earlier, in November 1998. On that occasion, I was selected by the director's office of the NIH to be the scientific presenter on adverse drug effects at the government's Consensus Development Conference on the Diagnosis and Treatment of ADHD. In addition to presenting these data in a verbal exchange on a panel with another expert who was denying the risk of stimulant-induced psychosis, I presented my analysis of the data in my published report in the Consensus Development Conference proceedings (Breggin, 1999b).

In preparation for my presentation, I used the Freedom of Information Act to obtain a summary of all adverse event reports for Ritalin sent into the FDA. When I tabulated the results, it became apparent that there were strong signals indicating that Ritalin was causing many psychiatric adverse events. I found hundreds of psychiatric adverse drug reactions coded in the FDA's summary as agitation, hostility, depression, psychotic depression, psychosis, hallucinations, emotional lability, and abnormal thinking as well as overdose, overdose intentional, and suicide attempt. I then broadened this warning in my publication "Psychostimulants in the Treatment of Children Diagnosed With ADHD: Risks and Mechanism of Action" (1999c) and in my book *Talking Back to Ritalin* (2001c).

If I was able to pick up the signal in 1998, then the FDA and the drug manufacturer Novartis, with their vast resources, should have been able to do so even more easily and more quickly. After I publicized the problem at the 1998 conference, the FDA and the drug companies no longer had any excuse for failing to conduct their own analyses to test and to confirm my observations. But they delayed for nearly a decade.

I presented at the 2006 FDA hearings on stimulant medication in the hope of encouraging the agency to take seriously our seemingly mutual concerns about psychiatric adverse stimulant effects such as suicide and violence. But the FDA was already withdrawing from its previous declarations about the risks associated with stimulants. Except for keeping the already existing Strattera black-box warning about suicide, the Pediatric Advisory Committee decided not to scare parents by adding a black-box warning about suicide to the stimulant labels. In reality, the panel members, many with ties to drug companies, did not want to scare their patrons about potential lost profits. The committee did, however, recommend mentioning in the stimulant labels that there have been reports of aggressive and suicidal events in association with these drugs, but the FDA would not even go that far.

In February 2007, nearly half a year after the conference, the FDA finally issued a press release announcing its intention to require label changes indicating psychiatric side effects such as "hearing voices, becoming suspicious for no reason, or becoming manic," but at a rate of only 1 per 1,000. This rate estimate of 1 per 1,000 (0.1%) actually made the threat seem less than doctors had previously supposed since a higher rate of 1% had been bandied about for many years.

There is no basis for the FDA's ridiculously low estimate of the risk of psychosis and similar reactions from stimulants. The study that looked most closely at the rates for psychotic-like reactions in children taking stimulants found that nearly 10% displayed these symptoms at some point during treatment (Cherland et al., 1999). Even more negligent, the FDA-approved label made no mention of stimulants causing suicide. Once again, the agency had grossly failed America's children.

## A TRIUMPH FOR THE AMERICAN PSYCHIATRIC ASSOCIATION

The FDA's cowardly retreat on the issue of stimulant adverse effects took place under fire from the psychiatric establishment. Earlier, in February 2006, the FDA's panel of advisors had shocked the agency and medical authorities by recommending a black-box warning for all stimulant drugs used in the treatment of ADHD concerning cardiovascular risks, including heart attack, stroke, and sudden death.

The impetus came not from psychiatrists and psychopharmacologists in the financial thrall of drug companies, but in particular, from a cardiologist named Steven Nissen, a consultant to the panel, and from professor of public health Curt Furberg, a panel member. The physicians saw a need to alert their colleagues to the risks and hopefully slow down the utilization of these drugs, a real no-no among the psychiatric and psychopharmacological leadership. Nissen went so far as to say, "I want to cause people's hands to tremble a little bit before they write that prescription" (Rosack, 2006). Nissen noted the FDA's estimate that 2.5 million children and 1.5 million adults are now taking stimulant medications during any 30-day period, presumably for ADHD. He called this "a major public health concern" and urged the FDA to consider much broader issues, including the effects of pharmaceutical industry marketing and direct-to-consumer advertising.

Did Nissen make the hands of drug prescribers shake? Instead, drug company hands began to tremble, and Steven Sharfstein (2006), as president of the American Psychiatric Association (APA), came to their aid, along with drug company–funded lobbying groups like CHADD. Sharfstein—reaching well beyond his role as APA president but well within his role

as defender of the psychopharmaceutical complex—responded that the FDA panel's stance was "unsupported by clear evidence at this time." Within hours, the APA had issued a formal statement criticizing some FDA panel members for taking an action that was "beyond the scope of their mission." He really meant that they threatened the mission of the APA and its partnership with the drug industry. The FDA listened and withdrew its fervor for improving the stimulant labels.

## STIMULANT DEPENDENCE

An editorial comment in the 1995 *Archives of General Psychiatry* stated, "Cocaine, one of the most reinforcing and addictive of abuse drugs, has pharmacological actions very similar to those of MPH [methylphenidate], one of the most commonly prescribed psychotropic medications for children in the United States" ("Editorial," 1995). Using PET, Volkow et al. (1995) found that the distributions of cocaine and methylphenidate in the brain were identical, but that the latter remained for a longer period of time.

Parents are seldom told that methylphenidate is speed—that it is pharmacologically classified with amphetamines and causes the very same effects, side effects, and risks. Yet this is well known in the profession. For example, *Treatments of Psychiatric Disorders* (American Psychiatric Association [APA], 1989) observed that cocaine, amphetamines, and methylphenidate are "neuropharmacologically alike" (p. 1221). As evidence, the textbook pointed out that abuse patterns are the same for the three drugs, that people cannot tell their clinical effects apart in laboratory tests, and that they can substitute for each other and cause similar behavior in addicted animals (APA, 1989; see also Breggin, 1991a; Breggin et al., 1994a, 1994b). The *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–IV*; APA, 1994) confirmed these observations by lumping cocaine, amphetamine, and methylphenidate abuse and addiction into one category. The federal government classifies methylphenidate in the highest addiction category, Schedule II, which also includes amphetamines, morphine, opium, and barbiturates (Goodman et al., 1991).

Before it was replaced by other stimulants in the 1980s, methylphenidate was one of the most commonly used street drugs (Spotts et al., 1980). Youngsters in middle school, high school, and college nowadays sell their prescribed methylphenidate to classmates, who abuse it along with other drugs, often by snorting it. In working with community groups, we often hear anecdotal reports of individuals who have graduated from using

medically prescribed methylphenidate to alcohol or street drugs. I have seen cases in my own practice.

Youngsters selling their prescribed Ritalin made *The Washington Post* (Welsh, 1995) in a discussion of conditions at local private schools:

> Students report that at two prestigious Virginia boarding schools, boys with prescriptions for Ritalin—a drug for attention deficit disorder—have been selling their pills to classmates looking to get high. At one school, a student said, "Ritalin rivals acid and marijuana."

Like any addictive stimulant, methylphenidate and amphetamine can cause withdrawal symptoms such as crashing with depression, exhaustion, withdrawal, irritability, and suicidal feelings. However, parents and teachers almost never recognize a withdrawal reaction when their student or child gets upset after missing a single dose. Instead, they mistakenly believe that the child needs to be kept on the medication.

## CONCERN AT THE DRUG ENFORCEMENT ADMINISTRATION

On October 25, 1995, the DEA (1995a) published a press release as an introduction to a substantial document (DEA, 1995b) concerning the extensive use of methylphenidate and the serious hazards associated with it. The press release began with the following series of points:

- Methylphenidate (MPH), most commonly known as Ritalin, ranks in the top 10 most frequently reported controlled pharmaceuticals stolen from licensed handlers.
- Organized drug trafficking groups in a number of states have utilized various schemes to obtain MPH for resale on the illicit market.
- MPH is abused by diverse segments of the population from health care professionals and children to street addicts.
- A significant number of children and adolescents are diverting or abusing MPH medication intended for the treatment of ADHD.
- In 1994, a national high school survey (Monitoring the Future) indicated that more seniors in high school in the U.S. abuse Ritalin than are prescribed Ritalin legitimately.
- Students are giving and selling their medication to classmates who are crushing and snorting the powder like cocaine. In March of 1995, two deaths in Mississippi and Virginia were associated with this activity.

The DEA (1995a) press release concluded its list of concerns with the following statement:

> Every indicator available, including scientific abuse liability studies, actual abuse, paucity of scientific studies on possible adverse effects associated with long-term use of stimulants, divergent prescribing practices of U.S. physicians, and lack of concurrent medical treatment and follow-up, urge greater caution and more restrictive use of MPH.

In 2000, in response to continuing drug company pressure to view Ritalin as a mild stimulant, the DEA's Christine Sannerud and Gretchen Feussner wrote an article asking "Is Ritalin an Abused Drug? Does It Meet the Criteria of a Schedule II Substance?" They documented that Ritalin is similar in its effects to amphetamine and cocaine:

> Like amphetamine and cocaine, abuse of MPH [Ritalin] can lead to marked tolerance and severe psychologic dependence. The pattern of abuse is characterized by escalation in dose, binge use followed by severe depression, and an overpowering desire to continue to the use of the drug despite negative medical and social consequences. The abuser may alter the mode of administration from oral use to intranasal or intravenous use to intensify the effects of the drug. (p. 35)

They described physical overstimulation, euphoria, and psychosis as consequences of Ritalin abuse. The two DEA officials wrote:

> In conclusion, animal studies have shown that MPH has an abuse liability similar to that of other Schedule II stimulants, including amphetamine, methamphetamine, and cocaine. Actual data on abuse indicate that the pattern of MPH abuse is similar to that of other potent psychostimulants and that MPH is diverted and abused to a similar extent as other pharmaceutical Schedule II substances. Taken collectively, the data indicate that MPH fits the profile of a Schedule II substance.

All of the DEA's observations run contrary to the Ritalin label as found in the *Physicians' Desk Reference* (2007), which continues to identify this potent, highly addictive drug as a "mild central nervous system (CNS) stimulant" (p. 2269), misleading doctors and consumers alike. Although the DEA and all responsible pharmacologists view Ritalin as essentially similar to amphetamine, the dependence warnings on the Ritalin label remain extremely weak in comparison to those on the Dexedrine and Adderall (amphetamine) labels.

Drugs that are addictive are especially brain disabling and spellbinding. The "overpowering desire to continue the use of the drug despite

negative medical and social consequences" described by Sannerud and Feussner (2000) is a central aspect of intoxication anosognosia or medication spellbinding. Addiction is caused by drug-induced brain dysfunction that comes to the surface as the dose wears off or is terminated. Addiction is an extreme form of spellbinding, rendering the individual wholly unable to appreciate the adverse psychiatric effects of the drug and often driving the victim to act in ways that would otherwise feel wholly alien and repulsive.

## NADINE LAMBERT STUDIES

Studies published since the last edition of this book should have laid to rest the question of whether or not taking prescribed Ritalin predisposes a child to stimulant abuse as a young adult. Nadine Lambert (Lambert et al., 1998; especially, Lambert, 2005) conducted a 28-year prospective longitudinal study of ADHD children and normal controls identified from among 5,112 elementary school students. The participants were followed through childhood and adolescence and evaluated three times in young adulthood. The authors found that independent of the diagnosis of ADHD, "stimulant treatment increased the odds of dependence on tobacco, cocaine, and cocaine/amphetamine." By contrast, "ADHD and problem behavior did not increase the odds of either daily smoking or lifetime use of any of the substances." It is not ADHD but the treatment for ADHD that puts children at risk for future drug abuse. This conclusion is entirely consistent with the fact that animals and humans cross addict to Ritalin, amphetamine, and cocaine and that exposure to Ritalin in young animals causes permanent changes in the brain.

## THE BRAIN-DISABLING, SPELLBINDING EFFECTS OF STIMULANTS

Consistent with the brain-disabling principle and medication spellbinding, experts generally agree that Ritalin affects normal children in the same way it affects diagnosed children. Golden (1991) observed, "The response to the drug cannot be used to validate the diagnosis. Normal boys as well as those with ADHD show similar changes when given a single dose of a psychostimulant" (p. 37).

Within an hour after taking a single dose of a stimulant drug, any child tends to become more obedient, narrower in focus, and more willing to concentrate on humdrum tasks and instructions. Parents in conflict with a little boy can hand him a pill, knowing he will soon be more docile.

It is commonly held that stimulants have a paradoxical effect on children compared to adults, but these drugs probably affect children and adults in the same way. At the doses usually prescribed by physicians, children and adults alike are spaced out, rendered less in touch with their real feelings, and hence more willing to concentrate on boring, repetitive, schoolroom tasks.

At higher doses, both children and adults become more obviously stimulated into excitability or hyperactivity. There is, however, great variability among individuals, and a number of children and adults will become more hyperactive and inattentive at the lower doses as well.

Although drug companies are putting market pressure on them, thus far, the British have remained more cautious than Americans about using stimulants for children. Grahame-Smith and Aronson (1992), authors of the *Oxford Textbook of Clinical Psychopharmacology and Drug Therapy,* suggested that stimulants may work in children in the same way they work in rats, by "inducing stereotyped behavior in animals, i.e., in reducing the number of behavioural responses" (p. 141). Stereotyped behavior is simple, repetitive, seemingly meaningless activity, often seen in brain-damaged individuals. The textbook states somewhat suggestively, "It is beyond our scope to discuss whether or not such behavioural control is desirable" (p. 141).

The stereotypical behavior mentioned by Grahame-Smith and Aronson (1992) has been carefully studied in the laboratory in regard to both amphetamine and methylphenidate, which produce identical results in animals. Randrup and Munkva (1970) described the stereotypical behavior produced in rats by subcutaneous injections of amphetamine:

> It begins within one hour after the injection and lasts for an hour or two. The behavior consists of continuous sniffing, licking, or biting the cage floor or the animal's own forelegs. The rat sits in a crouched posture and usually presses its body against the cage wall. Normal activities such as grooming, eating, rearing, and forward locomotion are absent; backward locomotion is seen occasionally.

Randrup and Munkva (1970) noted that the stereotypical behavior varies from species to species but always involves the suppression of normal behavior:

> The stereotyped activities are always performed continuously in the absence of normal activities, but the form of the stereotypy depends on the species. Rodents gnaw, lick, or sniff; cats move their head from side to side; and dogs run in circles or back and forth along a fixed route. The monkeys perform various repetitious movements with their

> hands, limbs, body or head, and locomotion along a fixed route has been observed in a few cases.

The authors considered stereotypical behavior similar to certain obsessive and compulsive behaviors seen in humans taking stimulants. They cited Scher (1966), who observed,

> One of the most peculiar phenomena which may occur in the course of the use of amphetamines, especially methamphetamine, is what is called "being hung up."
>
> An individual who is "hung up" will literally get stuck in a repetitious thought or act for hours. He may sit in a tub all day long, clean up the house or a particular item, hold a note or phrase of music, or engage in nonejaculatory intercourse for extended periods. The danger of getting "hung up" in this way seems to be peculiar to amphetamines.

Getting "hung up" is a manifestation of stimulant-induced compulsive behavior that includes overfocusing and stereotypical or repetitive behavior. Consistent with the brain-disabling principles, Kramer et al. (1970) identified these abnormal compulsive behavioral reactions as the sought-after effect in children and adults:

> They are no longer hyperresponsive to their environment and, for the first time, they focus on the object or task before them. For the first time in their lives they can accomplish a task like reading, which requires concentration, without responding to someone who's talking in the room. Some adults also take amphetamines before going to a party, because it cuts down on the peripheral distraction and the noisy background din.... Cats who are in this stereotypy mode cannot be distracted by stimuli in their periphery; you can wave your arms, etc., to no avail.

Because of its importance as a demonstration of the brain-disabling principles, I have previously reviewed at length the extensive scientific literature confirming the dual action of stimulant drugs on animals and children alike (a) reducing spontaneous behavior and (b) enforcing obsessive–compulsive behavior (Breggin, 1999a, 1999b, 1999c). The animal literature dramatically illustrates how stimulant drugs reduce spontaneity, exploratory behavior, and social behavior, while inducing compulsive behavior (e.g., Arakawa, 1994; Bell et al., 1982; Hughes, 1972; Randrup et al., 1967; Rebec et al., 1997; Schiorring, 1979; Wallach, 1974). Exactly as these drugs turn normal monkeys into passive, obsessive monkeys, they turn normal children into compliant classroom children.

**TABLE 11.5 Harmful Stimulant Effects Commonly Misidentified as Therapeutic or Beneficial for Children Diagnosed With ADHD**

| Obsessive–Compulsive Effects | Social Withdrawal Effects | Behaviorally Suppressive Effects |
|---|---|---|
| Compulsive persistence at meaningless activities (called *stereotypical* or *perseverative* behavior) | Socially withdrawn and isolated | Compliant in structured environments; socially inhibited, passive, and submissive |
| Increased obsessive–compulsive behavior (e.g., repeating chores endlessly and ineffectively) | General dampened social behavior | Somber, subdued, apathetic, lethargic, drowsy, dopey, dazed, and tired |
| Mental rigidity (called *cognitive perseveration*) | Reduced communicating or socializing | Bland; emotionally flat; humorless; not smiling; depressed and sad, with frequent crying |
| Inflexible thinking | Decreased responsiveness to parents and other children | Lacking in initiative or spontaneity, curiosity, surprise, or pleasure |
| Overly narrow or excessive focusing | Increased solitary play and diminished overall play | |

*Note*. Modified from Breggin (1999b). Reprinted with permission of Springer Publishing Company. References to 20 clinical trials provided in Breggin (1999b, 1999c).

Table 11.5 provides descriptions of stimulant adverse reactions from the clinical and research literature that are consistent with the brain-disabling principle. A broad array of stimulant side effects in fact provides the primary effects of the drug.

Stimulant drugs very commonly cause obsessive–compulsive reactions in children, but teachers, who too often value these traits in children, almost never interpret them as negative drug effects. The imaginative child easily becomes distracted by her own thoughts or imaginings, but on stimulants becomes compulsively overfocused, dutifully writing down everything the teacher says. The energetic youngster who cannot sit still all day long becomes drained of spontaneity and now

flops into his chair for the duration of the school day. The social butterfly who wants to chat with her classmates, especially when class gets boring, loses her social interest and now sits through every lesson as if she had no friends in class. Similarly, parents who have grown weary of their child's need for attention and resistance to homework or chores find relief in the child's drug-induced compulsive attention to homework or endless preoccupation with playing computer games. These quieter, preoccupied children provide a respite for their parents and even seem to be doing "better" when in fact they are suffering from stimulant drug toxicity.

I could find only one study that specifically looked for obsessive–compulsive symptoms in children taking stimulants (Borcherding et al., 1990), and these reactions were identified in 23 of 45 children taking stimulants. That is, more than 50% of the children taking methylphenidate or amphetamine displayed symptoms of drug-induced compulsivity. I have summarized the 23 cases in Table 11.6.

## BRAIN DAMAGE AND DYSFUNCTION CAUSED BY STIMULANTS

The following sections examine studies of underlying stimulant-induced abnormalities in various brain functions that in part account for the broad range of adverse drug reactions related to brain dysfunction. We begin with some of the most disturbing data concerning atrophy induced by methylphenidate.

### Brain Atrophy Caused by Methylphenidate

Nasrallah et al. (1986) found a small but measurable degree of atrophy of the brain in more than half of 24 young adults with prior stimulant-treated hyperactivity during childhood. The authors suggested, "Cortical atrophy may be a long-term adverse effect of [stimulant] treatment" (p. 245).

Several brain scan studies have claimed to demonstrate brain abnormalities associated with ADHD (Giedd et al., 1994; Hynd et al., 1991; Lou et al., 1984). Most of the studies have found relatively small brain structures in various parts of the frontal lobes and basal ganglia in children diagnosed with ADHD. The differences were based on comparisons between groups of normals and groups of children labeled ADHD. The findings are not perceptible on a case-by-case basis and cannot be used for diagnostic purposes.

**TABLE 11.6 Obsessive-Compulsive Adverse Drug Reactions to Methylphenidate (MPH) and Amphetamine (AMPH) in 23 of 45 Children (51%)**

| | | |
|---|---|---|
| 1. | 6 | AMPH: Perseverative drawing and writing at home; counting puzzle pieces |
| 2. | 6 | AMPH: Perseverative play with Legos and puzzles (36 hours with Legos with no breaks to eat or sleep) |
| 3. | 6 | MPH: Perseverative playing of piano |
| 4. | 6 | AMPH: Perseverative speech |
| 5. | 7 | AMPH: Rewriting work; overerasing; repetitive checking of work; overly neat and organized at home |
| 6. | 7 | MPH: Rewriting work<br>AMPH: Compulsively lining up crayons |
| 7. | 8 | MPH: Overly detail oriented |
| 8. | 8 | MPH: Coloring over and over the same area<br>AMPH: Repetitive checking of work; frantically goal directed; solitary activities |
| 9. | 8 | MPH: Perseverative playing of video games<br>AMPH: Cleaning room compulsively, buttoning and then folding dirty laundry |
| 10. | 8 | AMPH: Repetitive checking of work; perseverative with work in school |
| 11. | 8 | MPH: Overerasing; redrawing; excessive pressure on pencil<br>AMPH: Overerasing |
| 12. | 8 | MPH: Markedly detail oriented in drawings |
| 13. | 9 | AMPH: Overerasing; making lists (TV shows, model cars) |
| 14. | 9 | AMPH: Cleaning room compulsively; overly orderly at home |
| 15. | 9 | AMPH: Perseverative at school |
| 16. | 9 | MPH: Overerasing; rewriting; excessive pressure on pencil and crayons; perseverative speech<br>AMPH: Overly meticulous; inability to terminate school and play activities; perseverative speech |
| 17. | 9 | MPH: Inability to terminate school and play activities; repetitive erasing and redoing projects; overly detail oriented |
| 18. | 10 | AMPH: Cleaning room compulsively; folding dirty laundry |
| 19. | 10 | AMPH: Repetitive checking behavior; lining things up; excessive pressure on pencil; repetitive erasing and rewriting |
| 20. | 11 | AMPH: Overly meticulous work; overly neat and organized; cleaning room compulsively; raking leaves (7 hours) and then as they fall individually |
| 21. | 11 | AMPH: Lining up crayons; repetitive erasing and redrawing |
| 22. | 11 | MPH: Repetitive erasing; perfectionistic; excessive pressure of speech |
| 23. | 12 | AMPH: Overly detail oriented; excessive pressure on pencil and crayons |

*Note*. From B. Borcherding et al. (1990) (p. 87). Double-blind placebo-controlled crossover study. Both drugs increased likelihood of "repetitious, perfectionistic, overfocused behaviors" ($p < .01$). MPH associated with combination of abnormal movements and OCD ADRs ($p = .009$). Fourteen of the 23 (60.8%) suffered from "orofacial" tics or "stereotypy." Twelve of the 23 had orofacial tics and 6 had stereotypy, including 4 who had both. Note the similarity to animal studies in the combination of perseveration and abnormal movements.

The differences found between normal brains and those of children diagnosed with ADHD in reality are due to medication effects. At the 1998 NIH Consensus Development Conference on ADHD, Swanson presented a paper reviewing the range of genetic and brain scan studies purporting to show biological bases of ADHD (Swanson et al., 1998). A number of the studies involved Swanson's coauthor, Castellanos (Castellanos et al., 1998; Giedd et al., 1994). My own review (Breggin, 1998a) indicated that some of the studies failed to mention prior drug treatment, while drawing on populations, such as the NIH clinics, where the diagnosed children have extensive prior drug exposure (e.g., Giedd et al., 1994). Other studies alluded to previous drug treatment without attempting to correlate it with the brain changes (Hynd et al., 1991).

In the unpublished public discussion following Swanson's presentation, neurologist Frederick Baughman Jr. asked Swanson if *any* of the studies in his review involved children without a history of drug treatment. Swanson could not name a single study based on untreated patients and offered the absurd and untrue explanation that untreated children diagnosed with ADHD are difficult to obtain in the United States. On the basis of Swanson's confession that all the children had been exposed to stimulant drugs, I suggested in my presentation that Swanson's report be incorporated into mine as additional evidence of the brain-damaging effects of stimulants.

After hearing all the scientific presentations and discussions, the Consensus Conference panel concluded that "there are no data to indicate that ADHD is due to a brain malfunction" (National Institutes of Health, 1998a, p. 2). This important conclusion has a sound basis but was removed from later editions by NIH authorities after the consensus panel had been disbanded (1998b).

As previously described, psychostimulants have demonstrable toxic effects on both gross and biochemical functions of the brain, including the frontal lobes and basal ganglia. In sharp contrast to all the data confirming toxic effects of stimulants, any association between ADHD and brain pathology remains speculative and extremely unlikely. No valid ADHD syndrome has been demonstrated, and no neurological or other physical findings have been found in association with it (see subsequent discussion). Brain structural abnormalities found in children diagnosed with ADHD and treated with stimulants—to the extent that they are valid findings—are almost certainly due to the stimulants and other psychiatric medications to which they have been exposed. These studies add to the accumulating evidence that psychostimulants cause irreversible brain damage.

## Gross Brain Dysfunction Caused by Methylphenidate and Amphetamine

Volkow et al. (1997), in a PET study of normal adults given methylphenidate, found a reduced relative metabolic rate in the basal ganglia and other changes correlating with the distribution of dopamine receptors. Wang et al. (1994), using the PET scan in normal adults, measured the effect of methylphenidate (0.5 mg/kg IV) and found that methylphenidate decreased the overall flow of blood by 23% to 30% into all areas of the brain. The decrement was maintained when last tested (30 min after the final dose). The researchers warned that these effects "should be considered when prescribing this drug chronically" (p. 143). Bell et al. (1982), using rat brain tissue, found that methylphenidate reduced glucose metabolic rates in the motor cortex and increased in the substantia nigra and other deep structures. Porrino and Lucignani (1987), using methylphenidate (1.25–15.0 mg/kg) in conscious rats, found "significant dose-dependent alterations in metabolic activity" in numerous areas of the brain, even at the lowest dosage.

PET scans also reveal that normal adults exposed to an injection of 0.15 mg/kg of amphetamine will undergo increased glucose metabolism throughout most of the brain (Ernst et al., 1997). These studies demonstrate the effect of stimulant drugs on the brains of normal animals or persons.

Stimulant-induced reduced metabolic rate and reduced blood flow in the brain make a mockery of the concept that the medications are treating a disorder of the brain. Consistent with the brain-disabling principles of biopsychiatric treatment, the stimulants cause gross malfunctions in the brain that are then mistaken for improvement.

## Abnormalities of Brain Chemistry and Microscopic Pathology Caused by Stimulants

Studies show that methylphenidate and amphetamine bind to receptors throughout most of the forebrain, including the basal ganglia and frontal cortex (Unis et al., 1985). Many studies confirm amphetamine-induced persistent abnormalities in biochemical structure and function (Robinson et al., 1998).

### *Methamphetamine*

Because it is a common drug of abuse that is almost always obtained illegally, there is more research exploring methamphetamine-induced brain

abnormalities than the other stimulants that are obtained by prescription and promoted by clinicians and pharmaceutical companies. While methamphetamine is FDA approved for the treatment of behavioral disorders in children, thankfully I have never seen it prescribed.

The capacity of methamphetamine to cause neurotoxicity—including the destruction of brain cells—has long been demonstrated in animals. Chronic exposure to methamphetamine can produce irreversible loss of receptors for dopamine and/or the death of dopaminergic and other neurons in the brain (Melega et al., 1997b; Schmued et al., 1997; Sheng et al., 1996; Sonsalla et al., 1996; Wagner et al., 1980; Zaczek et al., 1989). Melega et al. (1997b), for example, found persistent neurotoxic changes in dopamine function (dopamine depletions of 55% to 85%) in vervet monkeys at 10–12 weeks with doses that were relatively small and acute (two doses of 2 mg/kg 4 hours apart).

After subjecting mice to methamphetamine, Sonsalla et al. (1996) also demonstrated dopaminergic cell loss of 40% to 50% in the substantia nigra. The doses were large but acute (four injections of 10 mg/kg spaced at 2-hour intervals). Battaglia et al. (1987) found that large chronic doses of methamphetamine also cause the death of serotonergic nerves in animals. The changes were described as "long-lasting neurotoxic effects with respect to both the functional and structural integrity of serotonergic neurons in brain" (p. 911). Brain levels of norepinephrine are also depleted in the frontal cortex for at least 6 months or more, indicating irreversible damage to that system as well (Wagner et al., 1980). Thus methamphetamine causes destructive changes in all three of the neurotransmitter systems that are stimulated by the drug (see also Zaczek et al., 1989).

Methamphetamine has been demonstrated to be irreversibly neurotoxic. Given the biochemical and clinical similarities to amphetamine and methylphenidate, this gives cause for grave concern.

### *Amphetamine*

Dextroamphetamine, or simply amphetamine (Dexedrine, Adderall), is another FDA-approved drug for treating behavioral problems in children. Yet the existence of amphetamine neurotoxicity has also been documented for more than 30 years (Huang et al., 1997).

Wagner et al. (1980) found that treating rhesus monkeys with amphetamine leads to a long-lasting loss of dopamine and dopamine uptake sites (receptors). Juan et al. (1997) confirmed that amphetamine produces a depletion of striatal dopamine that is measurable on autopsy of mice at 5 days and 2 weeks (the final experiment). The animals were administered four doses of 10 mg/kg spaced 2 hours apart.

Robinson and Kolb (1997) treated rats with amphetamine twice a day for 5 days a week for a total of 5 weeks with a dose that was gradually increased from 1 mg/kg to 8 mg/kg. Thirty-eight days later, they found lasting structural modifications in the nucleus accumbens and prefrontal cortex neurons, including increased length of dendrites and density of spines. In a microdialysis study, Weiss et al. (1997) treated rats with amphetamine (1.5 mg/kg injected twice a day for 14 days). Seven days after withdrawal, the animals continued to show a reduced dopamine release in the ventral striatum in response to stress.

Camp et al. (1997) administered a rising dose of amphetamine (1–10 mg/kg over 10 days) to rats and then withdrew the animals for 1–30 days. Using in vivo microdialysis, they found changes lasting 1 month in norepinephrine concentrations in the hippocampus as well as altered responses to amphetamine challenge. They concluded that amphetamine produces biochemical adaptations that far outlast the acute drug effects and may account for both transient and more persistent discontinuation effects in humans.

As previously noted, Melega et al. (1997b) used PET in vervet monkeys to determine presynaptic striatal dopamine function following the administration of amphetamine with small acute doses. The animals were given two doses of 2 mg/kg 4 hours apart. These doses produced marked decreases in dopamine synthesis (25% at 10–12 weeks) with a 16% reduction in one amphetamine-treated animal at 32 weeks. Biochemical analysis showed decreased striatal dopamine concentrations of 55% at 10–12 weeks. The authors concluded that acute amphetamine doses produce long-lasting neurotoxicity. In another study using larger, more chronic doses (4–18 mg/kg over 10 days), Melega et al. (1997a) found a gradual recovery from neurotoxicity in the striatum over a 2-year period after termination of treatment.

Addressing the use of stimulants for the treatment of children, Ellinwood and Tong (1996) concluded, "Drug levels in children on a mg/kg basis are sometimes as high as those reported to produce chronic CNS changes in animal studies" (p. 14). Juan et al. (1997) warned that when psychostimulants are indicated, as in ADHD, "it would seem prudent to prescribe methylphenidate rather than amphetamine, since methylphenidate appears to lack the DA [dopamine] neurotoxic potential that has been well documented for amphetamine" (p. 174). However, amphetamine has become increasingly popular among clinicians.

### *Methylphenidate*

Mach et al. (1997) used PET in rhesus monkeys to confirm the similarity of effects among methylphenidate, amphetamine, methamphetamine, and cocaine on dopamine release in the basal ganglia. It is inevitable that methylphenidate will produce similar neurotoxic effects as other psychostimulants.

Barnett and Kuczenksi (1986) found down-regulation of dopamine receptors after methylphenidate administration to animals but did not test for recovery. Mathieu et al. (1989) found reduction of the density of the norepinephrine receptors after treatment with methylphenidate. Lacroix and Ferron (1988), after 7 days of methylphenidate treatment in rats, found that "the efficacy of cortical NA [noradrenergic] neurotransmission is markedly reduced following methylphenidate treatment" (p. 277). Neurons became less responsive to various forms of stimulation, indicating desensitization. The changes persisted at the last testing, 18 hours after drug exposure. Juan et al. (1997) found dopamine depletion in the mouse striatum 5 days after terminating treatment with methylphenidate, but not 2 weeks after.

The few studies that have tested for longer-term dopamine depletion from methylphenidate have failed to document it (Wagner et al., 1980; Yuan et al., 1997; Zaczek et al., 1989). However, this does not rule out irreversible neurotoxicity. Given the findings of short-term abnormalities, and the lessons from amphetamine and methamphetamine, suspicion must remain high that irreversible changes are also caused by methylphenidate.

## THE LATEST OMINOUS NEWS ABOUT RITALIN

In 2005, a study appeared in *Cancer Letters* that would have evoked widespread media coverage if it had been about an illegal drug, rather than about a pharmaceutical company product (El-Zein, 2005). Researchers from the University of Texas examined 12 children treated with therapeutic effects of Ritalin to determine "whether this central nervous system stimulant produces cytogenetic abnormalities in pediatric patients at therapeutic doses." Using peripheral blood lymphocytes taken from the children, they found a 2.4-fold increase in chromosome aberrations and similar defects. They concluded, "These findings warrant further investigations of the possible health effects of methylphenidate in humans, especially in view of the well-documented relationship between elevated frequencies of chromosome aberrations and increased cancer risk."

More recent studies of the effect of methylphenidate on the growing animal brain have produced even more ominous results with direct connections to emotional and behavioral development. Carlezon and Konradi (2004), from Harvard's Department of Psychiatry, observed that some children are being treated with psychiatric drugs as early as age 2. They summarized their research:

> When we exposed rats to the prescription stimulant methylphenidate during early adolescence, we discovered long-lasting behavioral and

> molecular alterations that were consistent with dramatic changes in the function of the brain reward systems.

In a presentation at the annual meeting of the American College of Neuropsychopharmacology (ACNP) in late 2004, William Carlezon and his collaborator, Susan Andersen, explained that following exposure to methylphenidate when young, the animals' behavior became abnormal in adulthood. According to the reporter ("New Study Shows," 2004),

> The animals had a reduced ability to experience pleasure and reward, particularly when it was measured by sensitivity to cocaine. In addition, they found that the animals exposed to Ritalin during pre-adolescence were more prone to express despair-like behaviors in stressful situations (such as swim tests) as adults. Overall, the animals showed more evidence of dysfunctional brain reward systems and depressive-like behaviors in adulthood.

In 2005, Mague et al. published more on their research, again finding that methylphenidate caused changes in the young rat's brain that persist into adulthood. They concluded, "Reduced sensitivity to these various types of reward may reflect general dysfunctions of brain reward systems." None of this is good news for children and adolescents who have been treated with Ritalin products.

Nonetheless, the ACNP, an organization of experts beholden to the drug companies, came out spinning on this study, invoking the antiquated, unscientific myth that methylphenidate is specific for ADHD. Unconscionably, they claimed in a press release that the rat study only had implications for normal children and that properly diagnosed ADHD children would not suffer adverse consequences (Lobliner, 2004).

In an editorial in *Ethical Human Psychology and Psychiatry,* Leo (2005) ridiculed the ACNP's conclusions, which are based on the premise that the rats have normal brains but ADHD children, with abnormal brains, will be fixed by the drugs. Not only is this a bizarrely self-serving stretch of credulity on the part of these drug advocates, but it also flies in the face of the scientific reality that stimulant drugs have the same effects on normal individuals as children labeled ADHD, and in fact have been used by everyone from U.S. Army pilots to professional athletes and untold numbers of college students to focus more obsessively for brief spans of time. Moreover, as we have seen, the drugs even affect the behavior of *normal animals* in the same negative way that they affect children.

## DEVELOPMENTAL NEUROTOXICITY

The development of the human brain continues long after birth and infancy, with significant changes taking place in the number and organization of brain cells into adolescence. When the NIMH (1995) and the FDA held a conference on the future testing and use of psychiatric drugs for children, Vitiello (1998) made a critical disclosure:

> Now, we know from work in animals that if we interfere with these neurotransmitter systems at some crucial times, like the prenatal or the perinatal or neonatal phase of their lives, we can change in these animals the destiny of the neurotransmitters forever. We can cause permanent changes. (p. 29)

The term *plasticity* has been used to emphasize the brain's responsiveness and ability to adapt to changing environmental input. The brain creates new brain cell synapses and prunes old ones in response to experience (Greenough et al., 1992; Weiler et al., 1995). Caged animals with limited opportunities for spontaneous activity will not develop as many neuronal interconnections as more free-ranging animals. It is doubtful that the brains of children would be any less responsive to the environment than those of rats. If environmental influences, such as the frequency and quality of communication, can influence brain development, chronic drug exposure should be viewed as potentially dangerous. In addition, the stimulants make children less spontaneous, reducing their interactions with the environment and hence their brain development.

Reviewing the literature (see also Breggin, 1999a, 1999b, 1999c, 2001a, 2002c) produces a wide variety of *brain* dysfunctions induced by stimulants, including the following:

reduced blood flow
reduced oxygen supply
reduced energy utilization
persistence biochemical imbalances
persistent sensitization (increased reactivity to stimulants)
permanent distortion of brain cell structure and function
brain cell death and tissue shrinkage
cytotoxicity with chromosomal abnormalities
dependence, tolerance, and withdrawal symptoms

## GROWTH SUPPRESSION CAUSED BY STIMULANTS

For many years in many books and articles, I have made the point that the stimulants cause a persistent suppression of height and weight (e.g.,

Breggin, 1997a, 1999c, 2001c, 2002b), and for an equal number of years, medication advocates have rejected the evidence. Despite resistance from stimulant advocates, scientific research long ago demonstrated these inhibiting effects on height and weight (for example, see Klein et al., 1988a&b).

As a result of professional resistance to the facts about stimulant-induced growth suppression, very few young patients and their parents have been informed in advance that stimulant drugs will shorten the height and reduce the weight of the children.

The growth-suppression effects of stimulants are *not* due primarily to loss of appetite, as many doctors have proposed. Instead, it has been known for decades that stimulants impact on the brain and pituitary gland to disrupt growth hormone production (Aarskog et al., 1977; studies evaluated in Breggin, 1991c, 2001c).

Despite its extreme promedication bias, the MTA study settled the question, once again, when it found consistent suppression of height and weight in children taking stimulants (Swanson et al., 2007a; also see MTA Cooperative Group, 2004). Children with no previous exposure to stimulant drugs were treated with the medications for 14 to 36 months. Compared to the control group, the medicated children showed a 2-cm (0.8-inch) reduction in height, as well as a 2.7-kg (5.9-pound) reduction in weight.

Suppression of height, rather than merely weight, is a more serious finding because it indicates a stunting of the growth processes that cannot be accounted for by reduced appetite. The FDA-approved label for methylphenidate products such as Ritalin now includes a section titled "Long-Term Suppression of Growth" that confirms a suppression of height and weight during treatment with the medication over periods of 14 to 36 months (*Physicians' Desk Reference*, 2007). There was no evidence of "growth rebound" (p. 2270) or recovery. The FDA-approved labels also note that it is "likely" that amphetamine stimulants will have the same effect.

When a drug is generally toxic to the brain and also produces a specific dysfunction in the regulation of growth hormone, it should be assumed that brain growth is also being inhibited and distorted, if not stunted. If it were not for the power of the psychopharmaceutical complex, the suppression of growth by stimulant drugs would, by itself, contraindicate and ultimately stop their use in children.

## CONCLUSION

Stimulants cause permanent abnormalities in brain chemistry and anatomy. Even after only one or two doses, they impair metabolism and blood

flow in the brain. By disrupting the production of growth hormone, they suppress height and weight. They are addictive and predispose children to abuse cocaine in young adulthood.

Not only do the stimulants damage and disable the brain, but scientific research has also demonstrated how these physical disabilities are manifested in behavior changes. The stimulants impair behavior by crushing spontaneity and inducing compulsive behaviors. The less spontaneous, more compulsive children are seen as "improved" when in fact they are biologically and mentally impaired. The effect of the stimulants provides a clear-cut illustration of the brain-disabling principles described in chapter 1.

Meanwhile, the stimulants have no proven therapeutic effect beyond the first few weeks of behavioral suppression with enforced docility and compulsivity. Furthermore, they have no positive impact on learning, academic progress, or socialization. Instead, they disrupt learning by causing abnormal overfocusing, and they often induce obsessive-compulsive behavior, depression, and social withdrawal.

It is difficult to find strong enough language to communicate the folly—indeed, the tragedy—of using drugs to control and improve the behavior of millions of children. Children need parents, teachers, coaches, religious leaders, counselors, and other adults in their lives—not brain-disabling drugs. Children need the support of families, schools, and community organizations—not drugs in their brains. Children need healthy brains, not drug-drenched brains.

Ultimately, children grow up by learning to take control of their actions—by learning to be responsible and self-determined—something that diagnoses and drugs ultimately discourage. When they have difficulty growing up, children need increased attention from adults who are properly equipped to guide and to educate them in improving their self-control and academic skills. In my clinical experience, when we provide these children the needed psychological, social, and educational guidance, they thrive without drugs.

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CHAPTER 12

# Antianxiety Drugs, Including Behavioral Abnormalities Caused by Xanax and Halcion

No drugs are more obviously brain-disabling and spellbinding than the benzodiazepines (BZs). They produce a continuum of central nervous system (CNS) effects that begins with a feeling of relaxation, progresses toward somnolence, and, in sufficient doses, causes a coma deep enough to use as anesthesia in major surgery. The continuum of effects is very similar to alcohol, but the BZs can suppress the CNS without producing as much drunkenness (slurred speech and ataxia) and can more effectively produce the depth of coma necessary for surgery.

Experts who advocate the use of BZs for the control of anxiety want to believe that these drugs produce a specific antianxiety or anxiolytic effect, but there is no reason to believe this. The continuum of CNS suppression is smooth, and anxiety reduction is one of the brain-disabling effects of gradually shutting down the brain.

## FRONTIER RESEARCH IN ANESTHESIOLOGY CONFIRMS THE BRAIN-DISABLING PRINCIPLE

Because they have no ax to grind about treating anxiety with BZs and other CNS depressants, anesthesiologists have been more honest in evaluating their effects. All currently used forms of anesthesia work by

enhancing the effect of the neurotransmitter system receptors known as gamma-aminobutyric acid (GABA), in particular the receptor subtype A, or $GABA_A$. All BZs enhance GABA, including the long-acting diazepam (Valium) used to treat anxiety and the ultra-short-acting midazolam (Versed) used intravenously to produce anesthesia.

$GABA_A$ receptors exist throughout the brain and can be found on the great majority of neurons. This system dampens neuronal activities, regulating the overall level of CNS activity. When stimulated by drugs, GABA produces the continuum of CNS depression leading to coma.

The subtype $GABA_A$ has at least 19 subtypes of its own, and most of those subtypes have subtypes, producing a dizzying array of receptor subtypes (Hemmings et al., 2005; Orser, 2007). In addition, recent research has demonstrated that $GABA_A$ receptors are not limited, as originally thought, to the synapse. They line the outside of neurons as well, where they regulate neurotransmission by potentially inhibiting their capacity to become excited. Of course, this effect is so generalized that it cannot possibly be specific for one aspect of consciousness, the generation of anxiety.

In evaluating the latest advances in anesthesiology, Beverley Orser (2007), Professor of Anesthesiology and Physiology at the University of Toronto, discussed the mechanism of action of anesthetics, including BZs. Her description confirmed the brain-disabling principle in regard to these drugs:

> Because consciousness is a complex experience whose defining properties are still hotly debated by neuroscientists, it is not as easy to pinpoint a single anatomical source of unconsciousness during anesthesia. One leading theory holds that it is simply the result of "cognitive unbinding"—a severing of communication between the many brain regions that usually cooperate in higher cognitive processing. Even at the local level, if one imagines groups of neurons as forming lines in a vast telephone network, the effect of general anesthesia is analogous to pulling out the plugs at the switchboard.

This kind of general disruption of brain function and consciousness takes place when an individual undergoes anesthesia—or takes a BZ to relieve anxiety. Unfortunately, Dr. Orser's (2007) level of sophistication about the brain-disabling effects of BZs is sorely missing among psychiatric drug experts who persist in believing that their chemicals treat specific psychiatric disorders similar to the way insulin treats diabetes.

## THE DRUGS

Since the days when Valium was the most prescribed drug in America, doctors have become more cautious about prescribing addictive BZs.

According to the Drug Enforcement Administration (DEA, 2006), in 1999, there were about 100 million prescriptions written. According to IMS Health (2007), they have not yet fallen off the charts. The BZs were 10th in the nation in sales, with over 80 million prescriptions written. Antianxiety agents (anxiolytics or minor tranquilizers) remain among the most commonly used drugs in both medicine and psychiatry.

I could not locate any reliable recent estimates for the number of patients taking BZs. More than a decade ago, it was estimated that 15% of American adults used these or similar sedative/hypnotic agents during any given year, usually through a physician's prescription (Gold et al., 1995). Almost 2% of the population was using BZs more or less chronically (DuPont, 1986). In 1993, Xanax topped the list for frequency of use, followed by Klonopin.

Moore and Jones (1985) performed a review of all adverse drug reactions reported to the Food and Drug Administration (FDA) from 1968 to 1982 (see chapter 13 for an analysis of the FDA's system). Antibiotics ranked first with 33,959 reported adverse reactions, but so-called tranquilizers were neck and neck with 33,720. The BZs are frequently prescribed for anxiety or panic and for sleep. They are also given to counteract the stimulating effects of the antidepressants, especially Prozac, Paxil, and other SSRIs. Most of the antianxiety agents, including the more potent ones, are BZs. This chapter will focus on the brain-disabling effects of BZs, especially the short-acting, high-potency drugs alprazolam (Xanax) and triazolam (Halcion). Because they produce more frequent and intensive adverse drug reactions, Xanax and Halcion provide a magnifying glass for investigating the more general impact of all BZs.

With their trade names and half-lives in parentheses (the units are hours), current BZs include the following: alprazolam (Xanax, 6–20), chlordiazepoxide (Librium, 30–100), clonazepam (Klonopin, 18–50), clorazepate (Tranxene, 30–100 or 200), diazepam (Valium, 30–100), estazolam (ProSom, 10–24), flurazepam (Dalmane, 50–160), lorazepam (Ativan, 10–20), midazolam (Versed, 2–3), oxazepam (Serax, 3–21), prazepam (Centrax, 30–100), quazepam (Doral, 50–160), temazepam (Restoril, 8–20), and triazolam (Halcion, 1.5–5).[1] The appendix contains a more complete list.

Some BZs have been marketed as hypnotics or sleeping medications, or are more frequently prescribed for this purpose by physicians, without being substantially different in their characteristics from other BZs marketed for anxiety. As Ashton (1995) remarked, "The pharmacological actions of all benzodiazepines are similar; the distinction between tranquilizers and hypnotic preparations is based on commercial, not pharmacological grounds" (p. 159, note on chart). Flurazepam, for example, is sold as a sleeping medication, but its rather lengthy half-life will produce hangover effects the following day. Xanax, and to an even greater extent,

Halcion, do have a significantly different profile due to a greater capacity to bind to receptors and a shorter half-life. Halcion's very short half-life led to the hope that it would make a particularly good sleeping medication because its effects presumably would wear off by the morning. Instead, it has proven relatively ineffective and especially dangerous, often causing withdrawal reactions the following morning.

The brain-disabling or toxic effects of the BZs can be divided into several somewhat overlapping categories:

1. The primary clinical effect of inducing sedation (tranquility) or hypnosis (sleep), which is indistinguishable from a toxic effect, except in degree
2. Acute cognitive dysfunction, ranging from short-term memory impairment and confusion to delirium
3. Disinhibition and other behavioral aberrations, including extreme agitation, psychosis, paranoia, and depression, sometimes with violence toward self or others
4. Withdrawal, in which the individual experiences a continuum of symptoms from anxiety and insomnia after routine use to psychosis and seizures after the abrupt termination of long-term, larger doses
5. Rebound, an aspect of withdrawal, in which the individual develops anxiety, insomnia, or other serious emotional reactions that are more intense than before drug treatment began (withdrawal and rebound can take place between doses during the routine administration of BZs, especially the short-acting ones)
6. Habituation and addiction, along a continuum from feeling dependent on the drug to compulsively organizing one's behavior in a self-destructive manner around obtaining large amounts of the agent
7. Persistent cognitive dysfunction, persistent amnestic syndrome, and persistent dementia

## BRAIN DISABILITY AS THE PRIMARY CLINICAL EFFECT

As much as any psychiatric drugs, the brain-disabling effects of the BZs (or any sedative-hypnotic, including alcohol) are readily apparent. Much as for alcohol, there is a continuum of CNS depression from relaxation through sleep, and, in the extreme, coma. Prescribing is a matter of giving enough of the medication to the point where the patient experiences a desired effect without becoming too heavily sedated or comatose.

Neurophysiological studies show that the BZs potentiate the neuronal inhibition that is mediated by GABA. In doses used clinically, this results in a generalized suppression of both spontaneous and evoked electrical activity of the large neurons throughout all regions of the brain and spinal cord (Ballenger, 1995).

The binding of BZs to the GABA receptors is most intense in the cerebral cortex. Some BZs, such as Xanax and Halcion, bind especially tightly, increasing their tendency to produce more intense sedation and hypnosis, and also more severe cognitive deficits, behavioral abnormalities, rebound, and withdrawal.

People who use BZs to calm their anxiety will frequently use alcohol and other sedatives interchangeably for the same purpose, either in combination or at different times. As they switch from drug to drug, they tend to find little or no difference in the antianxiety effect. This confirms that BZs have no specificity for anxiety in comparison to other sedative/hypnotic agents.

## MECHANISMS FOR PRODUCING BEHAVIORAL ABNORMALITIES

There are at least two causes for the abnormal behavior produced by BZs. One mechanism is direct intoxication, resulting in impaired executive and cognitive function, including reduced judgment and impulse control. Fogel and Stone (1992) observed, "Benzodiazepines, given to reduce arousal or possibly to treat a hypomanic state, may aggravate impulsive behavior by impairing the inhibition mechanism of the frontal lobes. Barbiturates may have similar effects" (p. 341).

Especially in regard to the BZs, a second mechanism, *withdrawal or rebound,* can also cause severe psychiatric reactions. These *discontinuation symptoms* occur when the BZs are withdrawn or when they begin to lose their effectiveness (American Psychiatric Association [APA], 1990a). When exposed to BZs, the brain compensates by reducing the activity of the GABA system. The GABA receptors become down-regulated (less sensitive). The GABA system, in effect, becomes sluggish. There may also be a reduction in GABA itself to compensate for the drug effect, once again leaving the natural GABA system relatively inactive. In short, the natural inhibitory mechanism of the brain becomes relatively disabled and ineffective in the presence of BZs. When the BZs are then withdrawn, the brain is left with an ineffective or sluggish inhibitory system, resulting in anxiety, agitation, behavioral disinhibition, and loss of control.

BZ disinhibition differs in some ways from alcohol disinhibition. It can occur without a noticeable sedative intoxication, such as slurred

speech, lack of coordination, or impaired consciousness. Furthermore, the BZs are prescribed by a physician, often without providing the patient a warning about possible disinhibition. Unlike the experienced alcohol user, the trusting BZ user has little reason to anticipate losing control. Expecting to be helped, and not harmed, by the drug, the patient is less able to understand or manage potentially overwhelming feelings of anger or violence or other untoward emotional responses. Also, unlike with alcohol, some of the worst BZ behavioral reactions occur during withdrawal or in between doses, adding to the patient's confusion concerning what is happening. At the time, the patient may have little idea what is driving the unfamiliar behavior, and in retrospect, it may seem like a fragmented, poorly recalled nightmare. In addition, the BZs are very spellbinding, so individuals often suffer toxic effects on their brains and minds without appreciating or recognizing them.

## ADVERSE REACTIONS TO BENZODIAZEPINES (BZs)

The FDA-approved label for Xanax XR, the long-acting preparation of the drug, listed the following "psychiatric disorders" caused by the drug in short-term placebo-controlled clinical trials: depression, decreased libido, disorientation, confusion, depressed mood, and anxiety. It lists additional psychiatric symptoms under the rubric of "nervous system disorders," including sedation, somnolence, memory impairment, mental impairment, and hypersomnia (*Physicians' Desk Reference*, 2006, p. 2658). Memory impairment is listed as one of the reasons that patients stopped taking the drug. It is unusual for so many adverse psychiatric symptoms to surface in short-term placebo-controlled clinical trials, indicating that Xanax XR has an unusual capacity to cause them. The label for Xanax (not the XR preparation) indicated that it caused "disinhibition," even in the short-term placebo-controlled clinical trials (*Physicians' Desk Reference*, 2005, p. 2766).

Standard textbooks and reviews spanning more than two decades as well as a variety of clinical studies confirm widespread recognition of BZ-induced behavioral abnormalities (Arana et al., 1991; Ashton, 1995; DiMascio et al., 1970; Kochansky et al., 1975; Maxmen, 1991; Rosenbaum et al., 1984; Shader et al., 1977). My 1998(b) review titled "Analysis of Adverse Behavioral Effects of Benzodiazepines With a Discussion of Drawing Scientific Conclusions From the FDA's Spontaneous Reporting System" probably remains one of the most complete reviews in the scientific literature.

Salzman et al. (1974), in a placebo-controlled study, showed that volunteers taking chlordiazepoxide became more hostile when confronted

with a situation of interpersonal frustration. Salzman (1992) also reviewed the literature. He pointed out the then controversial nature of BZ-induced violence but went on to assert, "Recent observations, however, have confirmed that hostility can be seen with all benzodiazepines, including alprazolam and clonazepam."

Writing in *The Pharmacological Basis of Therapeutics*, Rall (1990) summarized:

> *Adverse psychological effects:* Benzodiazepines may cause paradoxical effects. Nitrazepam frequently and flurazepam occasionally increase the incidence of nightmares, especially during the first week of use. Flurazepam occasionally causes garrulousness, anxiety, irritability, tachycardia, and sweating. Euphoria, restlessness, hallucinations, and hypomanic behavior have been reported to occur during the use of various benzodiazepines. Antianxiety benzodiazepines have been reported to release bizarre uninhibited behavior in some users with low levels of anxiety; hostility and rage may occur in others. Paranoia, depression, and suicidal ideation occasionally also accompany the use of these agents. (p. 355)

Rall believed that "the incidence of such paradoxical reactions is extremely small." Whether or not that is true, they are extremely hazardous. They are more common in regard to the short-acting BZs.

Drug-induced disinhibition or loss of impulse control can cause serious harm to self and to others. I have evaluated in depth cases in which only one or two doses of a BZ such as alprazolam or clonazepam have led to suicidal or homicidal outbursts.

## The Production of Mania and Rage

As the above observations confirm, reactions to BZs can reach psychotic proportions. As noted in *Drug Facts and Comparisons* (2003–2007), the BZs in general can cause serious psychiatric problems, including psychosis. They can disrupt CNS function, producing, among other things, "disorientation . . . confusion . . . delirium . . . euphoria . . . agitation." A special Precautions section noted "paradoxical reactions," including "excitement, stimulation and acute rage" and "hyperexcited states, anxiety, hallucinations."

Mania is a special danger in regard to Xanax. Unlike any other benzodiazepine, the FDA-approved label for Xanax, as found in the 2007 *Physicians' Desk Reference*, specifically mentioned the risk of mania. *Drug Facts and Comparisons* (2007) also made a specific reference to Xanax under "Precautions," stating that "anger, hostility and episodes of mania and hypomania have been reported with alprazolam" (p. 1199). As another

example, Maxmen and Ward's (1995) *Psychotropic Drug Fast Facts* stated that "manic reactions" are "most often reported with alprazolam" (p. 287). It also stated that "rage reactions" and "violent episodes" have especially been observed with Xanax and Valium. Yet another example is the *Handbook of Psychiatric Drug Therapy* by Hyman et al. (1995). It singled out Xanax to observe that "increased impulsiveness, euphoria, and frank mania have been reported with alprazolam" (p. 177).

## The Production of Depression and Suicide

As already noted, there are reports in the clinical literature indicating that the BZs can cause depression. Some reviews mention the phenomenon but express skepticism, while nonetheless declaring that it should be taken seriously. Arana and Hyman (1991), for example, stated:

> *Depression:* All benzodiazepines have been associated with the emergence or worsening of depression; whether they were causative or only failed to prevent the depression is unknown. When depression occurs during the course of benzodiazepine treatment, it is prudent to discontinue the benzodiazepine.

Ashton (1995) observed that BZs can blunt the emotions in general, producing "emotional anesthesia." He reported, "Former long-term benzodiazepine users often bitterly regret their lack of emotional response to family events during the period that they were taking the drugs." Ashton also observed that BZs can precipitate suicide in already depressed patients.

The APA (1990a) task force report on BZs, in a discussion of toxicity, also observed that

> benzodiazepines have also been reported to cause or to exacerbate symptoms of depression. This, too, is not a frequent side effect, although the depressive symptoms may be potentially serious. (p. 41)

Great Britain's Committee on Safety of Medicines (CSM; 1988) recommended that "benzodiazepines should not be used alone to treat depression or anxiety associated with depression. Suicide may be precipitated in such patients."

Some psychiatrists believe that there is usually a predisposition toward depression and suicidality in the affected individual, but this position lacks evidence. As a medical expert, I have extensively evaluated cases of depression and suicide induced by benzodiazepines in individuals with no prior history of these emotional problems.

## Cognitive, Emotional, and Behavioral Abnormalities Caused by Halcion and Xanax

Several studies have demonstrated rebound phenomena the same night or the day following the ingestion of the short-acting BZ triazolam (Halcion). In a controlled study, Moon et al. (1985) found that "the results support previous reports that early insomnia and an increase in daytime anxiety are problems associated with short acting benzodiazepines, such as triazolam."

De Tullio et al. (1989) reviewed the charts of 72 adult male patients taking triazolam for sleep through an ambulatory Veterans Administration (VA) clinic. Thirty-nine of the patients were available for telephone interviews. Most of the patients were elderly (age 60 or older). Of the 39 patients interviewed, only 4 reported no adverse effects, and 23 experienced more than one. The most common were dizziness, rebound insomnia, and nightmares. "Rebound insomnia was defined as waking during the night or waking too early in the morning, and having trouble falling back to sleep." As a result of the study, the VA facility modified its policies on triazolam administration: "For outpatients on chronic triazolam therapy, a switch to a longer-acting benzodiazepine was instituted with tapering if therapy was not to be continued."

Public and professional awareness of the special dangers of Halcion began in 1978. At that time, C. van der Kroef (as cited in Dukes, 1980), a psychiatrist in The Hague, Netherlands, noticed abnormal reactions to Halcion in 4 of 11 patients he treated with the drug. Following is van der Kroef's description of one of his patients:

> The insomnia improved at once, but psychically she rapidly went downhill. Progressively she became paranoid. Several times she asked me what the hypnotic contained—LSD perhaps?—for she felt that she was bordering on psychosis. She felt shut off from the world; it was as if she no longer belonged to society. Her friends asked her what was happening to her, so strangely was she behaving. . . . After two months I too began to suspect, particularly in light of experience with an earlier patient, that all this might be a consequence of her taking triazolam. The drug was withdrawn and replaced with nitrazepam. Within a day she felt herself again. The people around her noticed the difference and recognized her old self again. The paranoid traits, the hypermotility urge and the hyperaesthesia disappeared in the course of two days.

Dukes (1980), a physician with considerable regulatory experience, commented on van der Kroef s findings. He observed that all of the BZs, including those used to induce sleep (hypnotics), have been known to produce reactions that are "frankly psychotic." While not common,

according to Dukes, "virtually every known drug in this class" has produced "hallucinations, delusions, paranoia, amnesia, delirium, hypomania—almost every conceivable symptoms of psychotic madness."

According to Dukes (1980), all the BZs used for the control of anxiety were also implicated in causing violence:

> If one—to begin at an arbitrary point—looks to the literature for evidence that the benzodiazepines can unleash aggression then one will find it. More than a dozen papers in the literature speak of irritability, defiance, hostility, aggression, rage or a progressive development of hates and dislikes in certain patients treated with benzodiazepine tranquilizers; all those products which are widespread have been incriminated at one time or another. The phenomenon has been demonstrated in animal studies and it has even been proved possible to show in human volunteers that these drugs can release pent-up hostility, particularly in highly anxious or action-oriented individuals.

Until the advent of Halcion, according to Dukes (1980), the older BZs commonly used to induce sleep were not known to cause violence. We shall find his observations confirmed later on by in-house studies at the FDA indicating that Halcion—but not the older hypnotics, Dalmane or Restoril—caused a vastly increased rate of violent activities.

I have been a medical expert in criminal cases involving abnormal behavior, including theft and violence, related to Xanax intoxication. I have also been an expert in civil suits involving suicide related to Halcion.

It is, of course, extremely difficult to demonstrate drug-induced behavioral abnormalities in highly selective, short, controlled clinical trials (see chapter 13 for a detailed analysis of why this is so). Nonetheless, several studies have confirmed some of the hazards associated with Halcion.

Gardner and Cowdry (1985) found an increase in dyscontrol in borderline patients taking alprazolam in a double-blind, placebo-controlled cross-over study. The dyscontrol included the following: "Overdose, severe"; "Overdose, moderate"; "Deep neck cuts"; "Transverse wrist cuts"; "Tried to break own arm"; "Threw chair at child"; and "Arm and head banging; jumped in front of car."

Gardner and Cowdry (1985) pointed out that there are some reports of borderline patients also improving on alprazolam. They concluded, "Caution should, however, be exercised, particularly in treating individuals with a substantial history of dyscontrol."

Bayer et al. (1986) conducted a 9-week, double-blind controlled study of triazolam and another hypnotic, chlormethiazole, in the elderly with sleep disturbances. They found daytime withdrawal effects from triazolam but not chlormethiazole. At week 3, significantly more

triazolam patients were rated as more restless during the day, "and they also appeared more hostile, less relaxed, more irritable and more anxious." Patients on triazolam also had more adverse events related to the CNS, requiring 4 of 22 patients to withdraw from the study; 3 of those withdrawn recovered after terminating the medication. One patient felt that the tablets were making him nervous. The others individually developed paranoid delusions, "increasing confusion and irritability," and irrational, irritable, and uncooperative behavior.

Adam and Oswald (1989), in a double-blind, placebo-controlled study of triazolam and lormetazepam with 40 subjects in each of the three groups, found that "triazolam takers became more anxious on self-ratings, were judged more often to have had a bad response by an observer, more often wrote down complaints of distress, and suffered weight loss. After about 10 days of regular triazolam they tended to develop panics and depression, felt unreal, and sometimes paranoid." According to the authors,

> Subjects' written comments suggested that from about 10 days after starting triazolam, they became liable to panic attacks, feelings of despair and derealization. There were descriptions of panic episodes in public places in seven subjects during triazolam intake, but none during placebo or lormetazepam.... Several reported their family relationships were changed.... A number of triazolam subjects became paranoid.... Two men developed paranoid psychoses. [During the withdrawal period, the anxiety of the triazolam patients] fell quickly to normal levels.

Soldatos et al. (1986) reported on serious adverse drug reactions in all five psychiatric inpatients during a clinical trial of 0.5 mg triazolam and placebo. The patients and nurses were blind in the study, but not the physician with medical responsibility for the patients. The study consisted of 1 week of placebo baseline, 2 weeks of triazolam administration, and 1 week of withdrawal on placebo. All five patients developed severe reactions to triazolam. Case 1 developed "anxiety and hallucinations on the last two days of triazolam administration and the first withdrawal day." Case 2 had a sudden increase in anxiety and became "irritable, uncooperative, and depressed." She became withdrawn and cried, and showed "considerable impairment of memory and orientation." On withdrawal of triazolam, "she became more incoherent, expressing paranoid ideas of persecution that persisted about a week." She required Haldol to control her delusions. Case 3 developed severe insomnia during withdrawal and "reported considerable anxiety and irritability along with an uncontrollable fear of death, which persisted to the next day when she additionally manifested a marked degree of memory impairment." Case 4, by

the end of the second week of triazolam administration, "became more depressed and manifested increasingly irritability and hostility." Case 5, on the second week of triazolam administration, "experienced increasing daytime anxiety and he became, for the first time since admission, irritable, hostile, and somewhat guarded and paranoid towards the unit staff." The authors suggested that some of the symptoms may have been related to disinhibition. They warned that these serious side effects "may not be rare when triazolam is used in patients . . . [with] major psychiatric conditions."

Rosenbaum et al. (1984) found that 8 of 80 patients treated with alprazolam in an outpatient clinical setting developed extreme anger or hostile behavior.

## Evidence From the Food and Drug Administration's Spontaneous Reporting System

In 1987, Bixler et al. reviewed adverse reactions to BZs recorded in the FDA's spontaneous reporting system (SRS). They compared triazolam with two other BZs commonly used to induce sleep: temazepam (Restoril) and flurazepam (Dalmane). They controlled the reports for the number and size of prescriptions for each of the three drugs. In regard to psychiatric adverse reactions, they found:

> in general, triazolam had much higher overall rates than did the other two drugs. Hyperexcitability and withdrawal effects were greatest for triazolam and least for flurazepam. Amnesia was reported almost exclusively with triazolam. Rates for other cognitive as well as affective and other behavior effects were also much greater for triazolam and about equal for the other two drugs.

The affective and other behavioral disturbances category of adverse drug reactions included "Depression, Psychotic Depression, Emotional lability, Euphoria, Hostility, Personality disorder, and Decreased libido."

Epidemiological studies at the FDA have consistently shown that alprazolam and, especially, triazolam produce more frequent and more serious adverse CNS effects, including drastic and life-threatening behavioral changes, than any other BZs. I have reviewed the in-house memos with detailed analyses generated by the Division of Epidemiology and Surveillance, which is responsible for the SRS. This division has consistently shown more concern about triazolam than has Paul Leber's Division of Neuropharmacological Drug Products, which originally approved the drug (see subsequent discussion; see chapter 13 for more

about Leber and the FDA). In the earlier edition of this book, the data from the epidemiology studies were described in detail for the first time in the literature.

Robert "Bob" Wise (1989), in a working paper for the FDA's Division of Epidemiology and Surveillance, made an executive summary concerning reports of hostility on triazolam. Wise addressed a syndrome that consists of "anger or rage, aggression, and some actual assaults and murders." He stated:

> More such reports of this type have been received by the FDA for triazolam and alprazolam than for any other drug product regulated by the Agency. Reporting rates, which adjust for differences in the extent of each drug's utilization, reveal much higher ratios of hostility reports to drug sales for both triazolam and alprazolam than for other benzodiazepines with similar indications.
>
> The public health importance of these reactions lies in their severity, with occasionally lethal behavior unleashed, in the context of large population exposures as the popularity of both drugs continues to rise.

After a brief history of the FDA's increased focus on BZ-induced hostility, Wise explained:

> Our concern with such reactions then broadened to the class of triazolobenzodiazepines, when another Increased Frequency Report included a reaction in which a 57 year old woman fatally shot her mother two hours after taking one-half milligram of triazolam. When we looked at reports received during 1988, we found that triazolam's 1988 reporting rate for hostility reactions was more than twice as high as alprazolam's.
>
> In the entire SRS…during early August, 1989, triazolam was the suspect drug in 113 reports coded as hostility, more than any other medication. It was followed by alprazolam, which accounted for 78 reports. Only nine other drugs were suspected in more than ten cases each. Another 318 drug products had fewer hostility reports, most often one (60.4 percent of 318) or two (14.8 percent).

Three fatalities were reported to the SRS for triazolam and one for alprazolam. Five reports of alprazolam overdose were associated with assaults, including two murders. Reactions were reported across the dose range. Men (29) and women (26) were almost evenly distributed.

Four alprazolam cases showed a reduction in hostility and rage reactions after a reduction in dose (dechallenge), confirming the drug's role in producing the behavior.

Wise (1989) summarized, "This apparently excessive number of rage and similar reports with triazolam and alprazolam, after adjusting

the differences in frequency of drug use, provides strong suspicion that a causal relationship may obtain." It should be added that the relationship to increased dosage seen in several cases further confirms causation. Wise concluded that these reports cannot "prove the presence of a causal relationship" to the drug but that they do "imply a substantial public health importance for the potential hostility syndrome."

Wise (1989) missed an extremely important aspect of his own data. Not only were Halcion and Xanax first and second in total reports of hostility, midazolam (Versed) was third in order. Versed, like Halcion and Xanax, is a very short-acting, tightly binding BZ. It is used exclusively as an intravenous injection for preoperative sedation and memory impairment. The total numbers of reports were Halcion (112), Xanax (77), and Versed (46). Valium (34 reports) was fourth. They were followed by Symmetrel (22) and Prozac (20).

Thus the database for all drugs in the SRS of the FDA—which includes all prescription drugs in the United States—showed that three short-acting, tightly binding BZs came in first, second, and third for reports of hostility as an adverse drug reaction. Furthermore, the three drugs are typically used under very different clinical conditions: Halcion orally, with one daily dose at night for sleep; Xanax orally, with several daily doses for daytime anxiety; and Versed intravenously, for preoperative purposes, usually on one occasion only. Despite the different uses, dosage schedules, and even routes of administration, they cluster at the very top of the list for producing hostility. This is convincing and seemingly irrefutable evidence that these kinds of agents can cause violence.[2]

On April 21, 1989, Wise wrote an increased frequency report for the FDA on the subject of alprazolam and rage. Wise explained that the analysis was undertaken because "over a 12 month period, Upjohn received six reports of rage, agitation, anger, aggression, and similar behavioral and emotional symptoms after exposures to alprazolam." All but one involved "manifested or verbalized murderous impulses." According to Wise:

> From spontaneous reports alone, we cannot estimate the actual incidence of alprazolam-induced rage reactions. But in light of the widely acknowledged, substantial underreporting to spontaneous surveillance systems in general and to the FDA's SRS in particular, it is entirely possible that six reports of this kind of reaction within a single year might reflect sixty or more in reality.

After reviewing all reports made to Upjohn and the FDA, Wise concluded:

> An increase in annual frequency of "rage" reports with alprazolam prompted us to compare hostility reports more generally across several

> anxiolytic benzodiazepines. Alprazolam appears to have an excessive reporting rate for events coded with "hostility," even after adjusting for differences in the extent of each drug's utilization. The numbers and potential gravity of these reactions and their possible relationship to dosage all appear to conflict with current labeling's brief description of "paradoxical effects" that occur only "in rare instances and in a random fashion."

On October 17, 1988, Charles Anello, Deputy Director of the Office of Epidemiology and Biostatistics, referred to an earlier FDA comparison of spontaneous reports concerning triazolam to two other BZs used to treat insomnia, temazepam (Restoril) and flurazepam (Dalmane). Anello stated that there was a proportionately increased number of reports concerning abnormal behavior in regard to triazolam. Anello reported on a further analysis comparing triazolam and temazepam, showing that for triazolam, the FDA received proportionally more adverse drug reaction reports (ADRs), more serious ADRs, and more reports of five selected behavioral drug reactions.

On September 12, 1989, Anello reported within the FDA on "Triazolam and Temazepam—Comparison Reporting Rates." He found that adverse drug reactions were reported 11 times more frequently with triazolam than with temazepam. The relative reporting rate was 46 to 1 for amnesia, 9 to 1 for "agitation, anxiety and nervousness," 16 to 1 for psychosis ("psychosis, hallucinations, paranoid reaction, and acute brain syndrome"), and 19 to 1 for "hostility and intentional injury."

Anello's (1989) analysis indicated that there were no convincing explanations for these differences other than actual drug effects, but he did not make a formal determination of causality. However, in a handwritten analysis attached to the document, obtained through the Freedom of Information Act, there is a summary titled "Other Evidence in Favor of Effect of Triazolam," which I quote in full:

1. Temporal relationship of reactions to initial dose
2. Large proportion of spontaneous resolution with drug withdrawal (pos[itive] dechallenge)[3]
3. A few reports of positive rechallenges[4]
4. Reports of reactions in otherwise normal individuals
5. Corroborating reports in literature (including WHO data—similar magnitude of reactions in Canada in data through 3/87)

The above note indicates some of the logical, scientific steps by which data from spontaneous reporting were used by an unidentified FDA official to confirm causality in regard to Halcion and adverse behavioral

effects. (For a further discussion of the scientific process in epidemiological studies, see chapter 13.)

In 1991, Diane Wysowski and David Barash, also from the FDA's Division of Epidemiology and Surveillance, published a report in the *Archives of Internal Medicine*. A footnote stated, "This article contains the professional views of the authors and does not constitute the official position of the Food and Drug Administration." Using the FDA's SRS, the authors compared triazolam and temazepam through 1985 for "confusion, amnesia, bizarre behavior, agitation, and hallucinations." They concluded, "Considering the extent of use, reporting rates for triazolam were 22 to 99 times those for temazepam, depending upon the reaction." Echoing the handwritten remarks appended to Anello's (1989) in-house report, the authors summarized:

> Factors that indicate a causal association between triazolam and adverse behavioral reactions include corroborating case reports and sleep laboratory studies in the literature, reports of reactions in otherwise normal persons, acute onset and temporal relationship to reactions with initial dose, spontaneous recoveries and return to normalcy with drug discontinuation, and occurrences of positive rechallenge. Also, the high benzodiazepine receptor affinity with triazolam has been postulated as a possible biological mechanism.

While unable to "completely exclude the possibility that some selection factors are operating to produce higher reporting rates for triazolam," nonetheless, Wysowski and Barash (1991) found that the evidence suggested a greater occurrence with triazolam than with temazepam. Andreadis and Schrimer (1992) responded critically for Upjohn with a letter, and Wysowski and Barash (1992) were given the opportunity to try to answer their objections.

## AMERICAN AND BRITISH RESPONSES DIVERGE

Finally, in November 1991, the FDA approved new labeling for Halcion (Food and Drug Administration, 1992). The new label emphasizes that triazolam *is* indicated for short-term use and specifies 7–10 days. Treatment lasting longer than 2–3 weeks requires a complete reevaluation of the patient. In addition, the label emphasizes the use of the lowest possible dose.

Following is the new warning on the Halcion label as found, for example, in the 1995 *Physicians' Desk Reference:*

> A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of benzodiazepine hypnotics,

> including HALCION. Some of these changes may be characterized by decreased inhibition, e.g., aggressiveness and extroversion that seem excessive, similar to that seen with alcohol and other CNS depressants (e.g., sedative/hypnotics). Other kinds of behavioral changes have been reported, for example, bizarre behavior, agitation, hallucinations, depersonalization. In primarily depressed patients, the worsening of depression, including suicidal thinking, has been reported in association with the use of benzodiazepines.

The warning concludes with the following:

> As with some, but not all benzodiazepines, anterograde amnesia of varying severity and paradoxical reactions have been reported following therapeutic doses of HALCION. Data from several sources suggest that anterograde amnesia may occur at a higher rate with HALCION than with other benzodiazepine hypnotics.

The final label change was negotiated and approved under the authority of Paul Leber, Director of the Division of Neuropharmacological Drug Products, the division responsible for Halcion's original approval. In several ways, the label seems to fall far short of conclusions generated by both the literature and the division responsible for postmarketing surveillance.

The FDA label does mention the disproportionate reporting of amnesia, but by omission, it leads the reader to believe that the behavioral effects did not occur with increased frequency. Instead of linking directly to Halcion the enormously increased risk for violence, psychosis, and other extremely hazardous behavioral abnormalities, the label notes that these changes have been "reported in association with the use of benzodiazepine hypnotics, including triazolam." As we documented earlier in this chapter, Charles Anello, Deputy Director of the Office of Epidemiology and Biostatistics, compared adverse drug reaction reports for Halcion and Restoril. For Halcion versus Restoril, the relative reporting rate for "agitation, anxiety and nervousness" was 9–1; for psychosis, 16–1; and for "hostility and intentional injury," 19–1.

Great Britain took a stronger stand and ended up banning Halcion. On October 1, 1991, the CSM gave notice of the withdrawal of Halcion from the market because of concerns about safety, especially in regard to causing memory loss and depression (Asscher, 1991; Brahams, 1991). On December 9, 1991, the CSM (1991) responded to Upjohn's appeal with a definitive scientific conclusion about the dangers of Halcion. It found what it called a clearly established causal relationship between Halcion and adverse psychiatric effects. These adverse effects occurred, in the CSM's opinion, far more frequently with Halcion than with other BZs.

The CSM declared that the SRS data from the United States and England confirmed or strengthened the connection between Halcion and various psychiatric side effects. Concerning the FDA epidemiological data, the CSM observed that despite differences of opinion within the FDA, the U.S. data provided a signal requiring further investigation.

Why would Great Britain take a tougher stand against Halcion? The answer lies partly in the greater power of the psychopharmaceutical complex in America and, in particular, the lavish spending of Upjohn in the maintenance of its self-avowed partnership with the APA. In response to my criticism in a letter to *The New York Times* (Breggin, 1992c), the medical director of the APA (Sabshin, 1992) defended taking a gift in the form of a check for $1.5 million from Upjohn on the grounds that the drug company and the psychiatric association have a "responsible, ethical partnership." Upjohn confirmed the so-called partnership in a letter of its own to *Clinical Psychiatry News* (Jonas, 1992). (Even after the controversy, the APA continued the theme of "our partners in industry" in a mass mailing to its membership (Benedek, 1993).

The manufacturer of Halcion, Upjohn, has been criticized in the media and in court for allegedly withholding from the FDA and the profession damaging evidence concerning the drug. Upjohn has denied allegations of intentional wrongdoing and has attributed errors in reporting adverse effects to innocent mistakes. The controversy continues in the FDA, the media, and the courts (Breggin, 1996; Carey et al., 1996; Kolata, 1992; controversy summarized from a legal viewpoint in Moch et al., 1995).

## OTHER RISKS IN BZ USE

### BZs As Instruments of Suicide

Some of the tricyclic antidepressants and barbiturates are probably more lethal than BZs taken alone. But when BZs are combined with other drugs, such as alcohol, their lethality is increased. Overall, the BZs account for many more suicides than most physicians probably realize.

A survey in Britain covering the decade of the 1980s demonstrated large numbers of successful suicides using BZs, either alone or in combination with alcohol (Serfaty et al., 1993; see also Buckley et al., 1995). Serfaty and Masterton (1993) found 891 fatalities with BZs alone and 591 in combination with alcohol. The total of all poisonings attributed to BZs was 1,576 during the 10-year period, putting them ahead of aspirin/salicylates at 1,308 as well as amitriptyline (1,083) and dothiepin at 981.

(The latter two drugs accounted for over half the fatal poisonings attributed to antidepressants.)

Among the BZs, two commonly prescribed for sleep, flurazepam (Dalmane) and temazepam (Restoril), had the most deaths per million prescriptions (15.0 and 11.9, respectively). They were more dangerous than about half the antidepressants surveyed by the same methods. Triazolam (Halcion) had far fewer deaths per million prescriptions (5.1) than Dalmane or Restoril, but it was still above the mean for anxiolytic BZs (3.2).

In estimated deaths per million patients, the rank order among all BZs in Britain was dominated by the hypnotics. Dalmane (90 per million) was first, Restoril (71) was second, the British hypnotic flunitrazepam (Rohypnol; 49) was third, and Halcion (30) was fourth. Another British hypnotic, nitrazepam (Mogadon and others; 26) was fifth.

In deaths per million patients, among the antianxiety drugs, prazepam (Centrax; 25) and alprazolam (Xanax; 24) were close behind triazolam and nitrazepam.

## Effects on Sleep and the Electroencephalogram

BZs are often taken to induce sleep, but in reality, they cause a disturbed sleep pattern. Disturbances in sleep patterns are a major source of abnormal emotional and behavioral reactions.

The effects of the BZs on the electroencephalogram (EEG) resemble those of other sedative/hypnotic agents, including decreased alpha activity and increased low-voltage fast activity, especially beta activity (Rall, 1990). Their effects on sleep are also similar to those of other CNS depressants and provide a window into the dysfunctions they produce (Rall, 1990).

Before the brain rebounds after one or more doses, the BZs decrease sleep latency (the time it takes to fall asleep) and reduce the number of awakenings. The overall time in REM sleep is usually shortened, but the number of cycles of REM may be increased later in sleep. Total sleep duration is usually increased. There are complex effects on the dream process.

Within a short time of starting Halcion, rebound begins to dominate the clinical picture, and insomnia worsens. Nishino et al. (1995) observed that short-acting BZs were initially preferred for elderly patients. They remarked, "However, it has since been found that short-acting BZs induce rebound insomnia (a worsening of sleep beyond baseline levels on discontinuation of a hypnotic), rebound anxiety, anterograde amnesia, and even paradoxical rage."

In general, the usefulness of BZs in insomnia is temporary at best. They do not provide for normal sleep, but rather for a disruption in various aspects of the normal cycle.

## THE *DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS* CONFIRMS BZ-INDUCED PERSISTENT AMNESIA AND DEMENTIA

Many physicians seem unaware that the BZs and other sedative drugs can cause persistent or irreversible harm to the brain in the form of persisting memory dysfunction and dementia. The failure to appreciate these adverse drug reactions occurs despite clear confirmatory diagnoses in the consensus document, the APA (2000) *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–IV–TR*). In the *DSM–IV–TR,* the BZ-induced disorders are included in the category of sedative-, hypnotic-, or anxiolytic-induced disorders. The BZs, such as Valium, Ativan, and Xanax, meet all three criteria; they are sedative, hypnotic, and anxiolytic. The *DSM–IV–TR* stated, "The sedative-, hypnotic- and anxiolytic (antianxiety) substances include the BZs, BZ-like drugs such as zolpidem and zaleplon, the carbamates (e.g., glutethimide, meprobamate), the barbiturates (e.g., secobarbital), and the barbiturate-like hypnotics (e.g., glutethimide, methaqualone)" (p. 284).

The *DSM–IV–TR* offers specific diagnostic categories for persistent disorders resulting from tranquilizing and sedating agents, including sedative-, hypnotic-, and anxiolytic-induced persisting *dementia* and sedative-, hypnotic-, and anxiolytic-induced persisting *amnestic* disorder.

In discussing the meaning of the diagnosis of substance-induced persisting dementia, the *DSM–IV* (APA, 1994) stated that

> this disorder is termed "persisting" because the dementia persists long after the individual has experienced the effects of the Substance Intoxication or Substance Withdrawal. (p. 169)

In the preceding discussion, the *DSM–IV* is very specific, as it is elsewhere, that "Substance-Induced Dementia can occur in association with the following classes of substances: alcohol; inhalants; *sedatives, hypnotics, and anxiolytics*" (p. 169, emphasis added).

Confirmation of BZ-induced dementia is also reconfirmed in the *DSM–IV–TR* in its Table I: Diagnosis Associated With Class of Substances. Among 12 classes of substances, only 3 are indicated as causing persisting dementia: alcohol, inhalants, and sedatives, hypnotics, or anxiolytics. Only two are associated with amnestic (memory) disorders: alcohol and sedatives, hypnotics, or anxiolytics. The table indicates that BZs are in fact associated with the whole range of disorders that are also associated with alcohol, including dementia.

Thus the APA's committee of experts confirmed a scientific consensus in the field that the BZ drugs can cause dementia and that the dementia,

by definition, persists long after the exposure to the drug. I stress this point because so many prescribing health care providers fail to understand the long-term risk of BZ-induced dementia and because I have extensively evaluated several tragic cases of BZ-induced dementia that could have been avoided had the physicians been alert to the risk and stopped the medication.

## Research Indicating Persistent Impairment and Dementia From BZs

A number of studies have demonstrated that long-term exposure to BZs can produce persistent memory and cognitive dysfunction, including dementia (e.g., Ashton, 1984, 1995; Barker et al., 2004; Bergman et al., 1989; Berzele, 1992; Golombok et al., 1988; Lagnaoui et al., 2002; Petursson et al., 1983; Rickels et al., 1999; Tata et al., 1994).

Barker et al. (2004) found and evaluated 13 studies that employed neuropsychological tests to evaluate cognitive performance after long-term BZ use. Despite the limitations of the studies, they concluded, "The observation that long-term benzodiazepine use leads to a generalised effect on cognition has numerous implications for the informed and responsible prescription of these drugs." The study did not address the potential persistence of these negative effects following termination of drug exposure.

Tata et al. (1994) used psychometric tests to follow up 21 patients 6 months after abstinence from long-term therapeutic doses of prescribed BZs. They also examined 21 normal matched controls. Pre- and post-withdrawal and 6 months afterward, "the results demonstrated significant impairment in patients in verbal learning and memory, psychomotor, visuo-motor and visuo-conceptual abilities, compared with controls." Lagnaoui et al. (2002) found increased dementia in elderly patients treated with BZs in a community setting.

Several studies demonstrated brain dysfunction and damage in association with the use of BZs, usually in the form of enlarged cerebral ventricles associated with shrinkage or atrophy of the brain substance, sometimes in association with neuropsychological deficits (Bergman et al., 1989; Lader et al., 1984; Schmauss et al., 1987; Uhde et al., 1987). Schmauss and Krieg (1987) gave CT scans to 17 BZ-dependent in-patients and recorded a dose-dependent enlargement of cerebral ventricles. Bergman et al. (1989) found an increased frequency of dilated cerebral ventricles and intellectual impairments: "The results suggest that despite some neuropsychological improvement cerebral disorder diagnosed in patients abusing sedative or hypnotics is often permanent through the years and that neuropsychological status is linked to

long-term prognosis." Several mechanisms are involved in causing persistent changes in mental function from BZs, including reduced cerebral blood flow and reduced utilization of glucose, atrophy of the brain, and down-regulation of the receptors (Buchsbaum et al., 1992; Mathew et al., 1985; Mathew et al., 1991).

## OTHER MEDICATIONS FOR SLEEP

Although many health care providers have been misled by drug company promotional efforts, the great majority of sleep aids share the same risks as the BZs (see the appendix for a list). Almost all are placed in Schedule IV by the DEA to indicate a risk of abuse and dependence. According the DEA (2006), Ambien and Sonata (zaleplon) are "benzodiazepine-like CNS depressants."

For example, Ambien differs in chemical structure from the BZs but affects the same neurotransmitter system, GABA. The 2007 FDA-approved label for Ambien CR, available in the *Physicians' Desk Reference,* warns that

> a variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that seemed out of character), similar to the effects produced by alcohol and other CNS depressants. Visual and auditory hallucinations have been reported as well as behavior changes such as bizarre behavior, agitation, and depersonalization. Amnesia, anxiety and other neuro-psychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

Also according to the drug label, in brief, 3-week controlled clinical trials, patients developed hallucinations, disorientation, anxiety, depression, psychomotor retardation (mental and physical slowing), depersonalization, disinhibition, euphoric mood, mood swings, and stress symptoms. Hallucinations were reported in 4% of the Ambien patients and none of the placebo patients.

The label for Ambien CR also describes separate subheadings for the discussion of memory problems, tolerance, dependence, and withdrawal. Another subhead, "Changes in Behavior and Thinking," lists the following bulleted drug reactions:

- more outgoing or aggressive behavior than normal
- confusion

- strange behavior
- agitation
- hallucinations
- worsening of depression
- suicidal thoughts

Many health care providers probably have little idea about the range of psychiatric risks associated with these drugs or their powerful tendency to become spellbinding. On March 14, 2007, the FDA (2007c) issued a new warning for a broad range of sleep medications, including all those in the appendix: "complex sleep-related behaviors which may include sleep-driving, making phone calls, and preparing and eating food (while asleep)." Sleepwalking in some ways epitomizes spellbinding; the individual is wholly unaware of carrying out potentially dangerous activities.

## DEPENDENCE AND WITHDRAWAL

In recent years, the FDA-approved labels for Xanax and Xanax XR have carried extensive warnings about dependence (addiction) and withdrawal. The Xanax XR label found in the 2006 *Physicians' Desk Reference* warned that dependence occurs in small doses over short periods of time. The label described both withdrawal and rebound symptoms, with interdose withdrawal occurring when the effect of each dose wears off during the day or on awakening in the morning. It reported a broad array of withdrawal reactions based on controlled clinical trials: heightened sensory perception, impaired smell, impaired concentration, clouded sensorium [mind], parethesias, muscle cramps, muscle twitch, diarrhea, blurred vision, decreased appetitive, and insomnia. Anxiety and insomnia were also reported as withdrawal symptoms, but the label suggests that these were difficult to separate from the patients' original psychiatric disorders. In reality, the abrupt surfacing of anxiety and insomnia on withdrawal from BZs is commonplace and well established by clinical experience and a variety of studies (e.g., Marks et al., 1989).

The label reported that severe withdrawal reactions made it impossible for many patients to stop taking the medication after the termination of controlled clinical trials. In two clinical trials of only 6 and 8 weeks duration, 7% and 19%, respectively, of patients were unable to withdraw. These are very high rates for the inability to withdraw from a drug after very short exposures.

Earlier in the chapter I pointed out that the Xanax label also carried many warnings about adverse psychiatric effects such as disinhibition, depression, and mania. I suspect that many physicians reading these new

labels would think twice about prescribing the medication. The manufacturer, Pharmacia & Upjohn, apparently came to the same conclusion because they decided not to include any information about Xanax or Xanax XR in the 2007 *Physicians' Desk Reference* (*PDR*). The *PDR* is the major source of data for health care providers concerning medication adverse effects. As a result of removing Xanax and Xanax XR from the *PDR*, the drug company protected its valuable products from medical scrutiny, leaving many prescribing physicians to fly blind, guided only by vaguely recalled older misinformation about the relative safety of Xanax.

Among the BZs used primarily for the treatment of anxiety or panic, alprazolam has an especially bad record. In the field of drug addiction, Xanax is the most frequently implicated psychiatric drug (Breggin, 1991b). Often, it occurs in cross-addiction with alcohol and other sedatives. Withdrawal problems and rebound increases in anxiety and panic were so extreme in key studies used for FDA approval of Xanax for panic disorder that many or most patients had more frequent or severe symptoms at the end of the studies than before they took the drug, and many had trouble withdrawing (Marks et al., 1989; reviewed in Breggin, 1991b).

In regard to short-acting BZs such as Xanax and Halcion, the American Psychiatric Association (1990a) Task Force task force report on BZs made the following observations:

> Abrupt discontinuation of short half-life benzodiazepines leads to rapid drug removal from the blood and brain, rapid uncovering of the receptor site, and relatively rapid onset of post-drug discontinuation syndromes.... Because of the severity of symptoms related to its half-life, short half-life benzodiazepines given for anxiety are frequently implicated in intense discontinuation syndromes.... With very short half-life drugs such as triazolam, rebound symptomatology has actually been described during the period of ingestion, especially when it is given nightly. (pp. 39–40)

Although Xanax is among the worst offenders, all BZs can cause serious withdrawal problems. The APA (1990a) task force presented a table of discontinuation symptoms. The complete list of *frequent* discontinuation symptoms includes "anxiety, insomnia, restlessness, agitation, irritability, muscle tension" (p. 18). Among many symptoms that are *common but less frequent,* it lists "depression" and "nightmares" as well as "lethargy" (p. 18). Clinical experience indicates that the combination of anxiety, insomnia, restlessness, agitation, irritability, nightmares, and depression can produce a spectrum of behavioral abnormalities, including

suicide and violence. Adding to the dangers, the task force's complete list of *uncommon* symptoms includes "psychosis, seizures, persistent tinnitus, confusion, paranoid delusions, hallucinations" (p. 18). There are estimates that 50% or more of patients taking BZs in therapeutic doses over a year will become physically dependent, developing withdrawal symptoms on abrupt cessation (Ashton, 1995; Noyes, 1992).

Abrupt withdrawal from BZs can be extremely painful, both emotionally and physically, and even lethal in the case of uncontrolled seizures. It is unclear if gradual withdrawal merely extends the process over time, rather than avoiding it (Noyes, 1992); but gradual withdrawal does help to protect against severe seizures.

Many symptoms can take weeks or months to fully subside, leaving the patient with prolonged anxiety or depression (Ashton, 1995). Sometimes the withdrawal symptoms never completely subside. I have treated patients who have not regained their predrug condition many years after stopping BZs. Some have suffered from permanent memory problems, difficulties with concentration, and other cognitive impairments. They have felt depressed and emotionally unstable. Some have continued to suffer from poor fine motor coordination, muscle cramps, and parethesias. A few cases have suffered from a little-known long-term effect, peripheral neuritis with extreme pain, especially in the feet (for descriptions of severe BZ withdrawal and lasting aftereffects, see Breggin, in press). These effects are more accurately viewed as irreversible effects of BZ toxicity rather than as withdrawal reactions.

Severe withdrawal can occur after relatively short exposures to BZs. I have treated patients who suffered from severe withdrawal problems after only 2 weeks of low-dose exposure to prescribed alprazolam and clonazepam. Lader (1984) and the APA (1990a) task force confirmed that therapeutic doses commonly produce severe withdrawal symptoms.

Kales et al. (1991), in a placebo-controlled sleep lab study, showed that even under "brief, intermittent administration and withdrawal" of triazolam (and, to a lesser extent, temazepam), patients experienced rebound insomnia, "thereby predisposing to drug-taking behavior and increasing the potential for drug dependence."

Some patients can find it difficult to withdraw from as little as 0.5 mg clonazepam each night for sleep. Even motivated patients have sometimes developed such a fear of trying to go to sleep without BZs that they cannot undertake a serious effort. The fear is usually based on previous disturbing experiences of rebound insomnia.

Physicians erroneously prescribe BZs in ever-increasing doses, mistakenly thinking that their patients' anxiety was spontaneously increasing, rather than rebounding from the drug. Even if the ultimate dose remains within the recommended range, patients can roller coaster with

anxiety or other mental aberrations through each day between doses. The patients' lives can become devoted to finding the right drug and taking it at the right time.

It requires a physician's patience and understanding, and often a period of many months, to wean some individuals from the BZs. At the end of the weaning, patients may discover that nearly all of their supposedly psychiatric symptoms were in fact drug induced. The general principles of drug withdrawal in outpatient practice are discussed in greater detail in chapter 15. Patients taking large doses of BZs may need detoxification in a hospital setting.

Patients who have not been properly monitored by physicians may end up taking large doses of BZs for prolonged periods of times. Their daily lives may cycle from periods of excessive sedation, when they appear drunk, to periods of hyperarousal and anxiety as they undergo partial withdrawal. Friends and family may attribute their symptoms to mental illness until, for example, the patient begins to stumble about in a drunken manner or collapses in a stupor after only one alcoholic drink during a holiday dinner. In retrospect, it will be apparent that the patient was medication spellbound for months, too intoxicated to properly evaluate his or her own condition or to exercise judgment in regard to the drug's effects. Often, the patient's memory for the period of time will be severely impaired. Sometimes he or she will have committed irresponsible and even illegal acts (Breggin, in press).

## CONCLUSION

The BZs are frankly brain-disabling drugs. Much like alcohol, their clinical effect is no different from their toxic effect—a continuum of suppression of neuronal function, leading eventually to sleep or coma. The sought-after reduction of anxiety or induction of sleep is the direct result of impaired central nervous system function.

These drugs are also extremely spellbinding so that individuals frequently become mentally and even physically disabled without fully recognizing their deterioration and without attributing it to the medication. Instead, they feel compelled to take more and more psychiatric drugs in a fruitless, self-defeating effort to end their suffering.

BZs can produce a wide variety of abnormal mental responses and very hazardous behavioral abnormalities: rebound anxiety, insomnia, psychosis, paranoia, violence, antisocial acts, depression, and suicide. They impair cognition, especially memory, and can cause confusion. There is strong evidence that they produce persisting memory dysfunction, dementia, and shrinkage of brain tissue reflected in ventricular dilation.

These drugs commonly cause abuse and dependence (addiction), and even in relatively short-term use at relatively small doses, they can produce severe withdrawal syndromes. Because the withdrawal symptoms are so distressing, many patients cannot stop taking these drugs. After stopping the medication, some individuals never fully recover from their toxic effects, including memory and cognitive problems, impaired fine motor coordination, emotional instability, fatigue, and painful cramps or peripheral neuritis.

Mixed with alcohol and other sedatives, their hazards multiply, and unintentional fatalities are possible. Successful suicides involving BZs, especially those drugs prescribed as sleeping medications—Halcion, Dalmane, and Restoril—are much more frequent than commonly realized by physicians.

Although the shorter-acting BZs such as Xanax (alprazolam) and Halcion (triazolam) seem to be the most toxic and most prone to cause dependence, any BZ can cause these untoward effects, including the commonly used Klonopin (clonazepam) and Ativan (lorazepam). Overall, the BZs and many related medications used to treat anxiety and insomnia are potentially very brain disabling and spellbinding, and entail much graver risks than commonly recognized by health care providers and their patients.

## NOTES

1. The data on the half-life were compiled from varying sources and should be considered rough estimates. *Half-life* is the time when 50% of the drug or its active metabolites have been eliminated.
2. Attorney Michael Mosher of Paris, Texas, directed me to the significance of the Versed data.
3. In dechallenge, the drug is withdrawn to see if the adverse reaction then stops.
4. In rechallenge, the drug is given again to see if the adverse reaction can be repeated.

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CHAPTER 13

# The Food and Drug Administration (FDA) and the National Institute of Mental Health (NIMH)

## *Drug Company Advocates*

By now, the reader may be asking, How does the Food and Drug Administration (FDA) allow such dangerous and often ineffective psychiatric drugs to reach the market? In reality, the FDA has been subject to considerable criticism and scrutiny over the years from the U.S. Congress and the media (summarized in Shulman et al., 1995), including allegations that the FDA is becoming more protective of drug companies (Skrzychi, 1996).

Since the publication of the 1997 edition of this book, criticism of the FDA has heated up considerably. In the past few years, a series of regulatory failures, highlighted by the discovery that the pain medication rofecoxib (Vioxx) and the diabetes treatment rosiglitazone (Avandia) boost the risk of heart disease, has led to increased criticism of the FDA.

A *New York Times* article was aptly headlined "At F.D.A., Strong Drug Ties and Less Monitoring" (Harris, 2004). Describing the travail of FDA whistle-blower David Graham concerning Vioxx, the editor of the *British Medical Journal* asked, Is drug regulation failing in the United States (Abbasi, 2004)? In 2004, the FDA came under fire from Congress for its handling of SSRI-induced suicidality, especially in children and youth (Rosack, 2004).

In 2005, Jerry Avorn wrote a prospective in the *New England Journal of Medicine* titled "FDA Standards—Good Enough for Government

Work?" Avorn pointed out that most of the FDA's energy was wasted on forcing the industry to jump through hoops on issues that had little to do with whether or not the drugs would help people. Then, in September 2006, the Institute of Medicine of the National Academy of Sciences, a government-sponsored organization, criticized the unresponsiveness of the agency to potential drug risks and recommended, for example, that the FDA review the postmarketing safety data of each drug every 5 years. It also sought to give the agency more power to force companies to "complete required safety studies" (Harris, 2006b). The FDA itself, after decades of criticism, is reexamining the issue of how many of its advisory committee members have drug company ties (Harris, 2006a), but it seems unlikely that the agency can disentangle these ties without unraveling the entire psychopharmaceutical complex.

The FDA responded by proposing a few minor changes, including an experimental program to review the safety of two or three drugs each year after they have been on the market for 18 months. The agency also declared its intention to start an online newsletter that would publish the safety reviews generated by the pilot program. Meanwhile, the FDA plans to continue its policy of withholding confidential, commercial data—that is, the sealed information necessary to determine if the companies are telling the truth about their commercial products. *The Wall Street Journal* commented that this is "a move likely to please the drug industry" (Mathews, 2007a). Unfortunately, the drug industry's pleasure comes at the expense of human lives.

In March 2007, a study commissioned by the FDA came out with similar conclusions to mine. The FDA had hoped the study would exonerate the agency, but instead it lamented the culture of conflict, avoidance, and waste inside the FDA when it comes to tracking adverse drug reactions (Mathews, 2007b).

Marcia Angell (2007), former editor of the *New England Journal of Medicine* and now senior lecturer at Harvard Medical School, raised the basic question: Who does the FDA represent, consumers or industry? In a column titled "Taking Back the FDA" in the *Boston Globe* on February 26, 2007, she concluded that the FDA was becoming more dedicated to serving the companies than to serving the consumer of psychiatric drugs.

The public may be catching on. A recent *USA Today* editorial headline summed up the national outcry: "Our View on Pharmaceutical Safety: Latest Drug Scare Shows Need for FDA Overhaul" (Our view on pharmaceutical safety, 2007). Americans need to know that the FDA is not their friend. It is the friend of the pharmaceutical industry.

Much of the tightening of FDA regulations over the years has been in reaction to disasters and tragedies. For example, in 1937, over 100

people, mostly children, died due to poisoning with an organic solvent used in the liquid form of the antibiotic sulfanilamide. In the following year, Congress passed the federal Food, Drug, and Cosmetic Act. The early legislation made requirements for safety, but not for efficacy.

In the early 1960s, thalidomide, a sleeping medication with no special advantages in regard to efficacy, caused an epidemic of birth defects. In 1962, the Kefauver–Harris amendment strengthened the FDA drug approval process to include controlled trials to demonstrate clinical efficacy. The amendment also required manufacturers to submit proof of efficacy for all drugs marketed between 1938 and 1962. In *The Therapeutic Nightmare,* Mintz (1965) provided a critical analysis of FDA functioning up to that period of time. In short, criticism of federal drug monitoring has been going on for a long time, with mixed success in reforming the agency, which too often panders to the needs of industry.

## GAINING APPROVAL TO MARKET THE DRUG

The FDA has evolved a complex plan for each drug application, beginning with animal experimentation and proceeding through four phases of human experimentation (Food and Drug Administration [FDA], 1977; Jorgensen et al., 1992). Phase 1 and Phase 2 involve experimentation with animals and human volunteers and early clinical testing to determine if larger and more elaborate clinical trials are warranted or safe.

In Phase 3, controlled clinical trials are used to compare the drug to placebo and to previously approved, similar medications. At least two of the controlled studies must show a statistically significant positive effect from the drug. A few thousand patients are usually involved in the total database developed during the psychiatric drug approval process, but this number is misleading. It includes almost everyone who has taken even one dose of the drug. Only a few hundred patients may be involved in the Phase 3 controlled clinical trails that the FDA finds adequate for evaluating efficacy, and many of these subjects have usually dropped out before completion of the trials (Breggin et al., 1994a).

The entire drug development process in the past could easily take 10–12 years, giving the public and the profession the misleading impression that the actual clinical studies were themselves very lengthy. Most of these years were spent completing various FDA requirements that did not directly pertain to clinical studies. Several years were often spent by the FDA itself in evaluating the company's new drug application (NDA),[1] a process the FDA is now speeding up (see DiMasi et al., 1994). But the actual clinical trials for psychiatric drugs usually last a mere 4–6 weeks.

## DEMONSTRATING EFFICACY BEFORE THE DRUG IS MARKETED

All of the studies involved in the FDA approval process are designed completely by the drug companies and conducted by physicians hired and paid for by them. Would physicians be rehired if they regularly failed to churn out positive results? In complex studies involving human beings, statistics can, of course, be endlessly massaged until a seemingly significant result is generated irrespective of what actually occurred. To prove that a drug is an effective antidepressant, for example, the company needs only to develop two positive studies, even if innumerable others are entirely negative. This regulatory policy is not consistent with the canons of science or statistical analysis. As we found in chapter 7 in regard to the testing of antidepressants, when all of the trials are taken into account, antidepressants do not prove to be significantly better than placebo.

The main concern of this book is safety, rather than efficacy, but the flaws in these trials (see subsequent discussion) will obviously affect both.

## CREATING THE LABEL FOR THE DRUG

The FDA approval process is about creating and obtaining a label for the marketing of the drug. The approval of the label by the FDA is the final step in the process before the government allows the drug to go to market.

Before approval of the label, the FDA negotiates with the pharmaceutical company concerning its contents. After approval, the label appears in package inserts. It is published by the drug companies in the *Physicians' Desk Reference (PDR),* a commercial book sent free to all practicing physicians and found in most treatment facilities and doctors' offices. A shortened form of the label with emphasis on adverse effects must be included in advertising and promotional materials.

The FDA-approved drug label is very important, especially in regard to defining dangerous side effects. Physicians often use the *PDR* to alert themselves to the dangers of drugs. Typically, it is the first place that physicians look when they have a question about a drug. Reviews in the literature are frequently based on it as well.

Phase 4 spans the entire period of time after the drug has been approved and entered the market. Phase 4 studies are implemented when the FDA requests a drug company to examine newly discovered drug hazards. In my interviews with FDA officials, they agreed that this crucial

process tends to be given relatively low priority compared to the approval process. They attribute this to congressional and consumer priorities (see Government Accounting Office [GAO], 1990). On occasion, drug companies simply neglect to pursue Phase 4 trials suggested to them by the FDA. For example, Eli Lilly never conducted Phase 4 trials on Prozac-induced suicidality, even though the agency had required it and the drug company had agreed to it. The FDA, in turn, did nothing to force Eli Lilly to comply with its demand.

## MONITORING AFTER DRUG APPROVAL

After the drug has been marketed, the FDA remains responsible for reacting to new information. It can remove a drug from the market if it proves too hazardous. It can also require a drug manufacturer to add newly recognized adverse drug reactions to a label or to strengthen the information concerning known adverse reactions.

The American Medical Association lobbied Congress to make sure that after a drug is approved, physicians are not legally bound to follow the FDA guidelines. In the case of Prozac, for example, physicians quickly began giving it to children, even though it was not approved for them. Drug companies are not allowed to promote their drugs for unapproved purposes but often do so on the sly through their sales forces.

## CONTINUING DRUG COMPANY RESPONSIBILITIES

After the FDA approves a drug, the companies have continuing responsibility to inform the FDA about adverse drug reactions discovered after marketing of the drug. The drug companies are also required to monitor the scientific literature concerning their medications and to report adverse drug reactions found in that source as well.

In some product liability cases in which I have been a medical expert for the plaintiff, drug companies have tried to claim that the FDA holds ultimate responsibility for the information that the company places on its label and, in particular, that the drug company cannot make changes to a drug's label without prior FDA approval. This is not true. Every pharmaceutical company is empowered by law to make changes to its drug labels without prior FDA approval, provided that the changes will "add or strengthen a contraindication, warning, precaution, or adverse reaction" or "add or strengthen a statement about drug abuse, dependence, or overdosage." The company can also "delete false, misleading, or unsupported indications for use or claims for effectiveness" (*Code*

*of Federal Regulations,* 1995, 314.70c, p. 124) without prior FDA approval. Thus each drug company retains responsibility for making sure that its drug labels are as current and accurate as possible concerning risks and hazards, even to taking unilateral action to upgrade safety aspects of its labels without prior FDA approval. After the company has made and published the change, the agency may then evaluate it to its own satisfaction.

## TESTING SAFETY BEFORE THE DRUG IS MARKETED

The media often treat the pronouncements of scientists and the results of scientific research with an aura of naïve and undue respect. Scientific endeavors are conducted by ordinary human beings, many of whom come burdened with heavy biases and overwhelming financial interests. Especially in the field of human sciences, where complexity is made infinite by the interaction between human nature and society, bias easily runs rampant. Nearly all the research conducted in the area of psychiatric drugs is funded, designed, and conducted by drug companies or their close associates and allies, eliminating any hope of obtaining unbiased results.

Fortunately, there are signs of a growing awareness in the media that science per se cannot necessarily be trusted (Hotz, 2007). Researchers have also begun to challenge the myth of scientific objectivity. John Loannidis (2005) published an essay titled "Why Most Published Research Findings Are False." He pointed out, in effect, that most research findings do not reflect reality as much as they reflect "prevailing bias" in their field. This is nowhere truer than in psychiatry, where bias rules and drug-company and professional interests reign triumphant.

Focusing on a scientific issue that is critical to psychiatric drug treatment, too much faith can be placed in premarketing clinical trials as a method of detecting adverse drug reactions. For example, it can be mistakenly assumed that controlled clinical trials are the paradigm of scientific investigation. In my forensic experience, drug companies have defended themselves in product liability cases by arguing that only a controlled clinical trial can prove the existence of an adverse drug reaction. This is a mistaken interpretation of the nature of science and scientific conclusions. (For an extensive review of drug product liability issues, including FDA–manufacturer relationships and responsibilities, see Dixon, 1995.)

In reality, proving safety in clinical trials for FDA drug approval is an even more flawed process than proving efficacy. Often, serious and even fatal reactions will not be detected in the studies used for drug approval.

In the past, the FDA (1995) itself has been vocal about the limits of premarketing testing and about the importance of the supposedly less scientific postmarketing spontaneous reporting system (SRS) in which

professionals like doctors and pharmacists, as well as concerned consumers, send in reports of possible adverse drug reactions. In the mid-1990s, the agency briefly stepped up its efforts to inform physicians and other members of the health community that drug approval by no means guarantees that all serious side effects have been detected and that more attention needs to be given to spontaneous reports generated after the drug has reached the market. The FDA distributed a dramatic white on black poster with the following point emblazoned on it:

> When a drug goes to market, we know everything about its safety. Wrong.

The FDA's June 1995 publication "A MedWatch Continuing Education Article" replicated the poster and made the following points in a section called Limitations of Premarketing Clinical Trials:

*Short duration*—effects that develop with chronic use or those that have a long latency period are impossible to detect

*Narrow population*—generally don't include special groups, (e.g., children, elderly), to a large degree and are not always representative of the population that may be exposed to the drug after approval

*Narrow set of indications*—those for which efficacy is being studied and don't cover actual evolving use

*Small size* (generally include 3,000 to 4,000 subjects)—effects that occur rarely are very difficult to detect.

The FDA (1995) made the following point concerning the probability of detecting an adverse reaction:

> Clinical trials are effective tools primarily designed for assessing efficacy and risk-benefit ratio, but in most cases they are neither large enough nor long enough to provide all information on a drug's safety. At the time of approval for marketing, the safety database for a new drug will often include 3,000 to 4,000 exposed individuals, an insufficient number to detect rare adverse events. For example, in order to have a 95% chance of detecting an adverse event with an incidence of 1 per 10,000 patients, an exposed population of 30,000 patients would be required.

The director of the FDA's MedWatch program, Dianne Kennedy (Kennedy et al., 1993), wrote:

> The safety profile of a drug continually evolves over time. Clinical trials that precede product approval typically include safety data on only

> a few thousand patients. New information is expected to be discovered as a drug is used in larger and larger populations, in subgroups not studied during the clinical trials (e.g., pregnant women, the elderly), or in patients with numerous medical conditions taking multiple other medications.

Writing in the *Journal of the American Medical Association* on behalf of the FDA, former Commissioner David Kessler (1993) declared:

> Even the large, well-designed clinical trials that are conducted to gain premarket approval cannot uncover every problem that can come to light once a product is widely used.... If an adverse event occurs in perhaps one in 5000 or even in 1000 users, it could be missed in clinical trials but pose a serious safety problem when released to the market.

In *The Pharmacologic Basis of Therapeutics,* Alan Nies (1996) made a similar point:

> Since only a few thousand patients are exposed to experimental drugs in more or less controlled and well-defined circumstances during drug development, adverse drug effects that occur as frequently as 1 in 1,000 may not be detected prior to marketing. Postmarketing surveillance of drug usage is thus imperative to detect infrequent but significant adverse effects. (p. 57)

To pursue Kessler and Nies's point, assume as a hypothetical example that Prozac causes suicide in 1 in 1,000 patients. If this were true, among the first 5 million patients to take the drug, 5,000 would die by suicide. Yet the problem could have gone wholly undetected in the trials. This, of course, gives even more weight to the actual finding of Prozac-induced suicidality in the controlled clinical trials (chapter 6).

Paul Leber (1992), at the time director of the FDA's Division of Neuropharmacological Drug Products, addressed the limitations of premarket testing and the importance of postmarketing surveillance. He pointed out that "even the best designed and well-executed premarketing evaluation programs may fail to detect risks that can have extremely serious consequences for the public health." Again using the illustration of a drug testing program involving 1,000 patients, he observed, "There remains a 5% chance that the drug, upon marketing, might regularly cause serious, even fatal, injury to one in every 333 or so patients treated."

Thomas Laughren (1992), then the group leader of the psychiatric drugs section in Leber's division, reviewed the standards and also the

limitations or problems inherent in using clinical trials to determine adverse drug effects. (The standards can be found in Center for Drug Evaluation and Research, 1988; see also Castle, 1986; Leber, 1992; Peace, 1987.) After describing the small size and short duration of the premarketing clinical trials, Laughren (1992) concluded:

> It is important to acknowledge this limitation of the typical development programs and to recognize that careful postmarketing surveillance is the most feasible method for detecting the more infrequent adverse events occurring with the use of a new drug.

Because the trials err toward missing adverse reactions, Laughren suggested that the FDA should lean toward assuming a drug connection when adverse events occur in association with it.

Paul Leber (1992) also pointed out that the risks may be even greater than a statistical analysis indicates. Additional factors include the following:

1. The patients and volunteers in the study are not likely to represent a true sample of the people who will be treated once the drug is marketed.
2. The studies are quite brief.
3. There may be differences in postmarketing dosing.
4. The "unique combination of concomitant illness, polypharmacy, and compromised physiological status" of real-life patients treated after the drug is approved cannot be anticipated.

In regard to the final point, Leber stated:

> In any event, whatever the reasons, it is likely that Phase III testing ordinarily fails to reproduce the conditions of illness and polypharmacy that occur in actual clinical practice with market drugs, and this may generate a misleadingly reassuring picture of a drug's safety in use.

Leber (1992) concluded, "In sum, at the time a new drug is first marketed, a great deal of uncertainty invariably remains about the identity, nature, and frequency of all but the most common and acutely expressed risks associated with its use."

Karl E. Peace (1987), Director, Research Statistics, SmithKline and French Laboratories, pointed out that "it is frequently impossible to design trials to provide definitive information about safety—particularly about adverse events." He described occasions when it has been possible to design adequate safety studies, but concluded, "However, for most new drugs in clinical development it is not possible."

In recent years, the FDA has become increasingly defensive about its approval process and increasingly protective of the drug companies when they are accused of overlooking or hiding data concerning adverse drug reactions. As a result, the FDA has stopped emphasizing and publicizing the limits of the controlled clinical trials used to obtain the agency's approval.

## MORE SUBTLE DIFFICULTIES IN EVALUATING CLINICAL TRIAL DATA

There are other difficulties that further compromise the clinical trials used for FDA approval. For example, the FDA routinely allows the drug companies to winnow out patients who might respond to placebo before placing them randomly in either the drug or the control group of the placebo-controlled clinical trial. During this so-called washout period, all of the potential subjects for the study are given placebo. If any of them improve on the placebo, and many usually do, they are dropped from the study. This then gives the drug an unfair advantage in comparison to the placebo in the subsequent placebo-controlled clinical trial, because the known placebo responders have been eliminated. Because placebo responders have been thrown out in advance, the drug is likely to look better in comparison to placebo than it really is. When I first discovered and wrote about this (Breggin et al., 1994), I could not believe that the FDA allowed this deceptive practice in testing psychiatric drugs and that drug "experts," all of them in the pocket of the drug companies, universally went along with the ruse. To this day, the FDA continues to condone this fraudulent science.

The numbers of subjects included in clinical trials is not nearly as large as the drug companies sometimes claim and doctors sometimes believe. While a thousand or more patients may enter the controlled clinical trials, the FDA will throw out many of the studies as scientifically invalid. In addition, not all of the patients will finish the trials that the FDA considers valid. Many subjects will drop out because they haven't been helped or because they have experienced distressing side effects.

The gap between drug company claims and reality can be enormous in regard to the numbers of patients tested. Eli Lilly, for example, gave the impression that between 6,000 and 11,000 patients had been given Prozac during the FDA approval process. When I laboriously reviewed each of the Prozac studies that the FDA considered valid enough to use for approval, I discovered that a total of only 286 patients had completed them (Breggin et al., 1994).

The ability to discern adverse effects is compromised by the fact that many of the individual studies may be relatively small, involving only a

few dozen patients or less. One principal investigator, for example, may supervise a project involving only 20 or 30 patients, half of whom are taking the placebo. He or she then sends in a report to the drug company, where its staff takes on the ultimate task of looking over the entire database from all of the investigators in search of patterns of adverse drug reactions. Even in the smaller clinical trials, the patients are not all taking the drug at the same time. Patients are included in the trial as they become available and sign up over a period of weeks or months. Some are starting the trial long after others have finished it. The principal investigator and associates are therefore not able to survey the group altogether or all at once but must rely on memory and on records to discern patterns of adverse drug reactions. They must do this over an extended period of many months while preoccupied with many other unrelated professional activities.

If an unexpected adverse reaction were to appear only once in one of the smaller projects, the local clinical investigator might easily miss its significance. He might not even bother to report it. For example, worsening of depression might easily be attributed to the patient's illness, rather than to the antidepressant drug, and go unreported as an adverse drug reaction. A seemingly bizarre abnormal movement may be attributed to the patient's schizophrenia, rather than to a drug-induced neurological disorder, and again go unreported.

Individual projects and investigators will also vary in their approach to evaluating adverse reactions. The ultimate database is not drawn from one consistent source, but from the variable efforts of different investigators often operating under somewhat different experimental protocols and with markedly different subjective perceptions.[2]

Leber (1992) addressed some of these issues when he stated:

> Finally, of course, clinical testing during premarket development may fail to detect drug associated risks for any number of commonplace reasons: poor or careless technique, uncooperative patients, incompetent professional staff, clerical mistakes, etc. Indeed, even in closely monitored inpatient environments, it would be naive to believe that every adverse event that occurs is observed. Further, even if an untoward clinical event is observed, there is no certainty that it *will* be recognized as drug related, or if it is, that it *will* be subsequently recorded and/or reported.

Especially for readers who have not been exposed to scientific research, the phrase *controlled clinical trials* is likely to conjure up something much more rigorous than individual patients signing up at various times in a doctor's office or in a clinic for an opportunity to participate in

a project that is probably being supervised and conducted by the doctor's assistant or nurse.

The treatment subjects in most controlled clinical trials used for FDA approval are not sequestered on a hospital ward. They return home to their everyday lives, including whatever undisclosed psychological or physical problems they may harbor and any legal or illegal drugs which they may take without informing the investigator.

Clinical experience and various studies have shown that patient compliance is spotty in regard to taking drugs at home. Rarely can the investigator be sure that the patient is taking the drug in question at all, let alone in the prescribed fashion. Efforts are seldom made to detect the drug in the subject's blood or urine to confirm that it has been taken. If an individual has signed up for the study to earn money rather than to seek a cure, he or she may have little motivation to risk taking the potentially dangerous drug.

The pool of individuals who sign up for drug testing has not been given adequate consideration in evaluating the usefulness of clinical trials. Often, the subjects are obtained from newspaper and radio advertisements that invite members of the public to sign up for a clinical trial for a new drug for anxiety, depression, phobia, or some other named disorder. Sometimes flyers for the trial are distributed at meetings or conferences of patients who suffer chronically from these disorders. The individuals to whom these promotions will appeal may be desperate for money, desperate for therapeutic relief, or both. Why else would they go into an unfamiliar setting to risk taking an experimental drug whose safety and efficacy have not been demonstrated? Their need to be in the experiment may influence what these subjects tell the investigators about their past histories as well as their responses to the drugs. Their hope for a cure or their desire to please the doctors may influence their own perceptions and communications (see subsequent discussion for recent pertinent disclosures).

The placebo control does not ensure that either patients or doctors will in fact remain blind to what the patients are getting. A drug like Prozac or Paxil, for example, often causes stimulating side effects such as nervousness and insomnia, enabling the investigator to guess that the individual is taking the drug rather than the placebo. Similarly, a drug like Zyprexa or Risperdal will cause patients to become inexpressive and sluggish, again making it easy to distinguish those who are taking the drug from those who are not. Fisher and Greenberg (1989) made the point that there are very few truly blind studies, even when controls are carefully implemented. The failure to keep the study blind may easily play into the patient's or the investigator's need to make a positive evaluation of the drug in regard to both safety and efficacy.

Since the individual drug trials are too small, too short, and otherwise inadequate to the task, it remains the ultimate responsibility of the drug company to go through the complete, combined database in search of patterns of adverse drug reactions. Even if drug companies were properly motivated, there is no foolproof way to oversee the entire group of several thousand patients.

Controlled clinical trials are not inevitably scientific. They may meet the canons of science, or they may not, depending on their structure and on how they are carried out. But even if they are performed to a high standard, they still do not by themselves prove anything. Their data must be scientifically interpreted—that is, subjected to reasoned analysis.

As the FDA has made clear, a reasoned analysis discloses that the controlled clinical trials used in the FDA process have grave limitations in regard to the detection of adverse drug effects. The FDA came to this conclusion without discussing some of the more subtle issues I have raised in this chapter.

## OTHER NEGLECTED AREAS IN THE FDA APPROVAL PROCESS

There are some obvious oversights in the FDA requirements imposed on drug companies, including some specific areas that are wholly neglected. First, the FDA does not require drug manufacturers to demonstrate through animal (or human) research that the brain recovers from any of the various biochemical imbalances and other malfunctions produced by every psychiatric medication. Information is frequently provided to the FDA concerning the impact of the drug on neurotransmitters and other brain functions in animals, while no information is provided concerning the potential for recovery. All of the neuroleptics and antidepressants as well as lithium produce profound changes in brain function during treatment, but to this day, there has been little research on the recovery of these functions (see chapter 6 in regard to Prozac; see also Breggin et al., 1994a).

Second, the FDA does not require intensive neuropsychological testing of human subjects to document cognitive impairment or other brain dysfunction associated with drug treatment. There is no follow-up to determine if cognitive and other functions return to normal after termination of drug treatment. For example, it took independent postmarketing studies to show that antidepressants (chapter 6) and lithium (chapter 8) can impair cognition.

Third, the FDA does not require the drug company to show that any patients actually recover from their psychiatric disorders as a result

of drug treatment. Instead, all measures aim at demonstrating relative degrees of improvement in comparison to placebo or other medications. To get into an antidepressant study, subjects typically must be shown to suffer from major depression, and to get into a neuroleptic study, they must be shown to suffer from schizophrenia. However, they are not usually evaluated at the end of the study to determine whether or not they have partially, largely, or fully recovered from depression or schizophrenia. Instead, improvement on a few items on a symptom checklist is usually sufficient to determine a positive outcome. Thus the drug companies avoid asking potentially embarrassing questions about actual recovery. In reality, drug treatment almost never leads to recovery, and that is why the drug companies never use recovery as one of the standards for evaluating treatment.

Fourth, for a drug to be approved, there is no requirement that the patients rate themselves improved as a result of it. Checklist ratings by outside observers, that is, drug company–paid researchers, are sufficient evidence for FDA approval, even if the patients rate themselves no more improved on the drug than on placebo. In many instances, psychiatric drugs are approved despite the fact that patient self-ratings do not indicate improvement.

Fifth, where there are known and even extreme risks in association with a particular class of drugs, the FDA does not require that the drug company specifically determine the new drug's risk in regard to these known dangers. For example, neuroleptics cause tardive dyskinesia (TD) and neuroleptic malignant syndrome (NMS). Yet, during the approval process of new neuroleptics, the companies are not required to demonstrate the specific risk that the new drug poses in regard to TD or NMS. A class warning may be required, for example, for TD or NMS, but there will be no requirement to test for the possibility of an increased risk with the new agent.

Finally, the FDA does not conduct any drug studies on its own. It relies entirely on research produced, monitored, and financed by the pharmaceutical companies. In the old days, thousands of hard-copy pages would be submitted in numerous cartons to the FDA for the agency to examine while hundreds and hundreds of cartons of background material remained unexamined at the company headquarters. Nowadays, the material is sent to the FDA in digital form, but the effect is the same. The FDA is inundated with pages of information, but a mountain more remains untouched by agency eyes. In *Talking Back to Prozac* (Breggin et al., 1994a), and more recently in my reports about Paxil (Breggin, 2006a–c) I have documented the far-reaching negative consequences of the FDA's dependence on data generated, collected, and analyzed exclusively by drug companies themselves.

## THE PROFIT MOTIVE

While the FDA has procedures for monitoring the drug companies during their application for new drug approval, the validity of the process nonetheless rests on the ethical and scientific integrity of the corporations. Drug companies have a strong financial incentive not to focus their attention on discovering or reporting adverse drug reactions that might threaten the approval of their product or cause future legal liability. They often fight hard against the passage of tougher FDA regulations and sometimes try to evade them after they are put into effect.

In reading drug company in-house communications and depositions, it is apparent that the overriding concern is to market a drug that makes a profit. When an adverse drug reaction becomes a public scandal, for example, the tendency is to campaign against the bad image, instead of evaluating the actual danger. A researcher, marketing representative, publicist, attorney, or CEO does not overnight become devoted to the public good simply because he or she takes a job with a drug company. Some product liability attorneys have told me, to the contrary, that the highly competitive pharmaceutical industry seems especially self-protective.

For example, in reviewing an NDA for a product liability suit against a drug manufacturer, I discovered that a company official had written a memo recommending a comparative study between the company's drug and an older one. In the hope that his company's drug was safer, he wanted to compare the frequency with which the two drugs caused the same serious side effect. Penciled into one corner of his memo was a note from another company executive stating that it was a bad idea to ask questions whose answers might prove embarrassing. The study was never done.

Bias may affect a drug company's overall analysis of the patterns of adverse reports from the clinical trials. In my forensic experience, the methodology of the analyses may deviate drastically from the scientific process. In addition, if the conclusions seem to threaten the future of the drug, the conclusions may be modified or kept secret (see chapter 14). In general, drug companies have learned to employ many of what Scott (2006) called tricks of the trade to make clinical trials produce exaggeratedly good results.

## MONITORING SAFETY AFTER THE DRUG IS MARKETED

By 1969, the FDA developed a systematic approach to collecting and maintaining adverse drug reactions after marketing. For many years, it was called the SRS. The regulations were updated in 1985, and the system has been renamed MedWatch (for the basic regulations, see Johnson

et al., 1991; for critiques, see the various citations below). Anyone, including patients, can initiate an adverse report by writing to the drug company or the FDA. In the past, the vast majority came from physicians and from hospital pharmacists, but increasingly, consumers have been sending in reports.

Unlike in England, in America, there is no formal requirement or readily available mechanism for health professionals to make these postmarketing reports. Nies (1996) estimated that over 40% of doctors do not even know that they can report adverse effects directly to the FDA.

In addition to the larger numbers of patients involved and the longer treatment periods, the postmarketing SRS has a number of advantages over the premarketing clinical trials.

First of all, most of the pharmacists and physicians making the reports from the field, unlike those conducting the clinical trials, are not being directly paid by the drug companies. They are likely to have much less vested interest in retaining the drug company's goodwill.

Second, the largest portion of those who send in spontaneous reports are hospital pharmacists. They are working in institutional settings, where they can overview hundreds of patient experiences with the drug. They are in an especially good position to spot something requiring scrutiny.

Third, spontaneous reports are sent in by professionals who are evaluating the drug under more natural field conditions. These patients have not been prescreened by the drug company as they are before clinical trials. Many of the patients are receiving other drugs; suffering from physical illnesses; or taking large, and sometimes excessive, dosages of the drug. Adverse drug reactions are more likely to show up under these complex and often more hazardous conditions. For example, adverse drug reactions typically occur more frequently at doses in excess of those used in the clinical trials. Reactions to excessive dosages can provide a signal that these reactions are in all probability occurring at more standard doses as well, although less frequently or less intensively. Advanced age and infirmity, usually screened out and hence untested factors in clinical trials, are more likely to be encountered in general practice and can be bellwethers. Tricyclic antidepressants, for example, will cause life-threatening cardiovascular problems much more frequently in the elderly. Similarly, neuroleptics cause TD much more frequently among the elderly. Because the SRS includes a larger variety of patients taking a broader spectrum of doses, it is much more likely to disclose adverse reactions than a controlled clinical trial conducted for FDA approval of the drug.

Fourth, the professionals making the reports have been alerted, through their own experience and through reports in the literature, to initially unexpected adverse reactions. They have the benefit of increased clinical awareness as well as hindsight in identifying adverse drug reactions.

Physicians are also more likely to know their patients well compared to clinical trial investigators and, like family members, may be better able to notice personality changes and other more subtle adverse drug reactions. Also, physicians are more likely to be in touch with family members who are largely ignored during controlled clinical trials.

## The Impact of MEDWatch (the Spontaneous Reporting System)

In describing the impact of the MedWatch spontaneous reporting system (SRS), the FDA's Kessler (1993) said:

> In response to voluntary reports from physicians to the FDA or the manufacturer, the FDA has issued warnings, made label changes, required manufacturers to conduct postmarketing studies, and ordered product withdrawals that have ultimately prevented patient deaths and suffering.

The FDA (1995) MedWatch publication makes clear that the SRS is the most important source of postmarketing information on adverse drug reactions. It frequently leads to scientific determinations for the need to modify drug labels or to withdraw drugs from the market. According to a 1990 Government Accounting Office report, more than 50% of all drugs approved by the FDA between 1976 and 1985 were found during postmarketing to have previously undetected serious side effects, sometimes requiring removal from the market. Fifteen psychopharmaceuticals were approved during this period, nine of which turned out to have serious risks during postmarketing, leading, in one case, to removal from the market (GAO, 1990). Since then, additional psychiatric drugs have been withdrawn from the market. For example, the antidepressant nomifensine (Merital) was found to cause massive intravascular hemolytic anemia—but only after it had been on the market worldwide for 8 or 9 years (Leber, 1992). As another example, the widely used antidepressant nefazodone (Serzone) was approved in December 1994 and not withdrawn from the market for another 10 years because of causing fatal liver failure. At that point, the FDA had received 55 reports of severe liver failure, 39 cases of less severe liver failure, and 20 deaths attributable to Serzone (Rosack, 2004). Even then, the company and *not* the FDA made the decision to stop manufacturing the drug, in part due to a flood of product liability lawsuits against it. As a third example, pemoline (Cylert) was approved by the FDA for the treatment of ADHD in 1975 but was not removed from the market by the agency until 2005—a period of

three decades. By that time it had already been removed from the market in Great Britain in 1997 and in Canada two years later. Like Serzone, Cylert causes death due to liver failure.

In each of the above three cases, the FDA decision to withdraw the drug had nothing to do with data generated by controlled clinical trials. The decision was based on reports made to the FDA's spontaneous reporting system and clinical reports in the scientific literature.

In addition to the three more recent withdrawals of Merital, Serzone, and Cylert, I have also reviewed the entire list of serious adverse reactions to psychiatric drugs detected during the postmarketing period in the GAO (1990) study. It seems probable that every one of them was discovered and confirmed through a combination of the SRS, individual case reports, and general clinical experience. As far as I can ascertain, not one of these adverse reactions was primarily, if at all, identified by means of a controlled clinical trial. As a result of postmarket discoveries, alprazolam (Xanax) had rage added to the label as a paradoxical reaction, and amoxapine (Asendin) had NMS added.

More recently, the FDA did use controlled clinical trials to verify that antidepressants cause suicidality in children, adolescents, and young adults. However, glaringly bright signals already existed from multiple sources (chapters 6 and 7) before the FDA turned to the clinical trial data. Furthermore, the drug companies failed to detect a signal in these same clinical trials until forced to reevaluate them under FDA supervision in 2004–2006.

## Drawing Scientific Conclusions From the MEDWatch SRS

There are a number of approaches that can be used to confirm from spontaneous reports that a drug is actually causing the adverse reaction. Chapter 12 described how several FDA officials went about confirming for themselves a possible or probable causal relationship between Halcion (and Xanax) and various behavioral abnormalities, including violence. To confirm causality, some of the following factors are useful:

1. a disproportionately high frequency of reporting or disproportionately large number of reports in comparison to other drugs, especially in the same or similar class of medications
2. a meaningful or strong enough association, as reflected in epidemiological and clinical data
3. an absence of alternative explanations for the increased frequency or number of reports

4. reports indicating a temporal relationship between the adverse reactions and initial doses of the drug or increased doses of the drug
5. reports of dose-dependent reactions, that is, increased frequency or numbers of adverse reactions with higher dosages
6. reports of resolution of the adverse reaction following drug withdrawal
7. reports of positive rechallenge: the adverse reaction is provoked once again by resuming the drug
8. reports of adverse reactions in individuals with no predrug history of similar symptoms
9. corroborating clinical experience (published and unpublished)
10. data from clinical trials, including controlled trials
11. a rational medical and/or neurochemical explanation for a causal connection between the drug and the adverse reaction, and the corresponding absence of a better explanation

The Federal Judicial Center (Bailey et al., 1994) has proposed a series of criteria that compact many of the points I have made. The difference in approach is, in part, due to their epidemiological emphasis in contrast to my clinical emphasis. Drawing on Koch's postulates, they stated, "Seven factors should be considered when an epidemiologist determines whether the association between an agent and a disease is causal." Put in the form of questions, they list the following factors:

1. How strong is the association between the exposure and the disease?
2. Is there a temporal relationship?
3. Is the association consistent with other research?
4. Is the association biologically plausible?
5. Have alternative explanations been ruled out?
6. Does the association exhibit specificity?
7. Is there a dose–response relationship?

None of the above individual criteria is an absolute requirement for coming to a scientific conclusion. One must weigh the best available evidence and come to as sound a conclusion as possible. Commonly, or even typically, decisions with a high degree of probability will be made with an incomplete set of data.

While it would be helpful to have confirmation from controlled clinical trials, it is typically impossible to obtain it, even in regard to known or proven adverse drug reactions. As we have already seen, the absence of findings from controlled clinical trials involving a drug cannot be used

to rule out a causal connection between a drug and an adverse reaction. To illustrate this again, we turn, in the next section, to the stories of NMS and TD.

## FOUR APPROVAL SYSTEM FAILURES

### Failure to Recognize Neuroleptic Malignant Syndrome

Earlier in the chapter, I examined several dramatic failures on the part of the FDA to withdraw drugs from the market until the passage of years and even decades, despite mounting reports of potentially fatal adverse effects. This section examines how long it can take before flagrant adverse effects are even noted in the drug label.

NMS (see chapter 4) provides an example of how a devastating, common disorder can be wholly missed in the clinical trials during the approval process. It also illustrates how long it can take drug companies and the FDA to give formal recognition to such a disorder.

NMS is a potentially fatal reaction to neuroleptic drugs such as Haldol, Prolixin, Risperdal, Zyprexa, Seroquel, and Abilify. It occurs at a relatively high rate, developing in somewhere from 1.4% to 2.4% of patients exposed to the older neuroleptics and at significant rates to patients exposed to the newer ones (chapter 4). By contrast, a reaction that occurs 1% of the time is considered *common* or *frequent* by FDA standards. This particular reaction is extremely dramatic and therefore not easily overlooked. Yet NMS was entirely missed in one study after another conducted by drug companies when applying for FDA approval of neuroleptic drugs.

The failure to detect NMS in clinical trials cannot be attributed to the need for longer studies since an estimated 80% of NMS reactions develop within the first few weeks of treatment (Davis et al., 1991). Nor can the failure be forgiven on the basis of inadequate knowledge about the disorder. Suggestions of its existence began soon after the neuroleptic drugs went into use, and it was clearly identified in the English language literature by 1968 (chapter 4).

In 1986, nearly two decades after NMS had become an identifiable syndrome, the FDA at last began to force the drug companies to add the adverse drug reaction to their neuroleptic labels. Since the disease is fatal in approximately 20% of cases when it goes unrecognized and untreated, the failure to properly inform physicians cost many lives and untold suffering.

There are important lessons from the history of NMS. First, for many years, neither the FDA nor the drug companies came close to fulfilling

their ethical and legal obligations by warning physicians and by adding the disorder to the neuroleptic label. The drug companies did almost nothing until forced to act by the FDA. Both the FDA and the drug companies were much too late, causing unnecessary death and suffering. Second, the history confirms that clinical trials cannot be relied on by themselves to identify even common, obvious hazards such as NMS.

## The FDA Caves In to Industry on Tardive Dyskinesia

TD occurs with extreme frequency in neuroleptic-treated patients, including both the older neuroleptics and the newer so-called atypicals (chapter 4). Research on the older drugs has shown that in relatively young, physically healthy adults, 4% to 7% per year will develop the disease. After a total of 5 years' exposure, at least one-third will develop this largely irreversible, disfiguring, and potentially disabling movement disorder. In older patients, the rate may exceed an astronomical 20% or more per year. Patients taking the drug for a lifetime will approach a 100% risk. While the rates for TD from the newer neuroleptics remain controversial, there is no doubt that they frequently cause the disorder (chapter 4). In the face of such an astronomically frequent risk, why is there nothing in the current FDA-required warning label for neuroleptics to alert a physician or patient to the extraordinary frequency of the risk of TD?

The neuroleptic drugs were in widespread use by 1954, and TD was documented within the first few years (chapter 4). Yet, for nearly 20 additional years, the drug companies and the FDA failed to provide an appropriate warning on the label of neuroleptic drugs. In the early 1970s, the agency finally forced a very weak uniform label statement about TD on the drug companies. It gave no hint about the frequency of the disorder, mentioning only that "some patients" might get it.

Even as the tragic news about TD accumulated, the drug companies did little or nothing to update their labels. Then, on February 24, 1984, Paul Leber called a meeting of the FDA's Psychopharmacologic Drugs Advisory Committee (FDA, 1984) to discuss the agency's proposal for an updated uniform class warning label for all neuroleptics. Leber explained to the committee that public pressure had caused the FDA to re-examine the problem. This public concern about TD had been generated in large part by a CBS-TV Dan Rather report. I had given CBS an advanced manuscript copy of my 1983 book on psychiatric drugs. It inspired the Dan Rather show, and I consulted on planning the program. Along with the publication of my book, I had also done my best to flood the general media with information, including many personal appearances on radio and TV to discuss the danger of TD.

In the 1984 meeting, Leber proposed a version of the label that included specific numerical estimates to underscore the very high rates. Seven expert drug consultants confirmed the need for mentioning actual numbers, and an eighth sent in a report taking the same viewpoint. On the basis of the American Psychiatric Association (1980b) task force report, some of the experts recommended citing a 20% risk in routine neuroleptic exposure. Others suggested a figure of 15% in the first 4 years. Leber himself observed that extrapolating from the data indicated that over a lifetime, "100% of patients may in fact develop the disorder" (FDA, 1984, p. 54). These are most extraordinary estimates for the rate of contracting a drug-induced, irreversible, and potentially severe disorder.

Approximately 5 months after the meeting, in the summer of 1984, Leber sent a formal letter to all neuroleptic manufacturers, suggesting a revision of the proposed class warning label. By then, almost surely in response to industry pressure, the proposed language had already been watered down. Without mentioning any figures, Leber's proposed label stated that TD would develop in a "substantial portion of patients treated with neuroleptics" (P. Leber, unpublished letter, 1984, p. 3). The meaning of *substantial* was left up to interpretation.

The FDA's Pharmacologic Drugs Advisory Committee met a second time on January 31, 1985, to discuss TD. Leber again mentioned the impact of the "clamor from the press" in the fall of 1983—the date of Dan Rather's TV report and the simultaneous publication of my book.

Leber told the assembled representatives of the drug companies that he would not act without their endorsement or approval. He stated that he had been through "a year and a half of trying to bring about change in the labeling of neuroleptic products that would be fair and that would be *acceptable to everyone*" (FDA, 1985b, emphasis added).

Leber described to the meeting participants the elaborate back and forth negotiating that had already gone on between the FDA and industry. He said that one of his aims was to obtain "equitable labeling that *did not cause injury to industry,* as much as it also should not cause injury to patients or physicians who have to use neuroleptics under trying circumstances" (FDA, 1985b, p. 9, emphasis added).

Can the FDA perform a watchdog function without biting industry? Without even growling at them? If the process of identifying dangerous drug effects were painless to industry ("should not cause injury to industry"), industry would not need the FDA to regulate it. A properly functioning FDA would at times have to cause injury to industry through diminished revenues and other sanctions related to marketing dangerous drugs. The neuroleptics were being prescribed with too little regard for their devastating adverse effects; if the new warning label had done its

job, neuroleptic sales would, of necessity, have dropped. There is nothing in the FDA legislation that urges the agency to protect industry. It is supposed to protect patients, despite the inevitable painful results for industry.

By this second meeting, Leber and the FDA had surrendered to industry. The somewhat ominous phrase *substantial proportion* was replaced by the entirely innocuous phrase *some patients,* implying a minimal risk. Ironically, it was the same phrase that appeared on the outdated 1973 label. No change had been made.

Ultimately, *some patients* was also dropped. The warning on the current neuroleptic label states that TD "may develop in patients" treated with neuroleptics—not even a hint of a serious risk, let alone an astronomical one, with millions of victims. In the critical arena of TD rates, the class warning label is possibly weaker, although more detailed, than the old one.

Partly owing to the persistently inadequate label, too many ill-informed physicians and their patients continue to believe that the risk of TD is insignificant. Leber succeeded in causing little or no injury to industry—but at what cost to patients, their families, and the health care system? Since that time, Leber has retired and become a consultant to the pharmaceutical industry.

The story of the FDA's handling of warning labels for NMS and TD leads to a dismal conclusion. When it comes to warning about the dangers of psychiatric drugs, the FDA is more responsive to the profit needs of industry than to the safety needs of patients.

## Massaged Data: The Prozac Approval Process

In *Talking Back to Prozac* (Breggin et al., 1994a), I examined the overall FDA approval process in regard to Prozac, reconfirming that in regard to psychiatric drugs, the FDA is more concerned about industry goodwill than the public good. What follows is a small taste of what went wrong in the Prozac approval process.

As noted earlier in the chapter, although several thousand patients were involved in studies of various kinds, I counted only 286 who actually finished the three placebo-controlled protocols (groups of studies) used for approval. Many patients dropped out because of adverse stimulant reactions. Prozac seldom proved any better than placebo and was not as good as the older antidepressants. It was so stimulating that sedatives were often given along with it.

In perhaps the most important study, called Protocol 27, the results indicated that Prozac by itself had no efficacy. To get a positive result, the FDA had to allow the drug companies to include all the patients who,

against the rules, were also given sedative and tranquilizing medications with their Prozac.

Protocol 27 was conducted by several separate investigators at sites in different cities. The individual study sites could not show that Prozac was any better than placebo, so the FDA allowed the negative results to be pooled and manipulated until a positive result was barely achieved.

The FDA's Laughren (1992), in an analysis of the drug approval process, observed, "Pooling of effectiveness data from independent studies is not standard and must be done with great care." Protocol 27 was not only made up of independent studies conducted at separate centers, but almost all of them had negative results. Furthermore, in the pooling process, one center was dropped entirely, eliminating 25% of the original data.

Lilly employees Stark and Hardison (1985) eventually published Protocol 27 in the *Journal of Clinical Psychiatry*. They did so without mentioning (a) that four of the five individual centers produced negative results before the data were pruned and pooled, (b) that even the pooled data were negative when Prozac patients taking sedatives and tranquilizers were excluded, (c) that the FDA had many criticisms of the study and its practices, or (d) that even the apparent success of the drug was marginal. The publication by Stark and Hardison claimed that Prozac was comparable to Tofranil in efficacy—a myth that gained considerable currency in the profession—when in fact, the older tricyclic outperformed Prozac most of the time.

## Falling Behind European Standards: Zoloft

The general perception in America is that the FDA is far tougher on drug companies than comparable European authorities. If that was ever true, it is not anymore, at least in the arena of psychiatric drugs where I have my greatest familiarity. As described earlier in the chapter, regulatory agencies in both Great Britain and Canada have at times been quicker than the FDA to take lethal psychiatric drugs off the market. In addition, as noted in chapter 6 in regard to antidepressants, the British and Canadian agencies were also ahead of the FDA in responding to the risk of suicide and, in regard to the Canadians, to the risk of harm to self and others.

On December 10, 1991, Thomas Laughren, then group leader for Psychiatric Drug Products, wrote a memo concerning Zoloft's upcoming approval. Laughren listed a series of concerns about the antidepressant drug expressed by several European nations as well as by FDA advisors. These included "failure to provide data on depressed inpatients, severely depressed patients, 'major depression,' etc.; failure to provide long term data, relapse efficacy, etc.; failure to provide comparative data, i.e., for

alternative antidepressant agents." Despite these problems with Zoloft, he concluded that "the data were sufficiently persuasive to justify approval of this product."

Spurred on by Laughren's (1991) critique, an exchange of memos occurred between Paul Leber and his boss, Robert Temple, Director, Office of Drug Evaluation 1. The continuing subject was the approval of Zoloft, whose efficacy as an antidepressant remained in doubt up to the last minute. Temple noted that Zoloft was not being approved in some European countries because of its "lack of robustness" in the efficacy trials. Zoloft often failed to do any better than placebo in studies in the United States and never did as well as the older antidepressant amitriptyline. Despite these pervasive failures, one positive study and two supportive studies were found sufficient to earn approval.

On December 24—a mere 6 days before the official approval letter was written for Zoloft—Leber (1991) responded to Temple's concerns about approving the drug. About the tougher standards in the European countries, Leber wrote:

> This turn of events may seem somewhat surprising in view of the fact that the agency is traditionally more conservative than its European counterparts. Obviously, changes are underway throughout Western Europe, perhaps in response to EEC's [European Economic Community] harmonization initiatives. In any case, with the exception of the UK's [drug approval authority], standards for antidepressant drug product approval seem to be becoming more demanding in regard to 1) the duration of controlled trials serving as sources of evidence of efficacy, 2) the need to document efficacy in hospitalized depressed patients (because these are presumed, arguably, to be more severely depressed), 3) the need to show efficacy in maintaining remission, 4) the need to show efficacy in preventing relapse in euthymic [normal mood] patients with a history of recurrent episodes of affective illness, and 5) a need to establish equivalency and/or superiority of a new antidepressant to already marketed products.

Having outlined these standards, Leber acknowledged their merit but stated that they could not be implemented in America's current political climate:

> Many of these foreign regulatory initiatives have potential merit, but, given the perceived urgency we express as an institution for expediting the public's access to new, potentially promising drugs, I do not believe we can successfully introduce similar, more demanding, requirements domestically, at least until there is a significant "sea change" in our society's collective attitude toward Federal regulation of new drugs.

Leber (1991) believed that Zoloft, despite its relative ineffectiveness, had met the FDA's official requirements for approval. He then concluded his memo with the following warning:

> Approval [of Zoloft] may, however, for the reasons enumerated above, come under attack by constituencies that do not believe the agency is as demanding as it ought to be in regard to its standard for establishing the efficacy of antidepressant drug products.

It is striking that these concerns and misgivings are being expressed less than a week before final approval of the drug. Temple did not respond for another week, until December 31, 1991—1 day *after* the date on the final approval letter. He agreed that the drug should be approved but concluded, "I would, however, strongly encourage formal thinking, in which I would be pleased to participate, about whether we should modify the advice we give to companies to assure that they examine aspects of their drug's effectiveness that are not being well enough studied."

Leber's claim, quoted above, that the FDA is stymied by "our society's collective attitude toward Federal regulation of new drugs" is disingenuous and self-serving. Above all others, Leber was personally in a position at the FDA to stand up for truth and honesty in drug regulation, but instead he constantly pandered to the drug companies, for example, by delaying for years FDA recognition of antidepressant-induced suicidality and by watering down the warnings on TD. This permissive and even promotional attitude toward drug company interests then allowed him, after retirement from the FDA, to develop a second career. He now owns a consulting firm that helps drug companies get their products approved by the FDA (Dolan and Altimari, 2003).

A significant portion of the public believes that the FDA moves too slowly and places too many barriers in the way of new drug products. Despite all the bureaucratic time it wastes, in the arena of psychiatric drugs, the FDA is nowhere near thorough enough. The approval of a psychiatric drug does not in reality demonstrate either its efficacy or safety. The postmarketing surveillance is equally flawed. Not only is the system too haphazard, the division responsible for psychiatric drugs often fails to make an appropriate response to the most extreme drug-induced reactions, such as NMS and TD, produced by neuroleptics like Risperdal and Zyprexa and suicidal, violent, and manic behavior caused by antidepressants like Prozac, Zoloft, Paxil, and Celexa.

The FDA is hampered not only by its own internal failures, but also by its reliance on the potentially fraudulent activities of the pharmaceutical companies in developing and marketing their products. Because the FDA never evaluates the primary data generated by the drug companies,

instead relying on the scientific integrity and ethics of each company, the agency often ends up evaluating fraudulent scientific data. Chapter 14 looks further at examples of drug company deception.

## NIMH

The NIMH is the federal agency funded to respond to so-called mental illness in America. When I was a full-time consultant to NIMH (1966–1968), it was fundamentally a psychosocial and educationally oriented institution. It sought ways to improve the nation's mental health through psychological, social, educational, and economic means. For example, it was greatly concerned with improving our schools and reducing poverty.

When I was on the staff at NIMH, biological psychiatry was relegated to a relatively small center in the larger psychosocial context. But then, with the shift in the political wind toward medicalizing psychiatry that I document in *Toxic Psychiatry* (Breggin, 1991c), NIMH was transformed in the 1970s into an institution for the promotion of biological psychiatry and drugs.

Eventually, NIMH completely shucked off its patient-service wing and became a research institute on behalf of biological psychiatry and the drug companies. As described in chapter 6, nowadays, NIMH conducts extremely expensive controlled clinical trials on behalf of the drug companies, trying to demonstrate the effectiveness of their products. Again, as previously described, when the antidepressants came under fire, the direction of NIMH spoke out in their defense.

In the mid-1990s, my wife Ginger and I discovered that NIMH and NIH, and even the Centers for Disease Control (CDC), were promoting an interagency racist biopsychiatric program aimed at identifying inner-city children as suffering from violence-inducing brain disorders. In addition to funding research, the aim was to conduct mass screening and treatment of potentially violent children who supposedly suffered from genetic and biological abnormalities. Fortunately, our national campaign caused the federal agencies to stop their attempts to fund the program (Breggin and Breggin, 1994b; Breggin and Breggin, 1998).

The NIMH puts out an enormous amount of literature on behalf of biological psychiatry and the drug companies. One example is its booklet *Schizophrenia,* available on its Web site (http://www.nimh.nih.gov; National Institute of Mental Health [NIMH], 2007). It promoted every myth of schizophrenia favorable to the use of drugs. Breggin (1991c), Cohen and Cohen (1986), Harding and Zahniser, (1994), Irwin (2004a&b), Joseph (2004a, 2006), Karon and Widener (1999), Lidz (1981), Mosher

and Burti (1989), Read and Ross (2003), Read et al. (2005) and Siebert (1999) provide analyses of the myths of schizophrenia.

The booklet (NIMH, 2007) declared, "Schizophrenia is a chronic, severe, and disabling brain disorder that has been recognized throughout recorded history." It certainly has not been recognized as a brain disorder since recorded history. In fact, it was often seen as a spiritual gift. Nor is there any substantial evidence that it is a brain disorder (chapter 5). It does not act like any other known brain disorder. It has no identifiable underlying pathology, it does not lead to deterioration in mental or neurological processes, and it responds to psychosocial interventions. That schizophrenia is a brain disorder is speculation, but one that biological psychiatry and the drug companies have turned into a battle cry on behalf of their authority, power, and economic success.

The NIMH (2007) booklet admitted that psychosocial interventions can help, but with a caveat: "Numerous studies have found that psychosocial treatments can help patients *who are already stabilized on antipsychotic medication* deal with certain aspects of schizophrenia." Given that NIMH estimates that 1% of the population suffers from this disorder, that is an enormous number of people who allegedly cannot live without psychiatric drugs.

In deference to drug company interests, NIMH makes no mention of the World Health Organization studies showing that patients diagnosed with schizophrenia actually do better in Third World countries, where they receive little or no drugs and are supported by an extended family (de Girolamo, 1996), as well as the many studies of psychosocial approaches to deeply disturbed persons cited in chapter 16.

Somewhat to its credit, NIMH (2007) does not claim that schizophrenia is a proven genetically determined disorder. The following may come as a surprise to readers who are convinced that schizophrenia, above all other psychiatric disorders, is known to be genetic:

> Several of these genes are thought to be associated with an increased risk of schizophrenia, but scientists currently believe that each gene has a very small effect and is not responsible for causing the disease by itself.

Then, to save the day, the government booklet (NIMH, 2007) added, "Although there is a genetic risk for schizophrenia, genes alone are not likely to be sufficient to cause the disorder. Interactions between genes and the environment are thought to be necessary for schizophrenia to develop." The careful reader may be able to discern that all of this is speculation, laced with hope for the discovery of some kind of genetic component. In fact, decades of research have failed to reveal a genetic

component, while instead confirming an environmental one (see Breggin, 1991b; see also Joseph, 1999, 2004a&b, 2006, and the discussion in chapter 1).

Meanwhile, recent research indicates that "childhood abuse is a causal factor for psychosis and 'schizophrenia' and, more specifically, for hallucinations, particularly voices commenting and command hallucinations" (Read et al., 2005). But even more to the point is a simple summary from *Medical News Today* ("Schizophrenia," 2005), paraphrasing the conclusions of Richard Bental, Professor in Experimental Clinical Psychology at the University of Manchester:

> Schizophrenia has been attributed to everything from genetic predisposition, brain chemistry, sufferers' home environment and even catborne viruses, but no consistent causal pattern has ever been identified. As a result, treatment outcomes for today's patients are not very different from those of patients treated 100 years ago.

No such honest skepticism in our government agencies. Both the FDA and NIMH are now agents of the psychopharmaceutical complex. They do virtually everything in their power to promote biologically oriented psychiatry and the products of the psychopharmaceutical industry.

## NOTES

1. The new drug application (NDA) is conducted under the Code of Federal Regulations, Title 21, Part 314.
2. A protocol is a series of clinical trials conducted under the same rules. One protocol—that is, one model for conducting studies—may be used at several centers during the drug approval process. Numerous different protocols are utilized in the overall NDA.

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CHAPTER 14

# Drug Company Deceptions

"Public Perception of US Pharmaceutical Industry at All-Time Low" (2005) warned a headline in the *Pharmaceutical Business Review.* The business review explained,

> Increased safety warnings attached to some drugs (such as Roche's Accutane and GlaxoSmithKline's Paxil) and the complete market withdrawal of others (for example, Merck & Co's Vioxx) have undermined consumer confidence in both the pharmaceutical industry and the products it produces. As a result, consumers now question whether pharmaceutical companies have their best interests in mind when marketing a product.

On the brighter side, *Pharmaceutical Business Review* looks forward to the restoration of the public confidence. The drug companies have the leverage to accomplish this. Every area of modern psychiatry is permeated, and even inundated, with the influence of drug company money. As I began documenting in detail in 1991 in *Toxic Psychiatry,* worldwide clinical research, medical school research facilities and professorships, journal publications, conferences, and professional associations all, nowadays, depend on infusions of cash generated by the sale of drugs. The Food and Drug Administration (FDA) itself now solicits funding from drug companies to expedite the process of drug approval.

As a recent study found (Cosgrove et al., 2006), even the development of official psychiatric diagnoses takes place under the sway of the pharmaceutical industry. The *Diagnostic and Statistical Manual of Mental Disorders* (*DSM;* American Psychiatric Association, 1994, 2000) provides the official diagnoses for use in clinical practice, insurance company reimbursements, basic research, and the FDA approval of drugs. Nearly all the diagnoses are used for justifying the prescription of medications. Of the 170 panel members who contributed to the two most recent editions of the manual, 56% had one or more associations with the pharmaceutical industry.

Most telling, if not chilling, 100% of the panel members involved in developing diagnoses for the categories of mood disorders and schizophrenia and other psychotic disorders had ties to drug companies. No wonder these diagnostic categories have become pharmaceutical company cash cows.

The most common ties among *DSM* panel members were through research funding (42%), consultancies (22%), and speakers' bureaus (16%). This puts these professionals in much more intimate connection with their patron drug companies than merely accepting free lunches for the office staff or a free seminar.

Meanwhile, considerable criticism is being leveled at the degree to which major medical journals, including the hallowed *New England Journal of Medicine,* kowtow to the drug companies. Echoing criticisms I first made in *Toxic Psychiatry* in 1991, Richard Smith, former editor of the *British Medical Journal* for 25 years, wrote a 2005 analysis called "Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies." Smith admitted, "Journal editors are becoming increasingly aware of how they are being manipulated, but I must confess that it took me almost a quarter of a century to wake up to what was happening." He saw the problem as a combination of drug company–manipulated trials and the failure of journals, dependent on drug company advertising, to do their task of properly evaluating the papers sent in to them. As a former editor of the *New England Journal of Medicine,* Marcia Angell (2004, 2007) even more vigorously lambasted the journals, including her own former journal, for its willingness to promote pharmaceutical industry interests.

Abramson and Starfield (2005) asked the right question in their article titled "The Effect of Conflict of Interest on Biomedical Research and Clinical Practice Guidelines: Can We Trust the Evidence in Evidence-Based Medicine?" Their answer is no. In reality, so-called evidence-based medicine is a concept largely owned by drug company advocates who are trying to compel the use of their patron's products. Abramson and Starfield referred to a British House of Common's report that found that "approximately 75% of clinical trials published in *The Lancet,* the *New England*

*Journal of Medicine (NEJM)* and the *Journal of the American Medical Association (JAMA)* are industry funded." Abramson and Starfield found that commercially funded studies are 5.3 times more likely to support their sponsors' products than noncommercially funded studies. They concluded with a point I have been emphasizing for many years:

> So what are dedicated clinicians to do? The first step is to give up the illusion that the primary purpose of modern medical research is to improve Americans' health most effectively and efficiently. In our opinion, the primary purpose of commercially funded clinical research is to maximize financial return on investment, not health.

## RELYING ON JUNK SCIENCE

Worse yet, as already emphasized in chapter 13, the FDA relies on the drug companies for the so-called science that is used to determine the safety and efficacy of drugs. On December 13, 2006, the FDA's Psychopharmacological Drugs Advisory Committee held a public meeting to discuss and evaluate the risk of antidepressants causing suicidal behavior in adults. The FDA had already added a warning to antidepressant labels concerning drug-induced suicidality in children and youth under age 18. As I had at earlier FDA hearings on antidepressants, I made a brief, 3-min presentation. As I also had done on previous occasions, I emphasized that the FDA was relying too much on data generated, culled, and manipulated by the drug companies and that the agency ought to avail itself of experts like me, who had actually evaluated the junk science produced by the drug companies. I told the agency,

> Fifteen years ago, I warned the FDA and I warned the country in *Toxic Psychiatry* that antidepressants were causing a stimulant, amphetamine-like syndrome that was resulting in suicide, violence, and murder. In 1994, in *Talking Back to Prozac,* I warned the country and the FDA, this time now with tons of scientific data, on the same issues.
>
> During that period of time, I was asked to be—and this is very relevant to your deliberations—the scientific investigator for the combined Prozac suits, almost 200 of them. I got to look at all the sealed data that Eli Lilly didn't want anybody else to see.
>
> About 20 books later now, and a few dozen scientific studies and innumerable product liability suits where I've looked at sealed data, I have come to tell you that you are evaluating *junk*. You are evaluating carefully edited expurgated data that I have seen and you have not.
>
> This is a most remarkable circumstance: that you…have people [like me] who have been inside the drug companies who can tell you what is happening inside the drug companies. Of course, you have avoided it.

> All the documents I am going to discuss now are on my Web site, www.breggin.com. They have all been given to you or sent to you via the FDA Committee.

I went on to describe how one drug company, Eli Lilly, had falsified, hidden, and manipulated data concerning Prozac-induced suicidal behavior in adults. The FDA paid no attention and instead blithely relied on the integrity of the data given to it by the drug companies to whom so many of the panel members owned fealty.

The public is beginning to catch on to the untrustworthiness of drug company data provided to the FDA and the medical community. A recent editorial in *USA Today* titled "Drug Thugs" (2007) described pharmaceutical company harassment of medical critics, something I am personally very familiar with. After discussing various remedies, it made suggestions consistent with what I have been saying for decades:

> Another approach would be to insist that the FDA do a better job monitoring and publicizing studies conducted by the drug companies themselves.
>
> More transparency would make it harder for drug companies to distort results. It would help to protect academic freedom at America's research institutions. And it would make patients more likely to receive the safest and most appropriate treatments.

This chapter once again presents evidence that drug companies cannot be relied on to present valid data about their drugs to the FDA, the medical profession, or the public, and instead, that they underestimate the risks and overinflate the benefits of their products.

The focus is on Eli Lilly, the manufacturer of Prozac, and on GlaxoSmithKline, the manufacturer of Paxil. I cannot say with certainty that these companies are any more negligent than others; they are simply the companies I have learned the most about as a result of my independent research and my work as a medical expert in product liability suits against them.

## ELI LILLY AND PROZAC

### Eli Lilly Knew From the Start That Prozac Acts Like a Stimulant

After all the data had been collected during Prozac's new drug application (NDA)[1] approval process, FDA psychiatrist Richard Kapit (1986b) wrote the official safety review of adverse reactions or side effects. Kapit

summarized, "Most frequently this new drug caused nausea, insomnia, and nervousness, which resembles the profile of a stimulant rather than a sedative drug." He thought this stimulant profile would "give rise to the greatest clinical liabilities in the use of this medication," including "insomnia, nervousness, anorexia, and weight loss." Later in his report, Kapit repeated his observations, stating that Prozac's "profile of adverse effects more closely resembles that of a stimulant drug than one that causes sedation and gain of weight." Kapit concluded:

> It is possible that these adverse effects of fluoxetine treatment may negatively affect patients with depression. Since depressed patients frequently suffer from insomnia, nervousness, anorexia, and weight loss, it is possible that fluoxetine treatment might, at least temporarily, make their illness worse.

Kapit repeated this concern in his summary, stating, "It is possible, therefore, that fluoxetine may exacerbate certain depressive symptoms and signs." He recommended that the label warn physicians about these dangers.

Later, in his safety update of the NDA on October 17, 1986, Kapit spoke of several cases of a "syndrome of fluoxetine-induced hyper-arousal and excessive stimulation . . . [that] resemble episodes of stimulant drug intoxication." It was especially likely to occur at higher doses, but it could occur at the standard 20 mgs. The state of overstimulation included "anxiety, agitation, insomnia, headache, confusion, dizziness, obnubilation [mental clouding], memory dysfunction, tremor, impaired motor coordination. Hyperactivity, hypomania, and mania may sometimes occur." In overdose, the drug produces an even more flagrant stimulant syndrome culminating in seizures. Thus there is a continuum of stimulation effects.

Showing concern for possible abuse potential that might show up in the future, Kapit (1986c) warned about "the fact that fluoxetine causes a set of adverse effects which resemble those caused by amphetamine" (p. 23).

Despite Kapit's function as the chief safety investigator for Prozac, the Division of Psychopharmacological Drug Products, under psychiatrist Paul Leber (see chapter 13), allowed none of Kapit's concerns to appear on the drug's label. The label does not indicate that Prozac is a potentially stimulant drug or that it can cause or worsen depression.

In a December 10, 1987, "Review and Evaluation," Kapit recommended that the company conduct postmarketing tests to study Prozac's potential to worsen the condition of patients already suffering from weight loss, anorexia, and agitation. Neither the FDA nor the manufacturer followed up on this.

It would take the FDA nearly two decades to finalize a new label for Prozac and all the newer antidepressants warning that patients can actually deteriorate as a result of taking these drugs (chapter 6).

## Eli Lilly Successfully Bamboozles the Legal System

Many of my initial revelations about Eli Lilly and its drug Prozac in the earlier edition of this book were generated through my work as a medical expert in the first product liability case to go to trial against Eli Lilly concerning Prozac (Fentress, 1994; see Breggin, 1994, for my testimony; see also Breggin, in press, for more details). In that case, Joseph Wesbecker entered his former place of employment in 1989, shot 20 people, killing 8 of them, and then committed suicide. He had been taking Prozac as well as other medications. The plaintiffs argued that Eli Lilly had failed to adequately study and then to warn physicians about the potential for Prozac-induced violence toward self and others.

Although the Wesbecker case was seemingly won by Eli Lilly by a divided 9–3 jury vote,[2] the presiding judge, John W. Potter, later concluded that Eli Lilly settled secretly with the plaintiffs before the case went to the jury (Castellano, 1995; Gibeaut, 1996; Potter, 1995; Scanlon, 1995; most extensively, Varchaver, 1995). The judge had not been informed of the settlement during the trial. To the contrary, both sides denied its existence to the judge (Varchaver, 1995).

As a part of the settlement, in addition to receiving money and agreeing not to appeal the case, the plaintiffs agreed to withhold from the jury certain damaging evidence against Eli Lilly (Gibeaut, 1996; Potter, 1995; and others in the previous paragraph). Meanwhile, the trial went on as if no special arrangements had been made. This created a mock or fake trial.

When he found out that the case had been secretly settled and that the plaintiff and defense attorneys had lied to him, Judge Potter tried to amend the official outcome of the case from dismissed by the jury without prejudice to settled with prejudice. The judge's attorney stated, "There was a payment of money to withhold evidence" (Wolfe, 1995). Initially, an appeals court overruled Judge Potter on the grounds that too much time had elapsed before his attempt to change the verdict (Varchaver, 1995; Wolfe, 1995), but the judge won his appeal to the Supreme Court of Kentucky (Gibeaut, 1996).

On May 23, 1996, the Supreme Court of Kentucky unanimously agreed in *Potter v. Eli Lilly & Co.* that Judge Potter could proceed to hold a hearing on the secret settlement under an inherent-powers doctrine allowing courts to protect the integrity of their procedures (Gibeaut, 1996). The Supreme Court justices wrote, "In this case, there was a serious lack

of candor with the trial court and there may have been deception, bad faith conduct, abuse of judicial process or perhaps even fraud" ("Trial Court's Authority…," 1996, p. 35; Gibeaut, 1996, p. 18).

Estimates of the secret settlement made by Eli Lilly and Company in the Wesbecker case have come through unrelated divorce suits. One plaintiff's attorney, presumably privy to the Eli Lilly settlement amount and involved in his client's divorce suit, stated, "The amount boggles the mind" (Gibeaut, 1996, p. 18).

Not only was the Wesbecker case settled secretly during the trial, but the plaintiffs lead attorney Paul Smith decided to settle all of his several other cases against Eli Lilly at that time. Eli Lilly can no longer claim it has never settled a Prozac case. It has settled several of them involving different attorneys.

## Eli Lilly Acknowledges to the Food and Drug Administration (FDA) That Prozac Frequently Causes Depression

In preparing my testimony in the Wesbecker case, I went through an additional mass of FDA documents obtained under the Freedom of Information Act (FOIA). I discovered a section of Eli Lilly's final draft of its Prozac label that was submitted to the FDA. The section, in conformity with the standard label, was titled "Other Events Observed During the Premarketing Evaluation of Prozac" (Eli Lilly, n.d.). It drew on the total database of 5,600 patients given Prozac. The label noted, "It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it."

In this final version of their label, under the heading Nervous System, the company listed depression as a *frequent* adverse effect of the drug. Frequent is equivalent to common and means occurring at least once in 100 cases. But the FDA, supposedly in a last-ditch editing attempt to shorten what it called Eli Lilly's laundry list concept, scratched a line through *depression* (Temple, 1987). The approved and current label lists only abnormal dreams and agitation as frequent or common. Depression went from being listed as a frequent adverse effect in the proposed official label to being wholly unmentioned in the final, approved label. This transformation took place at the very last minute, before the FDA's final approval of the drug for marketing.

The admission that the drug was frequently reported to cause both agitation and depression is consistent with Richard Kapit's original observations and is of great importance. Through research, clinical experience, and consulting as a medical expert, I have learned that many of the murders and suicides reported to have occurred during Prozac

treatment seemed driven by a combination of agitation and depression, specifically, Prozac-induced agitated depression (Breggin, in press; Breggin et al., 1994a).

As a result, for more than a decade there was nothing in the Prozac label, or the label for any other antidepressant, indicating that the newer antidepressants can cause depression. Therefore, when a patient on Prozac became more depressed, rather than less, the physician was likely to increase the dose, rather than to stop or taper the drug. Only with the label revisions of 2004–2005 (chapter 6) did the FDA finally alert the profession to the fact that antidepressants can in fact make patients more depressed and worsen their overall condition. Unfortunately, the information has taken so long to surface that most physicians are habituated to the idea that antidepressants cannot cause depression.

## Eli Lilly Hides the Implications of Prozac-Induced Mania

Even in the short clinical trials for the NDA, Prozac caused mania in slightly more than 1% of patients (Kapit, 1986c). But material that I turned up in the NDA indicates that Prozac poses a considerably greater danger of causing mania than the tricyclic antidepressants (Kapit, 1986c). In studies used for FDA approval, only 0.3% of patients on tricyclics became manic—a rate one-third that of Prozac. In addition, all the patients who became manic on tricyclics turned out to have a prior history of mania. Among the 33 reported cases of mania on Prozac, 23 occurred in patients who had never been manic before.

Mania frequently results in very destructive behavior toward oneself or others, including outright violence (chapter 6; Breggin et al., 1994a; especially Breggin, in press). Untold numbers of lives have been ruined by antidepressant-induced mania. The manic person can experience intense paranoid feelings and often feels enormous hostility, especially if thwarted in his or her own ambitions of the moment. The increased rates on Prozac once again confirm its stimulant quality.

## Eli Lilly Confirms and Hides Prozac Overstimulation

Pressured by the German drug regulatory agency, Eli Lilly asked Charles Beasley, from its Division of Clinical Neurosciences, to count the cases of agitation in their clinical trials (Breggin, 1994). He produced a secret in-house report titled "Activation and Sedation in Fluoxetine Clinical Studies" (Fentress Trial Exhibit 70; available on http://www.breggin.com), dated November 8, 1988. The report found that 333 Prozac patients became agitated in the trials, but only 16 placebo patients did so. Beasley called it an *activation effect,* including "nervousness, anxiety, agitation,

insomnia." He found that 38% of patients developed this effect on Prozac, and 19% developed it on placebo.

As mentioned in chapter 7, the totals for Prozac stimulation should have been even higher, however, because Beasley did not count several categories of overstimulation, including euphoria, mania, and hyperactivity. The rates of agitation would also have been higher if a large percentage of the Prozac patients had not been prescribed concomitant benzodiazepines and other sedatives.

In going through mountains of documents, I found no evidence that the FDA ever saw the crucial Beasley study that confirmed FDA investigator Kapit's frequently expressed concerns about the drug's similarity to stimulants, including amphetamine (e.g., Kapit, 1986c).

## Hiding the Risk of Prozac-Induced Mania and Aggression in Children

*Clinical Psychiatry News* (Sherman, 1995) headlined "Prozac for Kids: 'Landmark' Study Affirms Drug's Use." It described a placebo-controlled clinical trial led by Graham Emslie from the University of Texas Southwestern Medical School in Dallas. When I evaluated the data from the newspaper report, the rate of drug-induced mania turned out to be an extraordinary 6% (Breggin, 1995). In addition, during the question period after the article was presented, Emslie admitted to an increase in aggressiveness as well (Sherman, 1995). When the article was later published, the extraordinarily important 6% mania rate was buried in a section devoted to dropouts (p. 1003) and left out of the abstract, discussion, and summary (Emslie et al., 1997). The increase in aggression was wholly unmentioned. The research was supported by Eli Lilly.

## Eli Lilly and the FDA Ignore Reports of Aggressive Behavior on Prozac

As I described in *Talking Back to Prozac* (Breggin et al., 1994a), the FDA made a presentation at its 1991 hearings on antidepressants and abnormal behavior that showed a disproportionately high frequency of reports to the FDA of hostility and intentional injury on Prozac compared to trazodone, an older and less-stimulating drug. (The graph, titled "Hostility and Intentional Injury: Reports per Million Rx," Food and Drug Administration [FDA], 1991, is available on http://www.breggin.com.) The graph and accompanying data show that in 1998, the first year that Prozac was marketed in the United States—and before there was any publicity surrounding Prozac-induced violence—there were approximately 10 times as many reports of violence and intentional injury per prescription

for Prozac compared to trazodone. By July 1991, reports of violence and intentional injury for Prozac became roughly 50 times more frequent per prescription than for trazodone.

The reports were sent to the FDA through its postmarketing spontaneous reporting system (SRS). The FDA representative projected the data onto a screen, but the data were not included in the transcript of the meeting. Although this issue was of overriding, central importance to its deliberations, the FDA advisory panel made no response at all to it. It was as if the data, so critical to their conclusions, had been presented to an empty room.

In response to an FOIA request from me, the FDA claimed that the data could no longer be found. I contacted the author of the graph, and he, too, told me that the data were lost. However, Eli Lilly was compelled to produce the data under court order in the Wesbecker case (Trial Exhibit 120), and I used it in my court testimony (Breggin, 1994).

As emphasized in chapter 13, the data once again confirm the importance of the spontaneous reporting system compared to controlled clinical trials in revealing dangerous adverse drug reactions, in this case violence and aggression.

## Eli Lilly and the FDA Ignore Reports of Suicidal Behavior on Prozac

Another graph developed by the FDA for the 1991 hearing that compared Prozac to trazodone was called "Suicide Attempt, Overdose, and Psychotic Depression, Reports per Million Rxs" (available on http://www.breggin.com). Once again, these reports were far more common for Prozac. Beginning in 1988, the reports in this cluster for suicide, overdose, and depression were 4 times more frequent per prescription of Prozac. By 1990, they appeared to be approximately 50 times more common. The panel, which was rampant with conflicts of interest (Breggin et al., 1994a), gave little importance to these findings.

## Eli Lilly Hides Increased Suicidality on Prozac in Controlled Clinical Trials

In materials gained through discovery in the Wesbecker case, I found in-house documents from Eli Lilly clearly demonstrating an increased rate of suicide attempts in Prozac patients compared to placebo and to tricyclic antidepressants (Breggin, 1994; available on http://www.breggin.com). This was a shocking discovery as Eli Lilly claimed, and continues to claim, that no such data exist.

In the summer of 1985, Eli Lilly set out to respond to accusations, including those from the German regulatory agency, that Prozac could cause or contribute to suicidality. The company evaluated data from its basic 4- to 6-week controlled clinical trials. Twelve reported suicide attempts were found among the Prozac patients, but only one each in the placebo group and the comparison drug group (tricyclic antidepressant). This 12:1 ratio could not be explained by differences in size between the Prozac group and the placebo and the tricyclic groups. When the total patient days of exposure were taken into account, the ratio remained a significant 6:1 for increased suicide attempts in the Prozac group.

Consultants hired by Eli Lilly pruned down the original reports, excluding six of the suicide attempts on Prozac and one on either the comparison drug or placebo. That is, they decided to throw out a substantial portion of the data that reflected badly on their employer's drug. The ratio remained 6:1, and the consultants continued to find a borderline statistically significant ($p = .051$) increased rate for suicide attempts among the Prozac patients.

Furthermore, the removal of several of the Prozac suicide attempt reports was wholly unjustified even in hindsight. For example, one discarded case involved a patient who took 10 fluoxetine capsules spaced at 2-hour intervals over 5 hours while drinking a bottle of rum. Taking the pills slowly in this manner, along with alcohol, is done during genuine suicide attempts to avoid vomiting the medication. The complete data on another exclusion was as follows: "The patient had suicidal ideation at the beginning of the study and made a self-inflicted laceration of the skin with a razor blade."

In throwing out these cases, the Lilly consultants second-guessed the company's own clinical investigators, who had originally categorized these reactions as drug-related suicide attempts during the double-blind placebo-controlled clinical trials. In fact, this is highly unscientific and highly unethical because it undermines the entire concept of the double-blind study. The purpose of the double blind is to prevent exactly this kind of biased reanalysis of the data. Furthermore, the consultants made their decisions on their own personal impressions based on a mere few lines of clinical description. According to one of the company's executives, they did not contact the authors of the reports—their own clinical investigators—for more information (Beasley, 1994a, p. 245). Yet these clinical investigators, based on firsthand knowledge, had cited the cases as suicide attempts.

The blinded data was the only valid data. However, Eli Lilly ran roughshod over science by breaking the blind in providing its new evaluators data indicating what each of the patients were taking when they were found to have attempted suicide. Thus, when "evidence-based"

data did not meet the company's need to promote its product, the company simply ignored the evidence and hired biased investigators to re-evaluate the data while knowing which patients were taking Prozac and which were not. Eli Lilly's own consultant, biological psychiatrist David Winokur, offered an explanation for how Prozac could increase the suicide attempt rate: "A possibility which comes to mind is that Prozac might be somewhat more stimulating as a drug and that individuals may be slightly more impulsive although their thinking had not changed" (Breggin, 1994, pp. 3129–3130; available on http://www.breggin.com). Independently, in my writing and testimony, I had also developed the concept of Prozac as a stimulating drug causing impulsive behavior and suicide.

As far as I can ascertain, these extremely important facts and analyses about Prozac-induced suicidality were never submitted to the FDA or in any way made available to the government, the profession, or the public. To the contrary, Eli Lilly has maintained—and continues to maintain—that there is no evidence whatsoever for increased suicidality on Prozac. As an example, Eli Lilly did not make known its analysis of increased suicidality on Prozac at the 1991 FDA conference (FDA, 1991). Nor did they present the Beasley data on increased activation (Beasley, 1988; as for all documents in this section, available on www.breggin.com).

## Eli Lilly Employees Express Shame

Eli Lilly's successful attempts to hide suicide attempts by miscoding them resulted in expressions of shame and guilt within the company. On November 13, 1990, Eli Lilly employee Claude Bouchy (1990a; available on www.breggin.com) wrote a memo to Leigh Thompson, a high-ranking U.S. administrator in the company, and to five other company officials showing his concern about how the company was identifying or coding adverse drug events that physicians were reporting to the company. He protested the requirement for safety staff to change reports of suicide attempts to reports of overdoses and to change reports of suicidal ideation to depression. Bouchy spoke of another employee who also had "medical problems with these directions" and said, "I have grave concerns about it." Bouchy wrote:

> I do not think I could explain to the BGA [the German drug regulatory agency], a judge, to a reporter or even to my family why we would do this especially on the sensitive issue of suicide and suicide ideation.

Bouchy then went on to say that the issue had been "argued back and forth for about a month" between Germany and Indianapolis, Lilly's home

office, and that "therefore I am bringing it to your attention and await your directions."

One day later, on November 14, 1990, Bouchy again wrote from Germany to Leigh Thompson with copies to five other company officials, describing how Lilly was purposely hiding Prozac-induced suicidal ideation and acts under false and misleading categories. This time Bouchy (1990b) wrote:

> Finally, on a very simple and non-scientific basis, I personally wonder whether we are really helping the credibility of an excellent ADE [adverse drug event] system by calling overdose what a physician reports as suicide attempt and by calling depression what a physician is reporting as suicide ideation. . . . Of course by the end of the day we will do what we are told to do but Hans and I felt that we had to bring these to attention.

The FDA creates a list of preferred terms to be used to describe specific adverse drug reactions. By January 1989, the year before these memos were written, FDA's dictionary, called COSTART, clearly specified that suicide attempts should be listed as suicide attempts (available on http://www.breggin.com). But regardless of the FDA dictionary, Eli Lilly was clearly trying to hide suicidal thoughts and suicide attempts under more obscure categories.

Eli Lilly not only excluded suicide attempts from the list of adverse drug reactions by calling them depression or even failure to improve (Breggin et al., 1994a), the company instructed its principal investigators not to report possible adverse drug events from the controlled clinical trials if they could be attributed to the patient's mental disorder (Beasley, 1994b), further discouraging them from sending in reports of suicide attempts in depressed patients.

## Adverse Reactions to Prozac in Eli Lilly's Earliest Research

In the March 1986 safety review of the NDA (Kapit, 1986b), the FDA psychiatrist summarized five "serious clinical events" in the first 77 patients given Prozac, including 1 with paranoid psychosis and 1 with manic psychosis. There was also evidence in Eli Lilly's files—presented in my testimony—that some of the first human subjects responded very adversely to Prozac. In his deposition, Eli Lilly's top scientist, Ray Fuller (1994), confirmed the existence of an early in-house memo, in which he wrote:

> Some patients have converted from severe depression to agitation within a few days. In one case the agitation was marked and the patient

> had to be taken off the drug. In future studies, the use of benzodiazepines to control agitation will be permitted.

This is a smoking gun, indicating that Eli Lilly knew from the beginning that Prozac would make many patients so agitated that they would need others drugs to control it. Fuller (1994) admitted in deposition that the decision was made to add benzodiazepines to the NDA clinical studies because patients reportedly were becoming agitated on Prozac. As noted, the use of concomitant sedatives and minor tranquilizers became a common practice in the protocols preceding drug approval.

It should be emphasized, however, that giving tranquilizers or sedatives along with Prozac by no means guarantees that the patient will escape undergoing drug-induced agitation, depression, suicide, or violence. The benzodiazepines can have paradoxical effects, including agitation. They, too, can cause or aggravate depression, violence, and suicide (chapter 12). Many of the most bizarre adverse reactions in my clinical experience occurred on a combination of SSRI antidepressants and tranquilizers, especially Xanax. In general, the greater the number of psychoactive drugs the patient takes, the greater the risk of an adverse drug reaction.

## Prozac-Induced Aggression in Eli Lilly's Earliest Animal Studies

In preparing for the Wesbecker trial, I found more evidence than I originally suspected concerning Prozac-induced agitation and even violence in animals. I testified at trial (Breggin, 1994) concerning an Eli Lilly animal study documented by Brophy, an Eli Lilly project leader. He reported, "A total of six dogs, two males and four females, from the high-dose group were removed from treatment for periods of 1 to 17 days due to severe occurrences of either aggressive behavior, ataxia, or anorexia." In his deposition, Ray Fuller (1994), Eli Lilly's highest ranking scientist, stated that 6 of 20 dogs in the high-dose study group became unexpectedly aggressive. A number of mice were getting hyperactive, but not aggressive, on Prozac.

Slater et al., from the Eli Lilly Research Labs, published an article in 1978 concerning the inhibition of REM sleep in cats. Disruption of REM sleep can cause emotional disturbances. The Eli Lilly researchers reported that they were "at a loss to explain why cats receiving fluoxetine for several days began to hiss and growl or why this behavior decreased with continued treatment."

In defense of their company and their drug, these authors then explained, "The subjects who received fluoxetine in Phase I clinical trial have not described any change in mood nor have observers noted any change in affect." This claim is not supported by the facts as disclosed

in the NDA or in Eli Lilly's own documents. As the previous section documented, some of the first subjects given Prozac showed drastic, even deteriorating,[3] changes.

I can find no evidence that follow-up studies were done to further evaluate Prozac-induced agitation or aggression in animals. No primates were tested for behavioral effects.

## British and German Regulatory Authorities Inquire About Prozac-Induced Stimulation, Agitation, and Depression

The FDA was not the only regulatory agency to show concern about Prozac-induced agitation, stimulation, and depression. In my Wesbecker testimony, I described how the British Committee on Safety of Medicines (CSM; as cited in Breggin, 1994), prior to approval of Prozac, raised the same issue:

> It is possible that these adverse effects of fluoxetine treatment may negatively affect patients with depression. Since depressed patients frequently suffer from insomnia, nervousness, anorexia and weight loss [Prozac effects], it is possible that fluoxetine might at least temporarily make their illness worse. (p. 3094)

For a time, the CSM seemed determined to make Prozac contraindicated in underweight, anorexic, or agitated patients, but apparently, nothing came of it.

During the mid-1980s, the German Drug Regulatory Agency (BGA; *Bundesgesundheitsamt*) also raised doubts about approving Prozac. The agency worried about a possible increase in the suicide rate. They shared Kapit's concern about stimulating effects. (Consistent with my own impressions, the BGA also found that doctors in clinical studies were more positive about the drug than the actual patients.)

In 1984, Eli Lilly employees in Germany named Schenk and Weber (as cited in Breggin, 1994) wrote in a company memo, "The BGA suspects fluoxetine to be a stimulating/activating drug (side-effect profile, suicides, suicide attempts)" (p. 3151). Remarking on suicide associated with Prozac, they declared, "This is a very serious issue in the opinion of the BGA." According to the memo, the BGA had stated, "Considering the benefit and the risk we think this preparation totally unsuitable for the treatment of depression." The BGA was especially concerned about Prozac's potential to cause agitation before its antidepressant effect took place. The BGA, unknowingly echoing Kapit, but more strongly, warned, "During treatment with the drug, some symptoms of the underlying disease (anxiety, insomnia, agitation) increase, which as

adverse effects exceed those which are considered acceptable by medical standards."

The conflict between the BGA and Eli Lilly went on for many years. On February 6, 1991, Hans Weber, representing Eli Lilly in Germany, wrote to Ray Fuller at Eli Lilly. He described a meeting held between Eli Lilly representatives and the BGA. Weber (as cited in Breggin, 1994) stated, "The question was raised whether fluoxetine could be an amphetamine-like drug, which may explain its stimulating and anorectic effects" (p. 3154).

Eventually, the BGA did approve Prozac. Unlike the FDA, however, they required a label warning under the heading Risk of Suicide. It states that the patient may need an additional sedative along with Prozac until the antidepressant effect takes over. It notes that this would also apply to patients with extreme sleep disturbances or excitability.

Lilly's undisclosed in-house studies of increased activation and suicidality on Prozac were probably done in the hope of allaying fears expressed in Germany and elsewhere. When the studies instead confirmed the worst fears about stimulation and suicidality, they were never made known to the relevant agencies in England, Germany, or the United States.

## ELI LILLY HIDES AKATHISIA

As early as 1979, Meltzer and a team at the University of Chicago recognized that Prozac suppresses dopaminergic neurotransmission. Concerned about reports of neurological side effects that might stem from this dopamine suppression, Baldessarini and Marsh (1990) from McLean Hospital and Harvard demonstrated the effect in Prozac-treated animal brains.

Drug-induced disruption of dopamine neurotransmission is known to produce a variety of neurological side effects (see chapters 3 and 5). The neuroleptics suppress dopamine neurotransmission, causing a reactive hyperactivity of the system that produces a high rate of irreversible dyskinesias, cognitive dysfunction, and dementia.

Prozac's pharmacological mechanism for suppressing dopamine is more indirect than that of the neuroleptics. However, the clinical result can be very similar. Prozac can cause akathisia (agitation with hyperactivity), parkinsonism ("Fluoxetine," 1990), and dystonia (muscle spasms) (Meltzer et al., 1979; Reccoppa et al., 1990).

Drug-induced akathisia, dystonia, and parkinsonism can produce extreme discomfort. They can be disabling and feel like torture (see chapter 3 for details). In brief, akathisia can become an inner torment and anguish that drives the individual into hyperactivity.

Akathisia can contribute to the development of psychosis as well as violence against self or others. Dystonia often produces agonizing muscle

spasms in the region of the eyes, head, and neck but can also cause spasms that disable the whole body. Parkinsonism produces emotional dulling and immobilizes the body.

The original 1989 Prozac label, under the heading "Adverse Reactions of the Nervous System," mentions akathisia as infrequent. However, in the September 1989 issue of the *Journal of Clinical Psychiatry,* Joseph Lipinski et al. from McLean Hospital and Harvard Medical School described five cases of Prozac-induced akathisia, which they believed occurred "fairly frequently." They estimated the rate of akathisia in Prozac patients at between 9.7% and 25%. They stated that their cases were indistinguishable from neuroleptic-induced akathisia. In a case example, 5 days after starting Prozac, one woman "reported severe anxiety and restlessness. She paced the floor throughout the day, found sleep at night difficult because of the restlessness, and constantly shifted her legs when seated."

One year later, in June 1990, *Health Letter* (Public Citizen Health Research Group, 1990) estimated that akathisia affects a whopping 15% to 25% of Prozac patients.

How could such a frequent, distressing side effect go almost wholly unrecognized among the thousands of patients tested by Eli Lilly during the FDA drug approval process? In reviewing documents for product liability suits against Eli Lilly, I found that the company had not listed akathisia as one of the preferred terms for use in describing adverse effects in its clinical trials. That is, their researchers were not given the term akathisia as one of the categories or terms for reporting effects. As a result, few reports of akathisia cropped up. Instead, cases of akathisia were listed under more innocuous terms like hyperactivity or agitation, drug-induced symptoms not as closely associated with suicidality, violence, and overall mental deterioration as akathisia.

## LILLY COVERS UP PROZAC WITHDRAWAL REACTIONS

Withdrawal from SSRIs, Effexor, and the newer antidepressants can be difficult and sometimes impossible and can involve a broad range of symptoms (chapter 15). Patients can crash coming off SSRIs and Effexor and undergo severe depression and suicidal ideation (Breggin, 1992b; Breggin et al., 1994a). Here I want to emphasize that Eli Lilly knew about withdrawal problems from Prozac but hid them from the profession and the public. Einbinder (1995) described a patient who felt fatigue and dizziness with falling on withdrawing from Prozac. Interestingly, Einbinder stated, "The manufacturer was unaware of any reports of withdrawal symptoms on cessation of fluoxetine."

It is most remarkable if Eli Lilly told Einbinder that it was unaware of any reports of withdrawal symptoms associated with the use of Prozac. By January 24, 1993, the SRS of the FDA had received 94 reports of withdrawal syndrome from Prozac as well as 26 reports of drug dependency and 4 of drug addiction (FDA, 1993).

I myself made a report in the literature on Prozac withdrawal (Breggin, 1992b), and I sent it directly to the company as well. The company acknowledged receipt of the document (D. Marvel, personal letter, March 15, 1993) and filed it with the FDA using several event terms, including *withdrawal syndrome*.

There is no way that Eli Lilly could have been unaware of reports of withdrawal reactions from Prozac.

By the mid-1990s, there were also reports of severe withdrawal from Paxil and Zoloft. Debattista and Schatzberg (1995) reported on physical symptoms associated with a case of paroxetine withdrawal with vomiting, headache, and tremulousness, which they compared to a similar report concerning sertraline withdrawal (Louie et al., 1994).

## SIMILAR DRUG APPROVAL PROBLEMS WITH ZOLOFT AND PAXIL

Through FOIA, I have had the opportunity to review the Zoloft Summary Basis of Approval (1988). Many of the problems that plagued the NDA of Prozac were also rampant in the NDA for Zoloft, including numerous violations of protocol, the use of concomitant long-acting benzodiazepines, high dropout rates, many negative studies, and no evidence of efficacy in hospitalized patients. In fact, the efficacy of Zoloft was considered questionable until the last minute before its final approval (discussed in chapter 13).

Through FOIA and materials obtained as an expert witness in product liability cases against GlaxoSmithKline, I found similar problems to Prozac in regard to the approval process for Paxil, especially miscoding suicidal behavior as "emotional lability" and hiding or misinterpreting data on suicidality (see subsequent sections in this chapter).

## PROZAC INTERACTION WITH MONOAMINE OXIDASE INHIBITORS AND TRYPTOPHAN

When combined with other drugs that stimulate the serotonergic system, such as monoamine oxidase inhibitors, other antidepressants, or tryptophan,[4]

Prozac and the other SSRIs, as well as any antidepressant that blocks the removal of serotonin from the synapse, can produce a well-documented, severe condition called the *serotonin syndrome* (Sternbach, 1991). This disorder includes the usual signs of overstimulation, such as euphoria and hypomania, agitation, confusion, and gastrointestinal upset, including diarrhea. However, the serotonin syndrome additionally involves overstimulation of the brain stem and spinal cord, producing fever and chills, severe incoordination, muscle spasms, and hyperactive reflexes. It bears some similarity to neuroleptic malignant syndrome, and like NMS it can also be lethal (chapter 4).

## PROZAC IN COMBINATION WITH TRICYCLIC ANTIDEPRESSANTS

Psychiatrists and other physicians too frequently combine Prozac with other antidepressants, including the tricyclics, such as imipramine (Tofranil) and amitriptyline (Elavil). The combination is extremely dangerous. In a 1992 study conducted in Eli Lilly's own research laboratory by the team of Bergstromm et al., Prozac was found to increase the blood concentrations of tricyclics by as much as 10 times.

The tricyclics become toxic at blood levels not much higher than their therapeutic ones. A 10-fold or more increase in concentration of a tricyclic could produce, among other things, a fatal heart arrhythmia, a severe drop in blood pressure, CNS depression, or a grand mal seizure. It could also cause abnormal mental reactions such as confusion, panic, mania, or even depression.

One rat brain study showed that Prozac and tricyclics given together accelerate their joint impact on the brain (Baron et al., 1988). Down-regulation of adrenergic receptors (discussed subsequently) was greatly increased in rapidity and intensity by the combination.

## ELI LILLY MIRED IN CONTROVERSIES WITH LIFE-THREATENING IMPLICATIONS

Many other controversies involving Eli Lilly and Company, the maker of Prozac, have raised further questions concerning pharmaceutical industry adherence to ethical practices and FDA standards. The media and the FDA have investigated Eli Lilly's use of homeless alcoholics as normal experimental subjects in Phase 1 studies (Cohen, 1996; "NIH Queries

University," 1996). This is not an acceptable practice, according to the FDA. Because homeless, addicted people might feel compelled by the offer of large sums of money and a safe place to stay, they are not capable of freely consenting to experiments. The use of homeless, alcoholic people could also compromise the research results. Confused by their preexisting drug problems, they might fail to detect adverse reactions to the experimental drug. They might also be unwilling to report adverse effects for fear of being dropped from the study and left penniless and back on the streets.

An advertising campaign by Eli Lilly has raised the specter of unleashing more widespread adverse drug reactions on the public before these dangers can be detected or appreciated by doctors. Writing in *The Wall Street Journal,* physician Philip R. Alper (1996) asked, "Who to Trust: Drug Companies or Your Doctor?" Alper criticized Eli Lilly's promotion of a new, expensive form of insulin, Humalog, directly to the public through two-page ads in *People* magazine. The aim of these "market blitzes," according to Alper, "is to create consumer demand even before the doctor would be willing to use the drug spontaneously. Call it an end-run around the doctor, arm-twisting, manipulation, or whatever. The result is the same." These promotional tactics, Alper warned, will cause patients to press doctors to prescribe new drugs before their safety has been sufficiently demonstrated.

Before drug companies advertised directly to the public, the introduction of drugs into the marketplace was more gradual and hence safer. Many prudent doctors would wait to observe the results with new drugs before prescribing them to their own patients, knowing that serious or life-threatening adverse effects might not be detected before the drug was widely prescribed.

Alper (1996) expressed concern that Humalog and other drugs could meet the same fate as Eli Lilly's earlier medication, Oraflex, which, he says, was among the first to be promoted directly to the public. It caused fatalities and was taken off the market in 1982. Eli Lilly pleaded guilty to criminal charges in regard to Oraflex (FDA, 1985a; Shenon, 1985). Alper (1996) lamented bygone days, when Eli Lilly was a "bastion of the ethical drug industry." He attributed the problem to a general decay of ethical conduct within the pharmaceutical industry.

In another controversy, National Institutes of Health (NIH) researchers were conducting Phase 1 studies for a new Eli Lilly investigational drug called fialuridine (FIAU), as a treatment for liver disease ("FDA Tightens," 1994). The FDA accused Lilly of serious violations by failing to inform volunteers of all the risks and by failing to report severe drug reactions, including fatalities, until months, and even a year, afterward ("Hepatitis Drug," 1994). An NIH panel attempted to defend

the company and the institute from FDA accusations (Altman, 1994; Schwartz, 1994a; Thompson, 1994). The FDA (1994; Schwartz, 1994b) issued new proposed regulations that cited the failures of Eli Lilly in regard to its FIAU research.

Strattera (atomoxetine), the supposedly safer "nonstimulant" treatment for ADHD, turned out to be highly stimulating and is the only ADHD treatment required to carry a black-box warning, with a heading about how it can cause "Suicidal Ideation in Children and Adolescents" (chapter 11).

Lilly's new antidepressant, Cymbalta (duloxetine), was mired in controversy even before it was approved when a young woman committed suicide while taking the drug in a controlled clinical trial in which the drug was being tested for the treatment of stress urinary incontinence. Medical reporter Jeanne Lenzer (2005b) attempted to pursue the facts about this and other apparent deaths among patients taking duloxetine. Both Eli Lilly and the FDA stonewalled Lenzer on the grounds that duloxetine did not win approval for treating stress incontinence and therefore the information about that phase of its testing remained the private (and secret) property of Eli Lilly. Meanwhile, marketed as the antidepressant Cymbalta, duloxetine became another big moneymaking drug for the shrewd company. Once again, Eli Lilly put its financial interests ahead of science and public health.

Eli Lilly has a long history of minimizing the dangers of its products, resulting in unnecessary pain, suffering, and death. As an earlier example, several decades ago Eli Lilly began marketing Darvon (propoxyphene) as a relatively nonaddictive painkiller; but before long dependence and abuse became a problem of epidemic proportions. The controversy continues. The Public Citizen's Health Research Group (2006) petitioned the FDA to ban the drug on the grounds that there were over 10,000 "confirmed deaths" and 2,110 "accidental deaths" associated with the drug in the U.S. from 1981 through 1999. The analgesic is commonly prescribed in combination with the drug acetaminophen (Tylenol) as Darvocet and also as generic products.

Eli Lilly's methadone, used in drug addiction clinics as a substitute for other narcotics, has also drawn a great deal of persistent worldwide criticism. It has been diverted for illegal use as a highly addictive narcotic. It has caused many deaths, including a "public health crisis that involved an unusual spike in methadone overdose deaths in the Portland area," according to the Drug Enforcement Administration (2007).

Eager to take advantage of any drug-marketing niche that it can, Eli Lilly is often in the forefront of producing deadly chemical agents. This is nowhere more apparent than its attempts to hide the truth about its current big seller, Zyprexa.

## LILLY FIGHTS TO HIDE DATA ON DEADLY ADVERSE DRUG EFFECTS

Eli Lilly promoted Zyprexa as an atypical, and hence relatively safe, antipsychotic drug. It published badly skewed research trying to show that Zyprexa was relatively free of the risk of causing tardive dyskinesia when in fact it was not (chapter 4). More shocking, Zyprexa and other so-called atypicals turned out to produce an especially lethal adverse effect: acute and chronic diabetes. Once again, the Lilly product seemed to be among the worst offenders and became the center of another controversy in which Eli Lilly fought and continues to fight to hide the incriminating data, while paying out huge sums of hush money.

On June 15, 2005, in a multicase product liability suit, Eli Lilly settled for $690 million. Most of the case involved life-threatening diabetes caused by Zyprexa. I was hired as a medical expert by Hersh and Hersh, a California law firm involved in that multisuit, multistate legal action, and had the opportunity to evaluate sometimes lethal cases of diabetes and pancreatitis caused by Zyprexa. Some cases became chronic; other patients died within hours of onset. My Web site (http://www.breggin.com) contains more details on the Eli Lilly settlement. Meanwhile, similar cases have continued to be brought with potential payouts, or settlements, by the company estimated at $1.2 billion (Rosack, 2007).

Although Eli Lilly denies any wrongdoing whatsoever in the Zyprexa diabetes and pancreatitis cases, why would a company pay more than a *billion* dollars just to get the lawyers to drop false charges? That is hardly a nuisance settlement; it is a mammoth settlement. The answer lies in the part of the agreement that allows all of the incriminating documents to remain sealed.

Instead of trying to clear its name, and to conform with principles of transparency in business and medicine, Eli Lilly continues to fight for its right to hide itself beneath the dark mud of corporate secrecy. But in this case, the truth emerged (Creswell, 2006). Jim Gottstein, president of the Law Project for Psychiatric Rights (http://psychrights.org) in Alaska, obtained the sealed documents.[5] He then released the documents to the public, including evidence that Eli Lilly pushed the drug for off-label (unapproved) uses and hid the risk of Zyprexa causing pathological weight gain and diabetes—accusations that the drug company has denied (Creswell, 2006). The sealed documents became the basis of a series of *New York Times* articles (Berenson, 2006a, b&c; Creswell, 2006; "Playing Down the Risks," 2006). In an editorial on December 19, 2006, *The New York Times* discussed Lilly's hitherto secret documents and called for "congressional hearings that should focus on how well the industry

complies with existing laws and how effectively the FDA regulates the industry's marketing materials" ("Playing Down the Risks," 2006).

Eli Lilly went to court to fight Jim Gottstein's release of the documents and prevailed with the judge, who ordered them returned, but the documents were already sailing around the Internet. Writing in the *Journal of the American Medical Association,* physicians Aaron Kesselheim and Jerry Avorn (2007) viewed this as one of a series of positive events demonstrating the need for greater transparency in drug testing.

## GLAXOSMITHKLINE (GSK) AND PAXIL

### Paxil Overstimulation

Overstimulation is a common problem with all SSRIs and most of the newer antidepressants. For Paxil, as in the Prozac studies, agitation and insomnia were among the reasons for the dropouts. As documented on its official label, Paxil displays a similar pattern of stimulant effects: insomnia, tremor, nervousness, and anxiety. Like Zoloft, it also produces more somnolence and more sexual dysfunction than Prozac. In fact, somnolence (23.3%) is almost twice as frequent as insomnia (13.3%).

For Paxil, the list of psychiatric disorders reported in association with drug treatment is categorized under *nervous system.* Again, the company makes the point that these reactions were reported but not necessarily causally related. As of the early 1990s, the database included 4,126 patients. The list of *frequently* reported reactions includes, among others, central nervous system (CNS) stimulation, depression, and emotional lability. Chapter 7, table 7.1, lists many stimulant or stimulant-like adverse effects of Paxil summarized from the label, including hypomania/mania, euphoria, insomnia, nervousness, anxiety, agitation, hostility, psychosis, paranoid reaction, central nervous system stimulation, emotional lability, tremor, sweating, and palpitation.

Probably because Paxil is the most toxic and the most stimulating of the SSRI antidepressants, in recent years, I have been deluged with inquiries about cases of Paxil-induced mayhem, murder, and suicide (Breggin, in press). My experience is consistent with the FDA finding that among all of the antidepressants only Paxil, by itself and without being pooled with the other antidepressants, caused a statistically significant increase in suicidality in adults across the age groups (chapter 6).

Most of my inside information concerning Paxil was accumulated in late 1999 and remains valid to this day. At that time, I was asked by California attorney Don Farber to be the medical expert in a product liability

case that was brought by the family of Reynaldo Lacuzong in California against Paxil manufacturer GlaxoSmithKline (GSK).

## The Lacuzong Case[6]

Reynaldo Lacuzong drowned himself and his two small children in a bathtub. There was no evidence of any previous suicidality or violence on his part or of any animosity toward his children. He had never seen a psychiatrist, been to counseling, or displayed symptoms of psychiatric problems. For years, Reynaldo had received outstanding evaluations as an employee at a high-tech firm.

What had changed in his life? He was on the third day of taking Paxil 10 mg, the smallest available dose. It had been prescribed, most likely, to help him with the tension involved in giving up his customary one or two alcoholic beverages each evening.

Reynaldo quickly developed akathisia—agitation accompanied by a compulsive need to move—as well as other maniclike symptoms of irritability and anxiety. As described in chapters 6 and 7, antidepressant-induced akathisia can cause violence, suicide, psychosis, and an overall worsening of the patient's mental condition.

I became a medical expert in Reynaldo's case and was authorized by the judge in the case to examine the enormous volume of sealed drug company files concerning Paxil contained in GSK's record room. Attorney Don Farber and I, with the help of my assistant, Ian Goddard, devoted several days to examining the materials, including clinical trial data, adverse drug reaction reports and analyses, and telltale correspondence between the drug company and the FDA.

My July 21, 2001, expert report in the Lacuzong case was very lengthy and detailed charges of negligent behavior on the part of GSK, including the drug company's practices in developing and marketing Paxil and, in particular, its mishandling of information about the drug's dangerousness in regard to producing violence and suicide.

The Lacuzong product liability case against GSK was eventually resolved to the satisfaction of the Lacuzong family. The company, of course, denied, and continues to deny, all of the allegations made against it in the lawsuit. The settlement amount was not disclosed, but Mr. Farber went from working out of his home to working in a private office and has become one of a handful of highly experienced attorneys in the arena of antidepressant litigation.

As a part of the settlement, GlaxoSmithKline was allowed to keep secret its records, and I was not allowed to make public my findings. Because my findings were of grave public health significance, including my discovery that the company had manipulated data to minimize the threat

of Paxil-induced suicidality, Mr. Farber went to court to ask the judge to unseal the data, but the judge supported the company's right to withhold its proprietary information.

A few years later, after the Lacuzong case had been resolved, I became a medical expert in another Paxil suicide case, and I urged the new attorney to bring in Mr. Farber as a consultant. My report in this new case was limited in scope by the fact that everything I had learned in the earlier Lacuzong case was sealed, apparently including my original report. After my report was given to the court, GSK asked the judge in the U.S. District Court for the Southern District of Mississippi to dismiss the case on the grounds of insufficient evidence. Mr. Farber responded by producing my extremely detailed report in the Lacuzong case to bolster my accusations of negligence. As a result of the additional evidence, the judge allowed the case against the company to go forward.

A couple of years later, I discovered that the Lacuzong report was now available to the public by the U.S. District Court for the Southern District of Mississippi. Inadvertently, the submission of the report in the new court turned it into a public document available to anyone who requested it through proper channels. When I discovered that this was possible, I asked attorney Derek Braslow to obtain a copy of my report from the court, and then I placed the complete report on my Web site (http://www.breggin.com). I also wrote a series of three articles for *Ethical Human Psychology and Psychiatry* reviewing and excerpting large portions of it (Breggin, 2006a, b&d).

While I was writing the three articles in 2006, the FDA was in the process of requiring the antidepressant manufacturers to reevaluate their controlled clinical trials in regard to the risk of antidepressant-induced suicide in *adults*—the subject of my Lacuzong report. Before the last of my three reports was published, in May 2006, GSK published a Dear Healthcare Provider letter documenting that its reevaluation of its own clinical trial data showed that Paxil increased suicidality in adults, including all ages of adults suffering from major depressive disorder.

An important issue in the Lacuzong case was the capacity of one, two, or three daily doses of Paxil 10 to cause severe mental disturbances. During my site visit to the offices of GSK, I combed through adverse drug reaction reports to determine how early in treatment they began. I discovered that the first few days were the greatest time of risk.

My analysis of GSK's sealed documents confirmed that the company had hidden the true rate of suicidality by failing to report all suicide attempts on Paxil, by artificially inflating the number of suicides for patients taking placebo, and—in a fashion similar to Eli Lilly—by miscoding many suicides. The company had listed numerous suicide attempts under the relatively benign category of emotional lability (emotional

instability), making it difficult, if not impossible, to ever locate all of them.

Again like Eli Lilly, sealed company data also showed that the company systematically failed to report cases of akathisia and that some of the suicide cases were related to that anguish-inducing drug reaction. Again like Eli Lilly in regard to Prozac, the company disguised the stimulating effects of Paxil by constructing different subcategories for overstimulation, such as nervousness, anxiety, and hyperactivity, without adding them up to show the high overall rates of stimulation.

My search of the company files also disclosed correspondence from the FDA warning the drug company that its advertising and marketing practices were promoting an unfairly positive picture of the drug in comparison to other antidepressants and ordering the company to stop. All of these findings are documented in the series of three articles (Breggin, 2006a, b&d) and in the Lacuzong report on my Web site.

## PAXIL AND GSK CRITICIZED BY MEDICAL JOURNALS AND FOREIGN DRUG REGULATORY AGENCIES

Although the last year or two has seen exceptions (e.g., Kesselheim et al., 2007), it is rare indeed for medical journals to criticize drug companies. The journals are well-heeled partners in the psychopharmaceutical complex, deriving huge support from advertising. But the actions of GSK were so outrageous that journals took notice, at least in Canada and Great Britain.

On March 2, 2004, the *Canadian Medical Association Journal* reported on a 1998 internal GSK document that had been leaked to it (Kondro et al., 2004). The memorandum "advised staff at the international drug giant GlaxoSmithKline (GSK) to withhold clinical trial finds in 1998 that indicated the antidepressant paroxetine . . . had no beneficial effect in treating adolescents."

The leaked position paper prepared by the Central Medical Affairs team, a division of the company, referred to the drug by both its U.K. (Seroxat) and North American (Paxil) names, indicating that it aimed at influencing both markets. It provided guidance on how to manage two clinical trials conducted by the company. According to the position paper, the clinical trial results were "insufficiently robust" to support an application to regulatory authorities for the use of the drug in treating pediatric depression. GSK's Central Medical Affairs team recommended that the company "effectively manage the dissemination of these data in order to minimize any potential negative commercial impact."

The GSK document addressed two studies: In Study 329, paroxetine was no more effective than placebo, and in Study 377, placebo was actually better than paroxetine. The Central Medical Affairs team then explained that Study 329 would be published as an abstract (summary), but "it would be unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine."

Even worse, GSK made sure that Study 329 was eventually published in a whitewashed form in the prestigious *Journal of the American Academy of Child and Adolescent Psychiatry* (Keller et al., 2001). The title left no doubt about the scientific nature of the study: "Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial." The conclusion to the lengthy analysis, a mere one sentence long, left no doubt about what the reader was supposed to learn: "Paroxetine is generally well tolerated and effective for major depression in adolescents." That one sentence, so prominently displayed as the last line of the abstract, was a drug company public relations triumph, one bound to vastly increase the off-label prescription to children of their ineffective, dangerous drug.

With a list of 22 authors, many among the best known in the field, the GSK-engineered article is a living demonstration that America's psychiatric drug experts serve as a stable of horses kept and run by the pharmaceutical industry. Collectively, they manufactured a powerful go-ahead signal to the medical profession to liberally prescribe Paxil off-label to children.

## THE ATTORNEY GENERAL OF NEW YORK STATE TAKES ACTION AGAINST GSK AND PAXIL

When a drug fails to get FDA approval for a particular indication, such as GSK's Paxil for the treatment of depression in children, drug companies have exercised their proprietary right not to release information about the testing. In the case of Paxil, the company refused to release its clinical trial data for testing Paxil in children and adolescents, but as documented earlier in this chapter, it nonetheless used its influence with the journals and its sales force to spread the lie that the drug was safe and effective for children.

In withholding its data, the company hid behind the fact that the drug was not approved by the FDA for use in anyone under age 18 and therefore the data on testing children remained private property and could be kept secret. In taking this position, the company ignored the fact that it was surreptitiously promoting the drug, which was being widely prescribed to youth—a reality that meant doctors and consumers urgently

needed the truth. It also made a mockery of the need to protect America's children from adverse drug effects.

Partly inspired by the disclosures in the Canadian medical journal (see Sibbald, 2004) and events in Great Britain (see subsequent sections), on June 2, 2004, the attorney general of New York State, Eliot Spitzer, filed suit to force GSK to release its complete clinical trial data on Paxil and children (*People of the State of New York v. GlaxoSmithKline,* 2004; see also Office of New York State Attorney General Eliot Spitzer, 2004). This most remarkable document provided a detailed indictment of the drug company's activities.

The Spitzer suit claimed, "GSK has engaged in repeated and persistent fraud by misrepresenting, concealing and otherwise failing to disclose to physicians information in its control concerning the safety and effectiveness of its antidepressant medication paroxetine…in treating children and adolescents with Major Depressive Disorder."

The suit provided an analysis of efficacy in GSK's trials, indicating that the drug was often no better than placebo. In an analysis of safety, it found that several combined studies showed that "possibly suicide-related behaviors were approximately two times more likely in the paroxetine group than the placebo group." It disclosed that in five studies, "GSK coded suicidal thinking and acts, as well as mood swings, crying and similar behaviors, as 'emotional lability.'"

Spitzer's report revealed that internal GSK documents discussed how to spin negative studies into positive ones in an effort to "manage the dissemination of these data." As originally disclosed in the *Canadian Medical Association Journal,* this management included publishing a positive article about an essentially negative report (Study 329).

The suit alleged that GSK misrepresented the safety and efficacy of Paxil for children and youth to its own sales force, falsely stating, "*Paxil demonstrates remarkable Efficacy and Safety in the treatment of adolescent depression.*" This not only ignored withheld data but improperly pushed a drug for an unapproved use. According to the suit, "GSK would have had no reason to provide this information to sales representatives other than to use it to falsely characterize study 329 in their communications with physicians." As described in the previous section, the suit also described how the FDA, based on faulty information from GSK, lagged behind the British and Canadian regulatory agencies.

GSK settled the suit with the People of the State of New York and placed on its Web site the clinical trial data for the use of Paxil in children and youth. The Spitzer suit was one of the steps that eventually led to the FDA's label changes (Kesselheim et al., 2007).

## BRITAIN TAKES ACTION

The Committee on Safety of Medicines (CSM) of the British drug regulatory agency (MHRA) began a cascading assault on the SSRIs by coming down hard on the use of Paxil to treat depression in children and youth. Evidence from various clinical trials showed that episodes of suicidal behavior were between 1.5 and 3.2 times higher in children taking the drug than in those receiving placebo (Kondro, 2004).

In its September 2003 report, the CSM observed:

> An urgent meeting of the Group was convened on 4 June 2003 to consider clinical trial data which had just been received by the MHRA on the safety of paroxetine in the treatment of major depressive disorder in children and adolescents. Child and adolescent psychiatrists were invited to join the Group as visiting experts for the discussion of the data. The advice of the group informed CSM's announcement on 10 June, that paroxetine was contraindicated in patients under the age of 18 with major depressive disorder.

As a result of these British regulatory actions, GlaxoSmithKline was forced to issue a "Dear Healthcare Professional" letter concerning the risks associated with paroxetine, trade name Seroxat in Great Britain, and confirming that the drug was contraindicated in children and youth (GlaxoSmithKline, 2003):

> A recently completed programme of clinical trials in children and adolescents under 18 years of age failed to demonstrate efficacy in Major Depressive Disorder and there was a doubling of the rate of reporting of adverse events in the paroxetine group compared with placebo, including: decreased appetite, tremor, sweating, hyperkinesia, hostility, agitation, emotional lability (including crying, mood fluctuations, self-harm, suicidal thoughts and attempted suicide).
>
> Seroxat is now contraindicated in patients with major depressive disorder under 18 years of age.

GSK would never be compelled to issue a similar warning to U.S. healthcare providers, contraindicating the drug for the treatment of depression in those under age 18.

Great Britain went on to ban all of the SSRIs for use in depression in children except for Prozac, mistakenly giving credence to two clinical trials of Prozac conduced by Graham Emsley, a close associate of Eli Lilly (chapter 6).

Canada's regulatory agency, Health Canada (2004), followed with a warning to patients of *all ages* taking the newer antidepressants (SSRIs,

plus Wellbutrin, Zyban, and Remeron) about the risk of increased suicidality and violence (see also Kondro, 2004). The warning stated that these patients, *children and adults* alike, may "experience behavioural and/or emotional changes that may put them at increased risk of self-harm or harm to others."

Notice how far the FDA has continued to lag behind Great Britain. The FDA could have declared the SSRI antidepressants to be contraindicated in childhood depression, but it never did. Canada, although not banning the use of these drugs in children and youth, warned about increased suicidality in children and adults of *all ages*—also something the FDA has yet to do. In addition, consistent with warnings I have issued for more than a decade in my books and articles, Canada also warned about harm to others, the risk of violent aggression—something the FDA has yet to do.

Once the world's model for drug regulatory agencies, the FDA is now a model for accommodating the drug companies. However, events in Canada and Great Britain made it impossible for the FDA to continue to completely ignore what I had been warning about since 1991 in *Toxic Psychiatry* and in greater detail in the earlier edition of *Brain-Disabling Treatments in Psychiatry* as well as in several other books and scientific articles. Eventually, it put warnings on the labels for antidepressants about an increased risk of suicidality in children, adolescents, and young adults (chapter 6).

## British Psychiatry Versus American Psychiatry

As already described, the British drug regulatory agency declared that Paxil was "contraindicated" for children, taking a much stronger stand than the FDA. The Royal College of Psychiatrists (2003) then released a press release supporting the government's decision:

"The Royal College of Psychiatrists welcomes the clear advice from the Medicines and Healthcare Products Regulatory Agency banning the use of Seroxat [Paxil] in children and adolescents under the age of 18 in the treatment of depressive illness."

British medicine, including the Royal Society of Medicine, supported the ban on Paxil for treating depression in children. But as we have seen throughout this book, America's psychiatric and medical community have consistently fought against the FDA's label changes for antidepressants, even though they are weaker and do not call for a ban. As documented in chapter 6, organizations like the American Psychiatric Association, the *Journal of the American Psychiatric Association,* and the American College of Neuropsychopharmacology (e.g., Mann et al., 2006) rose up in outrage about the FDA doing anything to discourage the use of these drugs in children and adolescents.

Similarly, the press in Great Britain led the way in disclosing GSK's corrupt practices and in calling for a ban on the prescription of antidepressants to children, while the U.S. media did little or nothing. The BBC's *Panorama* helped push Britain's regulatory agency to take action and generated enough data to warrant analysis in scientific journals (Medwar et al., 2002; Medwar et al., 2003–2004). But in the United States, the press has remained largely indifferent and at times has stood fast with organized psychiatry and medicine in its resistance to the FDA's relatively weak measures.

What is the difference between Great Britain and the United States? Quite simply, the psychopharmaceutical complex has far greater influence in America, virtually dominating the health care industry and the media.

## BETTER THAN NOTHING?

Goodman and Gilman's textbook of pharmacology (Nies, 1996) warned that patients are unaware that FDA approval does not protect them from "even relatively common risks of new drugs." Not much has changed since then, other than the criticism of the FDA has escalated. The watchdog role of the Division of Psychopharmacologic Drug Products in particular is so diluted by its friendly relationship with industry, and its total reliance on their flawed data, that it often does more harm than good by lulling the mental health profession and the consumer into a false sense of security in regard to the safety and efficacy of psychiatric drugs.

The problem in regard to psychiatric drugs is compounded by the ideology of biological psychiatry. Since its inception in state custodial hospitals at the onset of the industrial revolution, psychiatry has always promoted the medical and biological model. Claims that new discoveries have been made that prove a biological basis for psychiatric disorders have been going on for centuries, with little change and no greater verification (Breggin, 1991c; Moncrief, 2001).

In reality, psychiatry can claim to be like medicine, but it cannot prove it. It can claim that depression or schizophrenia is like diabetes or cancer, but it can offer no evidence. There are no known biological and physical bases for the range of commonly diagnosed psychiatric problems, from attention-deficit/hyperactivity disorder (ADHD) to bipolar disorder and schizophrenia.

Approving a drug for the treatment of a real physical disease, such as pneumonia or diabetes, is very different from approving the use of specific drugs for expressions of human suffering that are psychological, social, and educational in origin. By giving its official imprimatur to the use

of drugs for the treatment of everything from ADHD to schizophrenia, the FDA takes sides in the conflict between biological and psychosocial psychiatry. It gives official government support to biopsychiatry and to brain-disabling therapies.

What is needed? To begin with, mental health professionals, physicians, and the public must become more skeptical, perhaps even cynical, and certainly more sophisticated about what psychiatric drugs and electroshock really do to the brain, mind, and person. Awareness of medication spellbinding and the brain-disabling principles of psychiatric treatment is key to this understanding. Psychiatric drugs do not cure mental disorders. Instead, their primary or essential effect is to cause brain dysfunction and compromise mental and emotional acuity.

Drug companies, the FDA, organized psychiatry, and other interest groups try to promote biopsychiatric interventions as grounded in good science. Instead, their widespread use defies both science and common sense and inflicts brain dysfunction and damage on millions of individuals. Unless they are responding to a placebo effect, even individuals who feel helped by the drugs are typically suffering from some degree of brain-disability and spellbinding.

## A FINAL WORD ON SPELLBINDING

How is it that highly toxic chemicals have become so popular for the treatment of mental and behavioral problems, creating a virtual plague of brain and mind dysfunction among adults and children? One answer is contained in this chapter: drug company promotion through every conceivable avenue, including the psychopharmaceutical complex and its latest innovation, direct-to-consumer marketing. Another answer is found in human nature, the ageless search for the easy solution to the inevitable suffering and frustration of life. But none of this fully accounts for why, year after year, human beings continue to imbibe substances that cause them more harm than good. That answer lies in chapter 1 in the concept of brain-disabling treatments in psychiatry, especially the newly described principle of medication spellbinding (intoxication anosognosia).

From alcohol and methamphetamine to Prozac, Valium, lithium, and Zyprexa, psychoactive substances disguise their adverse mental effects for the user. A person grossly mentally impaired by stimulants, benzodiazepine tranquilizers, mood stabilizers, or neuroleptics is likely to have little idea about how dysfunctional he or she has become. When the individual does perceive a change in himself or herself, positive or negative, it is almost never attributed to the causative agent: the drug. If the individual feels euphoric, it is attributed to good fortune and especially

to extraordinary personal attributes. If the individual feels angry or depressed, again, it is attributed to something other than the drug and usually blamed on oneself in a guilt fashion or on someone else in an angry fashion. Individuals who are given psychiatric drugs, especially stimulating ones like the newer antidepressants, often end up feeling that they are doing better than ever, when in reality their lives are falling apart. In the extreme, the drug-enthralled, spellbound individuals feel compelled to act in dangerous, destructive ways that are out of character and otherwise would feel wholly alien to them.

Even sophisticated individuals, including physicians, can fall prey to medication spellbinding (Breggin, in press). While educating individual patients and the public about adverse drug effects is important, it is not a flawless defense against being driven into apathy or mania, suicide or violence, by psychiatric drugs. The answer lies in restraint—in the medical profession and the public turning away from toxic chemicals as potential solutions to the frustration and suffering that afflicts so many human beings. It also lies in looking more toward psychological, social, and educational solutions for the wide variety of mental and emotional problems that are now so freely diagnosed and treated with drugs.

## NOTES

1. NDA is the manufacturer's basic documentation for the FDA in support of marketing the drug (see chapter 12).
2. One more vote against Lilly and it would have been a hung jury.
3. We must also doubt Lilly's methods of selecting Phase 1 subjects (see subsequent discussion).
4. The brain synthesizes serotonin from tryptophan, an essential amino acid found in a variety of foods. The ingestion of large amounts of tryptophan increases the production of serotonin.
5. Jim Gottstein is a board member of the International Center for the Study of Psychiatry (http://www.icspp.org).
6. The section about the Lacuzong case draws on a similar section in my book *Medication Madness* (in press).

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CHAPTER 15

# How to More Safely Stop Taking Psychiatric Drugs

There are no foolproof methods or blueprints for withdrawing from psychiatric drugs. Unexpected hazards can arise at any time. The following guidelines are drawn from a combination of the author's clinical experience and the scientific literature but cannot possibly cover all of the potential hazards involved in withdrawing from psychiatric drugs.

When health care providers decide to supervise withdrawal from psychiatric drugs, they must pay careful attention to the feelings or emotions of their patients or clients. Not only do patients deserve this respect and concern, their emotional reactions are the best gauge of how well the tapering process is going. Drug withdrawal requires a patient-centered approach.

When withdrawing a patient from psychiatric drugs, the health care provider should stay in close touch with the individual, especially at the start of the taper and toward the end, the times that serious problems are most likely to surface. In my practice, I try to see the patient at least once per week throughout the withdrawal process. Early in the taper or at other times of concern, I may arrange for phone call contacts in between sessions. If necessary, I will also stay in touch with family members who are informed about the drug withdrawal.

Once again, the patient's feelings are the most important barometer during tapering, and the health care provider and patient should stay in close communication.

In general, because the brain fights back against drug effects, withdrawal reactions tend to produce symptoms that are more or less the opposite of the drug's primary effect. That is, when the drug effect is removed, the brain's compensatory mechanisms are unmasked and take over.

For example, cigarettes "calm the nerves," and cigarette withdrawal causes the brain to generate extreme nervousness. Alcohol tends to sedate and suppress brain function, and alcohol withdrawal leaves the unmasked brain to react with overstimulation, anxiety, and even seizures. Similarly, sedative or antianxiety drugs such as the BZs can produce reactive overstimulation with insomnia, anxiety, and seizures during withdrawal. Conversely, stimulating drugs such as Ritalin (methylphenidate) and Adderall (amphetamine) tend to cause the brain to react during withdrawal with fatigue, sleepiness, and "crashing" during withdrawal. Lithium, a drug used to suppress manic episodes, causes manic episodes during withdrawal. The antipsychotic drugs can cause a new or worsening psychosis during withdrawal (tardive psychosis).

The most common withdrawal symptoms are emotional in nature. However, the same principle—that withdrawal reactions are the opposite of the primary drug effect—also applies to physical symptoms of withdrawal. A drug that controls blood pressure is likely to result in a reaction with excessively high blood pressure during withdrawal, and a drug that controls seizures can result in seizures during withdrawal.

There are exceptions, so very unexpected symptoms can surface during withdrawal, but it is helpful to keep in mind that withdrawal symptoms tend to be the opposite of the drug's primary or direct effect.

## BASIC PRINCIPLES

The literature on how to withdraw from psychiatric drugs is surprisingly sparse and fails to adequately describe the severity of the problem, the extreme care that must be taken. and the frequent need for collaboration. Nor does the literature mention how withdrawal spellbinds individuals, often rendering them unable to perceive their mental anguish as related to drug withdrawal (a typically insufficient discussion can be found in Shelton, 2006). The most detailed discussion of withdrawal from psychiatric drugs can be found in Breggin and Cohen's *Your Drug May Be Your Problem: How and Why to Stop Taking Psychiatric Medications,* first published in 1997 and updated in late 2007.

There are several key safety principles that should be observed during withdrawal from psychiatric drugs, especially if the drug exposure exceeds a few weeks or months or if the individual has serious preexisting

emotional problems. Some of the most basic safety principles include the following:

1. Drug withdrawal requires collaboration between the health care provider and the patient, in which a great deal of attention is paid to the patient's feelings about withdrawal and to the patient's reactions during withdrawal.

Except in emergencies, withdrawal should be done at a pace dictated by the patient's wishes and feelings of comfort. In no case should the patient's concerns be ignored or minimized. Some examples of emergencies requiring relatively rapid or immediate withdrawal include the development of signs of tardive dyskinesia or neuroleptic malignant syndrome caused by neuroleptics; diabetes or pancreatitis caused by atypical neuroleptics; serotonin syndrome, violence, or suicidality caused by antidepressants; seizures caused by neuroleptics, stimulants, and some antidepressants; and depression or tics caused by stimulant drugs. Many medications can cause emergencies involving severe skin rashes, liver failure, or kidney disease. Many drugs, as this book has documented, can cause mania or psychosis.

2. Someone close to the individual should help in monitoring potentially dangerous mood changes.

Drug withdrawal, like drug use, tends to be spellbinding. The individual undergoing withdrawal is likely to attribute the subsequent emotional instability and suffering to something other than the drug, resulting in harmful thoughts directed inward or toward other people. Typically, individuals tend to mistakenly attribute their withdrawal symptoms to their own underlying emotional problems, causing them to fear that they need to continue taking the medication.

To help monitor these mood changes, I usually invite the closest family member to a session with the individual undergoing the withdrawal. In the session, I describe typical withdrawal symptoms, especially the more dangerous ones, and warn that the patient may not recognize them. Also, on occasion, I discourage patients from withdrawing from medication on an outpatient basis after years of exposure to antipsychotic drugs, especially if they have an insufficient family or social network to support them during this potentially distressing and psychosis-inducing process.

3. Supervision by an experienced health care provider can be lifesaving.

When drug exposure has lasted for years, when multiple drugs are involved, or when the individual suffers from serious mental problems, clinical supervision during withdrawal is especially important.

4. The time required for tapering varies widely.

If the taper lasts at least 10 days, it will probably avoid potentially life-threatening physical reactions, such as seizures or blood pressure spikes, but most individuals need more time to soften the emotional suffering and instability that commonly accompany withdrawal from psychiatric drugs. As a rough rule of thumb, for every year of drug exposure, a month of drug tapering may be required. I use this very rough estimate to encourage people to be patient during their withdrawal from medications.

5. Informed consent is an ethical and legal requirement, and also a necessary part of educating the patient about potential problems during drug withdrawal.

The risks and benefits of withdrawal should be discussed with the patient before and during the process. Consent requires more than the reciting of information by the health care provider. It entails a back-and-forth discussion, in which the patient asks questions and obtains satisfactory answers. In the process, the patient will also become better educated about the pitfalls of withdrawal. Whenever feasible, I include family members in the process of educating the patient.

Many doctors seem to mistakenly believe that informed consent is a one-shot effort; you warn the patient about a few potential adverse effects and then forget about it. In fact, even patients who are functioning on a high intellectual level will misunderstand or forget what they have been told about potential side effects. During routine medication treatment and especially during withdrawal, the caregiver must regularly remind patients about potential adverse effects and to ask questions calculated to elicit information that may unearth a developing problem. For example, if a patient is withdrawing from antidepressants, I will ask *each session* about emotional instability, irritability, and angry or depressed feelings, as well as other adverse effects such as imbalance or headaches. Surprisingly, patients will often initially report that they have had an uneventful week but when asked will recall that in fact they had a nasty temper tantrum or very bleak few hours of feeling very depressed.

Driven by medication spellbinding, patients frequently fail to identify obvious drug withdrawal reactions, such as an abrupt increase in

irritability or mood instability, and some patients must be repeatedly reminded that they are experiencing withdrawal symptoms. As noted earlier, they will tend to attribute their symptoms, such as irritability or mood instability, to their own emotional problems or to provocative actions by other people.

## SPECIAL PROBLEMS

A number of issues routinely arise during withdrawal and are worth addressing. Of course, these are not the only special problems that come up, but they are among the more salient ones.

1. When the patient has been prescribed multiple drugs at once, it is usually easier and safer to taper one drug at a time.

Removing more than one drug at a time can increase the hazards of withdrawal. In addition, it makes it difficult or impossible to determine which drug is causing problems during withdrawal.

2. In the absence of an emergency or a special reason to the contrary, it is usually easiest and safest to begin by tapering the drug that has been most recently started. Drugs that have been taken for a relatively shorter period of time are generally easier to withdraw from.

Commonly, a patient taking several drugs will have started one in the last few weeks. This is usually the easiest and quickest one to taper. Sometimes the most recent drug can be stopped immediately. If that occurs uneventfully, another drug taper can be started the following week. However, I try not to begin a new drug taper until the patient has fully, or nearly fully, recovered from the previous one. If a problem develops while a patient is being withdrawn from more than one drug at a time, it can be difficult to figure out which medication is causing it.

3. It is generally preferable to remove sleeping aids last.

Loss of sleep is very distressing and can seriously impair any attempt to withdraw from drugs. Therefore, unless the sleeping medications are posing a serious problem in themselves, I suggest continuing them until the other drugs are withdrawn. It is especially necessary to delay removing sleeping aids when the individual is taking stimulants or stimulating antidepressants that may generate anxiety and insomnia.

4. Selecting the order of drugs for tapering requires taking a careful history of the patient's relative degree of sedation or stimulation.

If the patient is experiencing too much sedation, then it may be best to taper the sedatives first. Similarly, if the patient is overstimulated, it is a good idea to start by withdrawing stimulants.

5. When the individual is dependent on a controlled substance, such as a benzodiazepine or stimulant, it may be easiest to taper the patient off other drugs before addressing the drug dependence. In general, carry out the easier withdrawals first, leaving the most difficult one until last. That way, some of the drugs at least can be withdrawn more rapidly before the more prolonged withdrawal begins.

Withdrawing from benzodiazepines can be exceedingly difficult. If a patient has been taking Xanax for several years, it might be preferable to withdraw mood stabilizers or antidepressants first. When the patient gains confidence withdrawing from the other drugs, he or she may feel more confident in approaching the difficult benzodiazepine taper. As in every important clinical decision, this one should be made in collaboration with the patient. Especially in regard to benzodiazepines, treatment in a drug rehab facility may be necessary.

6. When a drug is taken several times a day, weigh the patient's needs in determining which of the doses to initially reduce.

For example, if the patient is taking a benzodiazepine three times a day, be cautious about withdrawing the morning dose since it may precipitate or worsen morning withdrawal. Similarly, be cautious about removing the nighttime dose since it may cause or exacerbate insomnia. Because of these concerns, it may be best to reduce the middle dose first. Also take into account what time of day your patient needs to be most alert.

7. If a physically painful or emotionally distressing withdrawal reaction develops during the tapering process, returning to the previous dose will usually ameliorate it.

For example, if a patient becomes extremely anxious or irritable 1–3 days after reducing Paxil from 20 mg to 15 mg, returning to the 20-mg dose will usually quickly relieve the withdrawal symptoms. Withdrawal might then be resumed at a later date with a 17.5 mg dose or by spacing

20 mg and 15 mg every other day. However, because it can be disruptive to brain function, I prefer not to give doses on alternate days until the end of tapering when the doses are becoming very small.

8. Avoid giving additional psychoactive drugs to treat withdrawal reactions.

For example, if a patient becomes very anxious while withdrawing from Paxil or Xanax, rather than adding another drug, it is best to return to the previous dose. Adding additional drugs makes it more difficult to evaluate the patient's progress and condition during withdrawal. Every psychiatric drug multiplies the biochemical imbalances in the patient's brain and makes it more difficult for doctor and patient alike to evaluate what's happening.

9. Very small doses may be useful and even necessary to stave off withdrawal symptoms during the last stages of tapering.

Although I know of no scientific explanation, some patients get relief in the last days or weeks of tapering by taking very small doses of a medication, for example, by breaking up a tablet of Xanax 0.5 mg into several relatively tiny pieces or by using an eyedropper to dispense 1 or 2 mg of fluid Paxil (paroxetine).

## AVOIDING LIFE-THREATENING RISKS

There are two different kinds of life-threatening adverse events associated with drug withdrawal: physical risks and emotional risks. The most common physical risks are seizures and blood pressure spikes. The most common emotional risks are violence against self and others and manic or psychotic reactions.

### Physical Risks During Withdrawal

The physical risks are the easiest to deal with. In the appendix, the drugs listed in Part III: Sedative, Hypnotic, and Anxiolytic Drugs (Tranquilizers and Sleeping Pills) have the potential to cause seizures during withdrawal. The only exception is Rozerem (ramelteon). In Part V: Lithium and Other Drugs Used as Mood Stabilizers, those drugs that are labeled as antiepileptic also pose the risk of withdrawal seizures. In regard to all of these drugs, if the gradual taper lasts at least 10 days, there is much less risk of a withdrawal seizure.

In the appendix, *some* of the drugs in Part V are antihypertensive agents. If those drugs are stopped abruptly, a dangerous spike in blood pressure may occur. Usually, a short taper is sufficient to reduce this risk. To determine how many days this taper should take, check the drug label in the *Physicians' Desk Reference* or another source of drug information.

## WITHDRAWAL SYMPTOMS ASSOCIATED WITH SPECIFIC DRUGS

### Withdrawal From SSRIs

The SSRI medications, such as Prozac, Paxil, Zoloft, and Lexapro, and the SRIs, such as Effexor, almost always produce withdrawal symptoms (see chapter 6). These often severe symptoms were ignored for years and even today are too often ignored by a psychiatric community bent on blaming the patient's suffering on so-called mental illness.

Consistent with my own clinical experience, Pasadena, California, psychiatrist Stuart Shipko (2002) listed the following major categories of SRI withdrawal symptoms:

1. vertigo, tinnitus, and dizziness
2. electric, shocklike sensations, mostly commonly in the head, neck, and shoulders (zaps)
3. nausea and vomiting
4. flulike symptoms
5. nightmares and insomnia
6. irritability
7. a severe depressive syndrome with characteristic easy crying, different in quality from any depression prior to taking the SRI
8. new onset of intense somatic and mental anxiety lasting minutes to hours not present prior to taking the SRI

Because of the capacity for antidepressant withdrawal to cause mania (Benazzi, 2002), I would add an additional major category:

9. euphoric or maniclike reactions, most commonly with shallow emotions, giddiness, and poor judgment

Withdrawal symptoms from SSRIs can be very severe and lasting. In a few cases in my clinical practice, patients have chosen to remain on very low doses for sustained periods of time because they were unable to

tolerate the dizziness (often a sensation of instability) or emotional turmoil resulting from the final stages of withdrawal. As mentioned earlier, sometimes I prescribe the medication, such as Prozac in liquid form so that the patient can titrate very small doses in the last stages of withdrawal. Shipko (2002) provided a checklist for SRI withdrawal symptoms that the clinician and the patient may find useful. SRI withdrawal is so spellbinding that patients need to be reminded again and again that they are undergoing a withdrawal reaction, not a mental illness. They need regular reassurance from a health care provider with whom they can remain in contact between sessions.

## Withdrawal From Tricyclics

Tricyclic antidepressants commonly produce withdrawal, frequently in the form of cholinergic rebound, with flulike symptoms such as nausea and vomiting, diarrhea, muscle aches, headache, fatigue, and anxiety (Breggin, 1991b). McMahon (1986) summarized:

> Autonomic symptoms are most common and include gastrointestinal disturbance (nausea, diarrhea), general somatic distress (myalgias, malaise, headache, rhinorrhea), sleep disturbances (insomnia, nightmares), and cardiovascular symptoms (arrhythmias, ventricular ectopy). Psychotic decompensation, withdrawal mania, and general anxietylike symptoms have been attributed to abrupt withdrawal of cyclic antidepressants.

Maxmen and Ward (1995) provided an extensive list of tricyclic antidepressant withdrawal symptoms. One group of withdrawal symptoms includes a flulike syndrome without fever: anorexia, nausea, vomiting, diarrhea, queasy stomach, and cramps. A second group involves sleep disturbances: insomnia, hypersomnia, excessive dreaming, and nightmares. A third group includes mania and hypomania. Maxmen and Ward pointed out that these symptoms can also be experienced between doses as the blood level drops.

In my clinical practice, I have seen relatively few cases of very severe, lasting withdrawal reactions from the older antidepressants in comparison to the newer ones, with which serious withdrawal problems are frequent.

## Withdrawal From Lithium and Other Mood Stabilizers

As described in chapter 8, it is now firmly established that withdrawal from lithium causes an increased rate of manic attacks in the 1–2 months after stopping the drug (Suppes et al., 1991). Cavanagh et al. (2004), in a 7-year follow-up, found that lithium withdrawal caused both mania

and depression, while stopping the medication did not worsen long-term outcome. Most clinicians seem to believe that medication is an absolute necessity for warding off future manic episodes, but I have not found this to be true, and the study by Cavanagh et al. confirmed that medication treatment leads to withdrawal reactions while doing without the medication does not worsen long-term outcome.

Withdrawing from lithium must be treated as a potentially high-risk event requiring clinical monitoring and as much family support as possible. Although the data are sparse, any drug used as a mood stabilizer should be considered a risk for causing withdrawal mania.

It bears repeating that any mood stabilizer that is also approved for use as an antiseizure drug presents the risk of dangerous withdrawal seizures, and any mood stabilizer used as a treatment for hypertension presents the risk of dangerous blood pressure spikes during withdrawal. Some of these drugs are listed in the appendix.

## Withdrawal From Neuroleptics

Many neuroleptics produce withdrawal symptoms that mimic the flu, including emotional upset, insomnia, nausea and vomiting, diarrhea, anorexia and weight loss, and muscle aches (chapter 4). This is particularly strong in drugs that have anticholinergic properties such as Thorazine and Mellaril.

During withdrawal from both the older and newer neuroleptics, the individual can experience severe abnormal movements during withdrawal. They can be painful and frightening and can become persistent in the form of tardive dyskinesia (chapter 4). Severe emotional suffering and psychosis are common withdrawal reactions (chapters 4 and 5). Children may undergo severe behavioral worsening. Depression can occur.

If an individual has been taking neuroleptics for several months or more, withdrawal can be very difficult. If the individual does not have a strong social and family network, it can be too difficult to attempt in an outpatient practice. Yet there are very few hospitals that will withdraw patients from neuroleptics, unless they are suffering from severe tardive dyskinesia, neuroleptic malignant syndrome, or some other catastrophic adverse drug reaction. As mentioned earlier, many patients who have come off neuroleptics after developing signs of tardive dyskinesia go on to enjoy a much better quality of life when drug-free.

## Withdrawal From Stimulants

With the exception of Strattera, all of the stimulants approved for the treatment of attention-deficit/hyperactivity disorder cause potentially

serious withdrawal reactions. Typical reactions including crashing with depression, exhaustion, social withdrawal, irritability, and suicidal feelings. They can occur between doses or after missing a single dose. Parents and teachers often mistake a withdrawal reaction for proof that the child needs medication.

Children and adults vary widely in the degree they suffer from withdrawal reactions. Many children are taken off stimulants during weekends, vacations, and summer recess without any serious difficulty. If a particular child is accustomed to these frequent withdrawals lasting a few days or more, he or she can probably withdraw from the medication with little or no difficulty. However, if the child has been taking the drug regularly without breaks for months or years, withdrawal must be done carefully and cautiously.

When withdrawing children from stimulants, I always work very closely with the parents, encouraging them to stay in close touch with how their children feel. After learning to check on how their children are feeling in the morning before school, in the afternoon and evening, and at bedtime, many parents happily maintain the practice after the withdrawal is over. I also work with parents on any difficulties they are having in developing a consistent plan for rational discipline and unconditional love (Breggin, 2001c & 2002b for more details). Sometimes I work with the child's teachers as well. Every child diagnosed with ADHD that I have removed from stimulants has greatly improved. Almost invariably, the parents have felt that they "have their child back."

The more difficult problems in helping children arise after the unfortunate youngsters have been exposed to long-term drug treatment with multiple medications that cause persistent harm to brain function. To compound the problem in those cases involving children on multiple drugs, the parents or adult caregivers are sometimes too dysfunctional to participate responsibly in therapy aimed at improving their childrearing practices. However, where the parents (or the single parent) are responsible and willing to learn new approaches, I have been able to remove many children from multiple medications administered to them over many years, leading to much happier and more productive lives (Breggin, in press).

## Withdrawal From Benzodiazepines

Withdrawal signs from benzodiazepines like Xanax, Klonopin, Ativan, and Valium often begin with insomnia, irritability, and nervousness, progressing to more serious reactions such as abdominal cramps, muscle cramps, nausea or vomiting, trembling, sweats, hyperarousal and hypersensitivity to environmental stimuli, confusion, depersonalization, loss

of impulse control, anxiety and obsessional states, psychosis and organic brain syndrome, and seizures (see chapter 12). Withdrawal from these drugs can be difficult and prolonged and may require hospitalization. Too abrupt a withdrawal can lead to dangerous seizures. Many people find that it takes months or years to recover after complete withdrawal, and some people manifest continuing long-term problems, including memory difficulties, weakness, and fatigue.

Most sleeping medications present similar withdrawal problems. They are listed in the appendix.

If doctors choose to prescribe BZs, they need to realize that their antianxiety effects are short lived and that long-term effects are potentially disastrous.

## PSYCHOTHERAPY DURING DRUG WITHDRAWAL

Psychotherapy or counseling during the withdrawal process should focus, first and foremost, on monitoring the patient for the development of destructive tendencies such as suicidal or violent ruminations. In addition, therapy should focus on reassuring the individual that any newly developing emotional disturbances or obsessive ideas are almost certainly due to the withdrawal process and will diminish with time. Finally, the individual should be reassured that absent an emergency involving a serious adverse drug reaction such as tardive dyskinesia or antidepressant-induced mania, there is no need to rush with the tapering process. During each session, patients should be reminded that if the withdrawal becomes unendurable, then they should communicate with the health care provider and return to the previous dose.

Insight therapy, including delving into the past, should be avoided during withdrawal. Individuals are sometimes tempted to attribute mood swings to their personal problems or to issues from the past, but little or no benefit can be gained from such explorations until withdrawal has been completed. The exploration of painful emotional issues during withdrawal can exaggerate them to a dangerous degree. During withdrawal, patients often feel guilty, frightened, or even horrified by unanticipated changes in their feelings. They may feel aghast at their desire to withdraw from loved ones, by their extreme mood swings, or by self-destructive or angry impulses. At this critical time, it is harmful to examine these emotions as if they have roots in the past or in predisposing factors. Instead, the individual needs to be reminded that he or she is undergoing a time-limited withdrawal. Patients need reassurance and competent supervision, not depth psychotherapy, during medication tapering. The brain dysfunction that inevitably accompanies withdrawal

makes it impossible for the patient to adequately participate in insight-oriented or depth therapy. Patients can be told that there will be time to explore such issues when they have regained their emotional equilibrium after the withdrawal is complete. At that time, in some cases, they may find that it is worthwhile to look for predisposing factors that influenced their emotions during withdrawal, but often, the painful emotions will disappear, removing any need to think about them further.

As a psychiatrist who offers psychotherapy, I often work with couples and families because I find that loved ones can empower each other to grow. During the tapering process, I especially like to see family members, or at the least to give them ready access to me, in order to have them help in monitoring the withdrawal process. Always remember that patients become spellbound by withdrawal and are likely to be the last to recognize that they are suffering from withdrawal symptoms.

## FACING THE AFTERMATH OF MEDICATION SPELLBINDING

When patients begin to recover from being medication spellbound, many issues may require attention from the health care provider. A man may realize that he rejected his beloved wife during a Zoloft-induced mania that lasted weeks or months, or a woman may realize that she neglected her children during a Xanax haze that lasted for years. These individuals may want help going through a period of mourning. During and after drug withdrawal, some people will begin to confront the horrific nature of their actions while spellbound by antidepressants, tranquilizers, or stimulants, including violent and criminal acts. Overcome with remorse as well as guilt and shame, they will need help in understanding the role played by medication spellbinding.

## CELEBRATING A NEW LIFE

Soon after successfully withdrawing from all psychiatric medication, many patients experience an enormous period of personal growth. In the case of children, they may literally undergo a physical growth spurt, and many adults may have a return of energy. But most important for children and adults, when drug-free, they will find themselves with more fully functioning brains and minds. Memory may become sharper, thinking may become more nimble, and emotions may grow more full. Their passion for life will be unleashed from its pharmacological chains. It can

be an especially productive time for therapy or counseling, especially with health care providers who welcome spontaneous feeling and creative change in their patients.

## THE THERAPIST'S HEALING PRESENCE

I have been focusing on what might be called technical issues. It is important for the therapist to have a good grasp of adverse withdrawal effects, but the two main points are simple and basic: Go slow and pay attention to the patient's feelings. Regardless of how you view psychiatric medications, the decision to withdraw from drugs must be made by your patient. Except in emergencies, I avoid encouraging patients to stop taking their drugs. I may explain that I will not prescribe medications indefinitely but that they can easily find other doctors to continue their drugs.

Once the patient has made the decision to withdraw from psychiatric medication, the health care provider can offer encouragement. But patients should not feel that they are stopping their medication because the doctor wants it. Patients should not feel guilty if they decide to continue or resume taking their medications. They should not feel that they have failed themselves or their doctors. Withdrawing from psychiatric drugs can become an overwhelmingly difficult experience, and in such cases, the patient's desire to remain on medication should be respected. In a few cases, when patients of mine have been unable to stop their medications, I have continued to prescribe for them. Although I never start my patients on psychiatric drugs, I respect that some of them may not be able to go through the process of withdrawing from them.

In addition to knowledge and experience, the health care provider offers what I have called a *healing presence*. Healing presence is the ability to be present, caring, and involved with patients while maintaining an ethical perspective that completely respects their autonomy and separateness. In *The Heart of Being Helpful* (Breggin, 1997b), I described the active process involved in developing a healing presence: To create a healing presence, we fine-tune our inner experience to the inner state of the other person. We transform ourselves in response to the basic needs of the person we are trying to heal and help. Ultimately, we find within ourselves the psychological and spiritual resources required to nourish and empower the other human being.

The final chapter continues the discussion of therapy and proposes 20 guidelines for working with very disturbed people without resort to psychiatric drugs, electroshock, or involuntary treatment.

CHAPTER 16

# Failed Promises, Last Resorts, and Psychotherapy

Although the focus of this book is on the brain-disabling, spellbinding effects of biological treatments in psychiatry, it is important to conclude with a reminder that there are better alternatives in the form of psychological, social, and educational interventions.

Adults who are negotiating life relatively well can often nonetheless benefit from individual counseling or therapy. Couples therapy can often help people lead happier, more fulfilled lives. Emotionally disabled adults, including those diagnosed as schizophrenic, usually need comprehensive help that involves responsible members of the family and community resources.

Children, especially those who have not reached adolescence, respond best to therapies that focus on the adults in their lives. When the adults improve their approach to the child, the child improves. Even with children who have been diagnosed with serious disorders, I spend much more time with the parents than with the child, teaching them improved ways of relating to their offspring. I may also work directly with the school to develop a consistent approach, or I may have the parents communicate with the school about how they are implementing new approaches to their child.

Children who are on the verge of being institutionalized in a mental facility or prison often need something more extensive than the services

of a single therapist. They need wraparound services, which includes home visits, family therapy, parenting classes, guidance in utilizing social services, and assistance in getting employment for the parents—all aimed at restoring some order to disintegrating families (Morrison-Velasco, 2000a, 2000b). I have described therapy with children in a number of my books, including *The War Against Children of Color* (1998), *Talking Back to Ritalin* (2001c), *Reclaiming Our Children* (2000b), and *The Ritalin Fact Book* (2002b).

## ACTUALLY TALK TO THEM?

Meanwhile, organized psychiatry has begun to realize that professionals have stopped talking to patients diagnosed with schizophrenia, hence an editorial in the *American Journal of Psychiatry* by Keith (2006) titled "Are We Still Talking to Our Patients With Schizophrenia?" It goes without saying that the journal is not going to recommend treating these people without drugs, but it does recognize that the profession has gone overboard, noting that the 30-year war between biological and psychoanalytic psychiatrists has left American physicians reluctant to carry on psychotherapy with patients diagnosed with schizophrenia. I would add that they lack not only the will but also the competence to relate in a caring and insightful manner to deeply disturbed human beings.

Similarly, in his March 3, 2006, column in *Psychiatric News,* American Psychiatric Association president Steven Sharfstein wrote a feature headlined "Psychosocial Treatment: We Owe It to Our Patients." He described how at last year's annual meeting, he had "decried the fact that for psychiatry the biopsychosocial model has become the 'bio-bio-bio model.'" Echoing what I wrote in *Psychiatric Drugs* in 1983 and in more detail in *Toxic Psychiatry* in 1991, he observed with unusual candor, "Psychiatry has, for what I would argue more for economic reasons than anything else, focused on the psychopharmacological model to the detriment of the psychosocial aspects of care." Addressing the treatment of "schizophrenia," he concluded, "Bio-bio-bio is not enough. We owe our patients no less than to recommend and promote the use of psychosocial interventions that have been demonstrated to be beneficial for this devastating disorder." Of course, he has no plan whatsoever to give up medicating the patients while offering them psychosocial interventions, and as we saw in chapter 11, he fought against any attempt by the Food and Drug Administration (FDA) to increase the warnings about stimulant drugs for fear of discouraging their already inflated prescription rates for children.

Meanwhile, the latest push within establishment psychiatry is for treating patients labeled schizophrenic with cognitive therapy (Turking-

ton et al., 2006), a limited, focused approach to guiding the patient in replacing self-defeating ideas with more effective ones. It lacks emphasis on what very disturbed patients need most of all—a trusting therapeutic relationship—but the modern psychiatrist has no training or inclination to relate in a caring, therapeutic manner to people whom he diagnoses as schizophrenic. Even worse, in a psychiatric setting, one of the main goals of cognitive therapy is *compliance:* getting patients to accept the idea of taking psychiatric medication. It is a case of using therapy to manipulate patients into submissively accepting highly toxic chemicals.

## AN EXTENSIVE LITERATURE

There is an extensive literature on nondrug alternatives for every severity of psychiatric problem, including those patients labeled schizophrenic (e.g., Bratter et al., 2006; Breggin, 1991b, 2006c; Colbert, 2001; Fergusson, 2000, 2002; Irwin, 2004a, 2004b; Karon, 2003, 2005; Karon et al., 1981; Karon et al., 1999; McCready, 1995, 2002; Mosher, 1996; Mosher et al., 2004a; Mosher et al., 1989; Mosher et al., 2004b; Read et al., 2003; Stanton, 1999). Most of these reports describe working with children and adults within institutions. All of them emphasize a noncoercive, nondrug, caring approach, even for the most difficult patients.

Mosher's, McCready's, Fergusson's, Stanton's, and Karon's publications focus on helping the most disturbed children and adults, including those who would often be incarcerated and diagnosed as schizophrenic. Mosher (Mosher, 1996; Mosher et al., 2004a; Mosher et al., 1989; Mosher et al., 2004b) developed Soteria, a residential homelike treatment model for patients with severe, acute emotional breakdowns ("schizophrenia"). He used nonprofessional therapeutic aides selected for their empathic qualities who were supervised by a social worker who emphasized patient autonomy and healing relationships. In controlled trials comparing this nondrug residential treatment with admission to a mental hospital, Soteria patients did better, and of course, they did not suffer from multiple, dangerous neuroleptic adverse effects.

I have described Soteria and other alternatives, including a state hospital volunteer program that I led in the 1950s, in *Toxic Psychiatry* (Breggin, 1991c). I have also coedited a compendium of articles by therapists who offer a variety of approaches to helping deeply disturbed patients, including psychotherapy, family therapy, residential milieu therapy, and peer counseling (Breggin and Stern, 1996) and another compendium that focuses on empathy as the central aspect of healing for all human beings (Breggin et al., 2002). In *The Heart of Being Helpful* (1997) I look most closely at my own approach to therapy.

A Finnish study demonstrated the effectiveness of using a therapeutic, family-oriented approach to treat persons diagnosed with their first schizophrenic episodes (Seikkula et al., 2003). A meta-analysis of existing therapy studies confirms the efficacy of psychosocial approaches to people labeled schizophrenic (Gottdiener et al., 2002). Irwin's (2004b) review of controlled trials comparing psychosocial and drug approaches to patients diagnosed schizophrenic summarized, "Neuroleptics interfere with long-term recovery and, if appropriate psychosocial interventions are available, are not even necessary for short-term behavior control" (p. 99).

Studies by the World Health Organization have shown that patients diagnosed by conventional standards with schizophrenia recover much more frequently and rapidly in Third World countries, where they can benefit from the support of extended family and where they are less likely to receive neuroleptic drugs (de Girolamo, 1996). Conversely, they recover more poorly in Western countries, where they have weaker family support systems and are exposed to toxic psychiatric drugs.

Antonuccio et al. (2002) reviewed the literature confirming the ineffectiveness of antidepressants and the literature on the effectiveness of psychotherapy in treating depression and concluded that psychotherapy is safer and more effective. Most of the individuals were treated in outpatient settings.

Not surprising, lifestyle changes can help more than psychiatric drugs, with no adverse effects on the brain and mind. A number of studies have also described the antidepressant effects of exercise (Babyak et al., 2000; Blumenthal et al., 1999).

## PSYCHIATRIC DRUGS AS A LAST RESORT

A young man named Maurice came to see me about his episodes of severe anxiety. He would become abruptly frightened; adrenaline flooding his body would make his heart beat faster and his palms sweat; and he would feel doomed, as if he were going to die. Maurice knew he was not going to die, but at the moment of these attacks, he felt in acute danger. To abort these episodes, he carried a plastic pill container with a few tranquilizer tablets. He had not used one in months, but their presence in his pocket gave him a sense of security. He felt sure he would have an anxiety attack if he did not carry the pills along with him.

Our whole society has become like this young man. Pills have become our source of security and our last resort. Most of us can imagine life without electroshock or lobotomy, but few of us seem able to imagine it without having psychiatric drugs as a source of security and a last resort, if

not for ourselves, than at least for other people. Our society now tolerates the psychiatric drugging of 2-year-old children, although even some leaders within the medical profession show alarm over this (Coyle, 2000).

Even for people who do not necessarily turn to them, psychiatric drugs linger in the backs of their minds as the last resort. They have heard that so-called mental disorders are caused by genetic and biochemical defects in the brain and that psychiatric drugs can correct these defects. These people do not consciously think to themselves, "I have faith in biochemical imbalances and drugs," but in fact, that is how their minds are working.

Even if we do not want to take these drugs for ourselves, we imagine that they must be necessary for other people who become so depressed that they cannot get out of bed or so violent that they are a menace to society. People may not know how to define "schizophrenia" or "bipolar disorder," but they know that these conditions are psychiatric disorders that can only be treated with drugs. They may have little idea what goes into making the diagnosis of attention-deficit/hyperactivity disorder, but they know that some children need drugs to control their behavior so that they can go to school and learn. Many people would fear for society if psychiatric drugs were not readily available and widely used.

In Maurice's case, he had ample reason to feel anxious. He had grown up in an alcoholic family, and his father had sometimes beaten his mother in front of him. As a child, Maurice suffered from spells of terror in anticipation of his father losing control. When his father hit his mother, little Maurice would cower in fear, guilt, and shame. As a young adult, Maurice's anxiety attacks erupted as he tried to come to grips with becoming an independent man who could take command of his life. The deepest roots of his anxiety were buried in the feelings of fear and helplessness that were emblazoned on his mind in childhood. Now the fear and helplessness resurfaced, making it hard for him to take charge of his adult life in a brave, loving, and creative manner. During the attacks of anxiety he reverted to feeling like the child who had no hope and no options for taking control of his life. In therapy he learned to identify the childhood origin of these disabling attacks of anxiety and to use his adult powers to control them in the interest of making rational choices.

In regard to the most commonly relied on drugs, antidepressants and stimulants, there is so little evidence for their effectiveness, and so much evidence for their dangerousness, that it is a wonder that anyone wants to resort to their use. Yet millions of children and adults are taking these medications. Drug companies, federal agencies, insurance companies, and organized medicine and psychiatry have combined to push psychiatric drugs on the consumer as the *first* and the *last* resort—indeed, the *only* resort—in times of emotional distress and suffering. The way

we see ourselves, each other, and the solutions to both psychological and cultural problems have been taught to us through a multi-billion-dollar marketing campaign that began as the congressionally mandated "Decade of the Brain" in the 1990s. More recently, the FDA has allowed the drug companies to advertise medications directly to the public, encouraging millions of people to fear that they have "mental disorders" requiring drug treatment, thereby leading them to pressure their physicians to write prescriptions for them.

But even this barrage of prodrug propaganda cannot account for the willingness of so many individuals to succumb to these advertising and public relations campaigns. The brain-disabling, spellbinding effects of all psychoactive drugs reinforce both the propaganda produced by the Psychopharmaceutical Complex and the personal desires of many individuals to find a shortcut to solving their emotional problems.

Once under the influence of psychoactive agents, individuals are no longer able to make a clear assessment of their condition. The drugs blunt inner resources that they might otherwise draw on. Adverse effects, such as emotional rollercoastering, anger, and anxiety, are accepted apathetically. Often, the spellbound victims blame the drug-induced symptoms on themselves and their mental illness or on the provocations of other people in their environment. Sometimes patients think that they feel better than ever when they are in reality suffering from adverse psychiatric reactions to their drugs. And in the extreme, they become profoundly disturbed, violent, or suicidal.

Meanwhile, health care professionals working with these patients tend to ignore the adverse drug effects until they have devastating results, and even then, they often tend to increase the dose or add another drug on the grounds that the patient has been undertreated. When the patient develops a serious drug-induced reaction that cannot be ignored, such as psychosis or mania, then the health care provider blames the patient's supposed underlying disorder, rather than the offending drug, and prescribes yet more of these toxic agents.

Even Sigmund Freud began as an advocate for drugs, in his case, a newly isolated chemical derived from a natural source, the leaf of a plant. It was called cocaine. Freud saw it not only as a last resort but also as a healthy solution to the ordinary stresses and disappointments of life (Byck, 1974). The future founder of psychoanalysis was positively rhapsodic in promoting cocaine in the medical literature and mailed samples for his fiancée to use. As a result, Freud and many others who listened to him became addicted to cocaine. Freud's disastrous love affair with cocaine was a classic example of medication spellbinding, or intoxication anosognosia. Drugs—even when advocated by famous doctors—do not make a good first or last resort.

In the 1960s in America many intelligent and educated young people decided that their personal lives, and even society itself, could benefit from their smoking marijuana and indulging in a variety of hallucinogenic substances, from poisonous mushrooms to LSD. When they were indulging their passion for psychoactive drugs, many drug-spellbound individuals felt more creative and happier than ever before, but nearly all of them ended up realizing that they were causing their lives to deteriorate, and few continued indefinitely to inflict these toxins on their brains and bodies. In the last several decades, I have met and treated many of these refugees from the 1960s, many of whom feel that they permanently impaired their mental function during those years of romanticizing drug intoxication.

## THE SURGEON, THE COMPUTER SPECIALIST, AND THE PSYCHIATRIST

Nowadays, people are encouraged to believe that going to a psychiatrist is like going for treatment to an internist or a surgeon, but the comparison is flawed. An internist or surgeon deals with your body and not your soul; with physical ailments, rather than spiritual struggles and longings; with the workings of physiology, rather than mental processes; with mechanics, rather than with ideas, feelings, values, beliefs, and aspirations. The internist or surgeon tries to find out what is wrong with your body, rather than with your life. Of course, a more holistic physician may indeed deal with your lifestyle—issues of exercise, good eating, and even psychology—but he or she does so in response to a physical problem in your body.

Patients tend to trust their doctor to do a good job and to trust that medicine as practiced in America today has some rational and scientific basis. In this regard, going to the physician is similar to going to an auto mechanic or computer specialist. The consumer trusts the person and the engineering principles that are being utilized.

Unfortunately, going to the psychiatrist is an entirely different affair from seeking help for the repair of mechanical devices or the treatment of a physical disorder. When an engine stalls, the consumer puts his Ford sedan in the mechanic's hands. When a bone is broken or a heart malfunctions, the patient puts his physical body into the doctor's hands. But when a person suffers emotionally, the patient puts not only his body but also his mind and his journey through life in the doctor's hands.

The auto mechanic or the computer specialist is not going to change the Ford or the PC in some fundamental way. It will still be the same Ford or the same PC after the repairs. The car's engine may be retuned and the

computer's hardware may be upgraded, but the odds are great that these modifications will improve overall performance without changing anything essential or fundamental and without causing any adverse effects in the functioning of the machines.

When a patient goes to the psychiatrist and receives a drug or electroshock, his or her brain will be fundamentally changed. Its processes will be disrupted. It will not operate on the same physical principles that it operated on before the treatment. The actual function of the brain, the way the neurons communicate with each other, will have been distorted, and in some cases, brain cells will have been killed or caused to grow abnormally. Instead of having new spark plugs or upgraded memory, the brain will be injured and partially disabled by the treatment. If anything, the treatment will be akin to dirtying the spark plugs of your car or degrading some of the memory capacity of your computer.

## THE MORAL FOUNDATION OF GENUINE PSYCHOTHERAPY

Psychotherapy, unlike psychiatry, does not—or at least, should not—pretend to be analogous to medical treatment. The best hospitals in the history of psychiatry thrived during the era of so-called moral psychiatry in the 18th and 19th centuries. Moral hospitals were run by Quakers and other religious denominations, often in outright opposition to medical authorities and approaches (Bochoven, 1963, described the moral era in detail; see also Breggin, 1991c). They were successful in dealing with the most difficult patients of the era, including so-called violence maniacs and those forsaken by medicine and psychiatry.

Recently, my friend, British psychiatrist Bob Johnson (http://www.truthtrustconsent.com), gave me a copy of Samuel Tuke's 1813 treatise *Description of the Retreat: An Institution Near York for Insane Persons of the Society of Friends* (Tuke, 1996). Tuke clearly opposed the then commonplace use of restraint, except under direst circumstances:

> Except in the case of violent mania, which is far from being a frequent occurrence at the Retreat, coercion, when requisite, is considered as a necessary evil; that is, it is thought abstractly to have a tendency to retard the cure, by opposing the influence of the moral remedies employed. (p. 166)

Why was violent mania infrequent at the Retreat? According to Tuke, it is partly because the staff were taught not to *provoke* the inmates into reacting with violence.

Moral treatment appeals to the remaining free will, or *moral powers*, of the individual:

> Insane persons generally possess a degree of control over their wayward propensities. Their intellectual, active, and moral powers, are usually rather perverted than obliterated; and it happens, not unfrequently, that one faculty only is affected. The disorder is sometimes still more partial and can only be detected by erroneous views, on one particular subject. On all others, the mind appears to retain its wonted correctness. . . .
>
> We have already observed, that most insane persons, have a considerable degree of self command; and that the employment and cultivation of this remaining power, is found to be attended with the most salutary effects. (pp. 133–134, 139–140)

In other words, insane individuals retain moral or ethical faculties that make them amenable to psychological, moral, or religious interventions. These faculties can be appealed to with patience, with "kind persuasions" and with "moral and rational inducements." This is exactly what many successful therapists do when treating deeply disturbed patients.

Tuke (1996) described the necessity of approaching disturbed patients in a most ethical and considerate manner, but unfortunately the caregivers were easily provoked into overreacting by the "often half rational, conduct of the patient":

> It is therefore an object of the highest importance, to infuse into the minds of these persons [the caregivers], just sentiments, with regard to the poor objects placed under their care; to impress upon them, that "coercion is only to be considered as a protecting and salutary restraint"; and to remind them, that the patient is really under the influence of a disease, which deprives him of responsibility; and frequently leads him into expressions and conduct the most opposite to his character and natural dispositions. (p. 175)

After illustrating his point about empathy with a poem, Tuke went on to say:

> But even this view of the subject [as lacking responsibility] is not exempt from danger; if the attendant does not sufficiently consider the degree in which the patient may be influenced by moral and rational inducements. (p. 175)

In my clinical experience, Tuke's observations are as pertinent today as they were in the early 19th century. Psychiatrists, nurses, hospital attendants, and mental health caregivers in general too often use drugs,

threats, and restraints to control their "patients" while forsaking any use of kindness and moral persuasion. Too often they try to enforce submission or to encourage compliance rather than to empower their patients by respecting and encouraging their autonomy and decision making. Yet in my experience, beginning as a college volunteer on the back wards of state mental hospitals in the 1950s (Breggin, 1991c; Umbarger et al., 1962), I have found that even desperately disturbed human beings will almost always respond to patience, empathy, and respectful guidance grounded in kindness.

Critics may complain that love cannot cure patients; but I make no claim that love or caring by itself is enough. As I describe in *The Heart of Being Helpful*, (1997), in dealing with very difficult, disturbed, and disturbing people, the clinician needs all of the confidence, moral determination, sound principles of living, and life experience that one individual can bring to helping another. With experience, the clinician learns not to overreact and not to become frightened in the face of disturbed behavior but instead to welcome the expression of feeling and to help with understanding it, while explaining the necessity of mutual restraint and consideration. In *The Heart of Being Helpful*, I summed up the essence of the clinician's role, especially in dealing with profoundly upset people, as "the creation of healing presence."

Tuke (1996) understood the dilemma of treating people who have lost their sense of self-control and personal responsibility by encouraging them to restore these qualities. It is an empathic challenge:

> To consider them at the same time both as brothers, and as mere automata; to applaud all they do right; and pity, without censuring, whatever they do wrong, requires such a habit of philosophic reflection, and Christian charity, as is certainly difficult to attain. (p. 176)

With Tuke, I believe that this charitable habit of philosophic reflection is central to therapy. This is another way of describing what I call the healing presence and characterize as empathic relating.

Instead of threats and punishments, the patient is offered "rational society," "different kinds of amusing employments," and books to read:

> Since whatever tends to promote the happiness of the patient, is found to increase his desire to restrain himself, by exciting the wish not to forfeit his enjoyments; and lessening the irritation of mind, which too frequently accompanies mental derangement.
>
> The comfort of the patients is therefore considered of the highest importance, in a curative point of view. (pp. 177–178)

The cure lies in kindness and consideration, not in humiliating, punitive measures and deprivations typical of institutional psychiatric treatment, then and now.

Patience in the encouragement and promotion of the patient's rationality and reason is another key to cure:

> Those who have had the opportunity of observing the restoration of reason, will be aware, that she does not, in general, at once, resume her lost empire over the mind. Her approach resembles rather the gradual influx of the tide; she seems to struggle to advance, but again and again is compelled to recede. During this contest, the judicious attendant, may prove the most valuable ally of reason; and render to her the most essential assistance, in the recovery of her lawful throne. (p. 180)

Tuke (1996) warned on more than one occasion that medical treatment and institutional care often worsen the conditions of patients. He found that releasing patients from restraint actually makes them less dangerous. Even as a college student volunteer, I made these same observations and then implemented them more fully as I became a physician and a psychiatrist.

Moral treatment grew out of the converging Enlightenment trends, rational philosophy, and "Christian charity." In keeping with this combination, Tuke the Quaker (1996) concluded his work with a quote from Montesquieu about the need for even the most virtuous to be restrained in their power because "experience continually demonstrates, that men who possess power, are prone to abuse it: they are apt to go to the utmost limits" (p. 187).

I have taken time to quote the lessons of moral treatment because these ethically based approaches remain alien to modern psychiatry. Yet these principles were proven effective nearly 200 years ago, when institutions treated people without the so-called advantage of mind-numbing drugs, electroshock, and lobotomy.

According to J. Sanbourne Bochoven (1963), himself a former state hospital superintendent, the moral era produced at least as good results reclaiming the mentally disturbed as today's best hospitals, and of course, it was accomplished without damaging the brains of the patients. All of Tuke's (1996) basic principles, expressed in the moral era of psychiatry, are embodied in my guidelines for therapists (see subsequent discussion).

Using the same moral terminology, but without the accompanying all-important empathy for suffering, Freud thought that psychotherapists should be viewed as *secular moralists* or ethical guides. Inspired by this, I devoted one of my earliest articles to "Psychotherapy As Applied

Ethics" (Breggin, 1971). Before the 20th century, psychology and moral philosophy were one and the same, but this natural alliance is denied in modern schools of psychology and philosophy. And the field of psychiatry has divorced itself from both psychology and philosophy in its effort to claim medical and biological legitimacy.

Some therapists start out with sound ethics; some do not. Some know a great deal about life—that is, they have wisdom—and some do not. I am not trying to discourage people from practicing or from seeking psychotherapy or counseling. I am trying to be realistic. There is nothing standardized about therapy. Every therapy will vary depending on the therapist's theoretical and practical approaches, ethics, experience, and personality. As no two people are alike, no two therapies are alike.

Indeed, the term *therapy* itself is misleading, lending itself too easily to a medical model with artificial diagnoses, manipulation, and medication. The term *counseling* is in many ways preferable and arises out of a tradition that is more respectful of the autonomy and human needs of the individual. Similarly, the word *patient* is also potentially misleading and might better be replaced with *client*. But since I am a physician and psychiatrist and do not wish to add undue confusion to this book, with these caveats I will continue to use the terms *therapist* and *patient*.

At best, therapy and counseling should be one approach to helping an individual with personal or life problems, but not as another kind of last resort. As a psychiatrist and therapist, I discourage clients from thinking of me as their last resort. It is not good for my patient to think that any one human being is his or her last resort. And it is certainly not good for me to think about myself in such unrealistic, grandiose terms.

## My Clinical Practice of Psychiatry and Psychotherapy

My own career in psychiatry began as a college student when I was chairman of the Harvard–Radcliffe Mental Hospital Volunteer Program (Breggin, 1991c) and coauthored my first book (Umbarger et al., 1962). In the mid-1950s, we changed the environment of the local state mental hospital, moving it in some ways from a custodial to a therapeutic milieu. In addition to these more general effects on the institution, we developed a case aide program, in which individual college volunteers were assigned their own patients.

Working under group supervision by a social worker, in the first year of the case aide program, 11 of our 14 patients were released from the hospital, and only 3 returned during follow-ups that lasted 1 or 2 years. These abandoned people were so-called back ward patients, individuals on whom psychiatry and the community had given up. The staff referred

to many of them as burned-out schizophrenics. But we were able to place them into much better circumstances in much more advantageous local community homes or with their families. I gained valuable lessons from this experience, from the futility and destructiveness of drugging, shocking, and lobotomizing people to the wonderful power of offering them help and caring guidance.

The volunteer program lasted for many years after I had graduated, until finally, with the domination of biological psychiatry, it withered away. Working in the hospitals in those years just before the so-called miracle drugs became the only treatment, I learned how basic human relationship could revive, and even restore, the lives of the most chronically disturbed patients, even those who had experienced years of abuse in a state mental hospital.

## THE FUNCTION OF SUFFERING

Suffering cannot be pulled out of the brain like a splinter from a foot. It cannot be obliterated from the brain like a tumor subjected to radiation. Emotional or psychological suffering should not be viewed as something alien to human nature or as something to be gotten rid of. Most of the great religions view suffering as an avenue to understanding life and God. In psychological terms, suffering is a signal. In anxiety and depression, and even in mania, our soul, psyche, or self is crying out for attention and desperately seeking solutions or relief.

In my therapy practice, I welcome suffering as a sign of life. Instead of trying to dull it or to snuff it out with toxic agents, I encourage my patient to share it with me—to bring it fully out in the open and to examine it with the aim of understanding what the suffering is saying about the individual's life.

Human suffering is proportional to our sense that life can and should be better. For example, when people feel depressed, they have lost hope and feel paralyzed in regard to achieving their goals, such as love and happiness. They would not feel this frustration and despair unless they had a corresponding vision, however unconscious, of a better life that was going unfulfilled. My patient's suffering tells me that he or she is alive and has a marvelous energy that can be transformed into a creative force: a love for life. Unlike the biological psychiatrists, I have no desire to destroy my patient's suffering and along with it my patient's brain function. Instead, I want to become comfortable with the suffering, to welcome it and see through it with my patient to the message it is giving about my patient's unfulfilled needs and my patient's desire to find a better understanding and approach to life.

## DRUG-FREE THERAPY

Since starting my private practice in 1968, I have treated all of my patients, children and adults, many severely disturbed, without resort to medication. In all my decades in full-time private practice, perhaps half a dozen of my patients have required hospitalization. To my knowledge, none of my patients has committed suicide. Very few have gotten worse during treatment, an unfortunate circumstance that frequently occurs in traditional practices, where patients are medicated, electroshocked, or forcibly hospitalized.

To make it absolutely clear, to this day I never start my patients on psychiatric drugs. I only prescribe drugs to patients who have come to me already taking medication, and then almost always for the purpose of eventually withdrawing them. In a few cases, when withdrawal reactions have proven unendurably painful, I have continued patients on low doses of antidepressants or benzodiazepines because there has been no satisfactory alternative.

In rare cases where patients do not want to try to taper and withdraw from their psychiatric medication but want my help as a therapist, I usually recommend that they obtain their medication from other doctors while seeing me for psychological help. I do not want to enable the use of medications that I feel will harm them in the long run and, of course, they have no trouble finding someone else to prescribe for them. Usually the individual has continued in therapy and eventually stopped taking medication. Despite my rejection of medication treatment in my practice, my clinical experience with medication is extensive. As a doctor who works with patients who come for help in withdrawing from multiple medications, I frequently have to prescribe medications as a part of the process of tapering patients off them. And as a medical expert in many medication cases, where I also work directly with the legal clients, I have also garnered considerable firsthand experience with psychiatric medication over the past 40 and more years. And of course, I have extensively researched, written, and consulted on the subject of medication.

In my psychiatric practice, I find that very disturbed persons respond well to individual and family therapy aimed, first and foremost, at providing them a safe space in which to dare to begin trusting another human being. As I described in *Toxic Psychiatry* (1991c) and in *The Heart of Being Helpful* (1997b), psychosis is a loss of connectedness to other human beings. The individual who withdraws into a fearful, self-protective, irrational fantasy world responds best to being treated with kindness, respect, and the gradual building of rapport. The required skill in working with the most emotionally disabled persons, especially during the initial period of emotional crisis, has more to do with empathic relating

and sound guidance than with deep insights or psychological interpretations. More subtle or insightful therapy can be effective only after the individual no longer feels overwhelmed and emotionally helpless.

Often, the more acute or flagrant symptoms will begin to calm down during an initial session in which the vulnerable, overwhelmed person discovers an opportunity to relate to another person in a safe space. The most difficult people to help are those who have already been humiliated by oppressive psychiatric approaches and whose brains have been damaged by electroshock and neuroleptic drugs.

*Psychosis* is a loosely defined word that reflects in its broadest sense "a loss of touch with reality." At least in the extreme, hallucinations and delusions are the hallmarks. At its worst, perhaps, psychosis becomes a living nightmare, in which the individual's mental processes resemble a solipsistic, terrifying nightmare from which the person cannot be fully awakened. The individual becomes so withdrawn and preoccupied with these highly personal and irrational processes that no one can reach him.

If we look for the common element of all psychotic or profoundly disturbed mental processes, they involve a loss of connection to other human beings. In the extreme, other people become like fragmented objects in the individual's shattered awareness. Other people are imagined to be conspirators with the FBI or CIA who are out to get the victim. Or they are seen as aliens from another planet. Or they are poisoning the victim's food. Most commonly, perhaps, they are whispering humiliating things about the victim.

If the psychosis has a manic, rather than a withdrawn, quality, then other people are seen as menacing, especially if they thwart the ambitions of the person who is living on an emotional "high." Or other people are treated as objects without regard for their feelings as the individual grandiosely tries to manipulate everyone around him. Underneath all the bravado and displays of superconfidence, the manic individual feels as overwhelmed as the withdrawn one but compensates by acting all-powerful.

I am not trying to elaborate a new psychiatric diagnostic system but merely to confirm that all severe psychiatric disturbances are disturbances of interpersonal relationship. The deeply disturbed person is deeply disturbed in his or her relationships with other people. In all these expressions of psychosis, the individual feels overwhelmed by other people and by life and unable to connect to other people and to competently handle life. Psychosis is a breakdown of human relationship, a disturbance in the fabric of the person's social life, accompanied by an inability to cope with everyday stresses. All effective therapies for deeply disturbed persons begin with the concept of building or rebuilding relationship,

while providing a certain amount of guidance in dealing with immediate emergencies and crises. As relationship is restored with one other human being—the therapist—and as the immediate crisis no longer seems so catastrophic, the individual can grow less overwhelmed, more trusting, and less disturbed in general. The individual can begin to venture into relationships with others and to make more rational decisions.

Sometimes this restoration of relationship and rational judgment can begin in minutes if the disturbed person quickly senses that he or she can dare to trust the new person, the therapist. On many occasions, I have been able to calm down seemingly crazy persons and to begin a somewhat rational discourse in a matter of minutes. Sometimes the process will take weeks or months.

Sometimes a particular therapist, including me, may not be able to help a particular patient. In response to the failure of the therapeutic relationship, the therapist should not advocate drugs. If therapists fail some of the time, drugs fail all of the time, at best suppressing overall mental function and at worst damaging the brain and ruining the individual's capacity to enjoy life for the remainder of his or her life. When a therapeutic relationship is not working, it is best to help the patient find other psychosocial alternatives, including a different therapist. However, in my experience, the therapist rarely has to direct the patient elsewhere. If the therapist is not coercing, manipulating, or drugging the patient, a disappointed patient will be able to seek help elsewhere on his or her own.

In my own experience, if there are well-intentioned family members, then working with the family is the most effective way of helping a disturbed individual restore his or her relationships with other human beings. It is far better if other family members, rather than the therapist, become the patient's primary resort and the place where relationship is recovered.

When the person is so disturbed that he or she cannot function in a private office or clinic setting, a therapeutic setting can be more helpful. The goals, however, remain the same: providing a setting that is safe and relationships that are safe so that the individual can begin to trust other human beings and emerge from his or her deeply disturbed state. Traditional mental hospitals are extremely controlling, authoritarian, humiliating, and physically dangerous places—exactly the opposite of what already overwhelmed people need.

I wish I had a range of residential alternatives to offer prospective patients and their families, but few exist, and those that work well are often opposed and even destroyed by the psychopharmaceutical complex (Breggin, 1991c). The best source of potential information about residential alternatives can be found on the Web site of the International Center for the Study of Psychiatry and Psychology (www.icspp.org). Another alternative is to meet therapists and to learn about alternatives at the

organization's annual conferences, which usually takes place in October and which can also be located on the Web site.

Being an effective therapist begins with being a person that other people can trust with their most vulnerable feelings. In this regard, by creating an authoritarian and manipulative attitude, most contemporary training programs in psychotherapy do more harm than good. They almost always teach a relativistic, self-protective ethic (doing what works; collaborating with psychiatrists; using drugs along with therapy; making cookie-cutter diagnoses; referring desperate or suicidal patients for drugs, electroshock, or incarceration).

There are a handful of inspired and inspiring humanistic psychotherapy training programs around the country. However, they can be hard to locate, and the quality of individual programs may vary from year to year. As an aspiring professional or teacher, the best way to find these programs is through meeting people at the conferences of the International Center for the Study of Psychiatry and Psychology (ICSPP); by looking up the affiliations of the authors in its journal, *Ethical Human Psychology or Psychiatry*; or by reviewing the background and credentials of authors you respect. By searching for "humanistic psychology training programs" on the Internet, I found a number of familiar and useful sources.

## 20 GUIDELINES FOR TREATING DEEPLY DISTURBED PERSONS

Here are 20 principles for providing therapy to deeply disturbed persons. Many of them are elaborated in *The Heart of Being Helpful* (1997b), and all of them draw on the "Principles of Life" that I present in *Medication Madness* (in press). While the focus is on providing help to emotionally disturbed and disabled patients who seek individual therapy in a private practice or clinic, the same principles apply to residential and milieu treatment as well. In a more general way, these 20 guidelines can also be applied to our experiences with other people in our workplace, families, and everyday life.

1. Every session, welcome the person as you would a new friend, someone you have been eagerly awaiting, someone you feel privileged to meet, someone you would never offend, someone whose feelings you will treat with exquisite tenderness.

Yet you must be careful not to come on too strong. To conduct yourself in this well-centered manner, you will have to find a very comfortable place inside yourself that is not threatened by other people's craziness, and you will have to see the person and not the symptoms.

The Quakers speak of relating to "that of God" in each person. Find your own way of conceptualizing your respect and concern for the preciousness of each human being. Build your helping relationships around Martin Buber's (1968) I–Thou relationship that treasures the other human being.

When you feel a tendency to look down on your clients, to diagnose them, or to lack empathy for them, remember how tough their lives have been compared to your relative safety and security. Then repeat to yourself the mantra of good therapists: "There but for the grace of God go I."

2. Dare to be caring.

A caring relationship is the core of healing; everything else is icing and comes in many flavors. By caring, I do not mean a sad or even sympathetic attitude. You do not want to be dragged down by your patients' plight, or you will drag them further down with you. You want to be interested and empathic. Through your attitude, your questions, your recollection of what you have already been told, and your expressed concern, you want to show that you care about your client.

Many aspects of psychotherapy help different people at different times, but people find that the most helpful aspect of therapy is talking to someone who cares about them and their problems and provides them with an opportunity to develop better self-understanding and confidence in dealing with life.

As the relationship becomes safer, the therapist can express more of his or her caring feelings and empathy for the patient. In many cases, patients learn to do the same, showing an interest in another human being—the therapist—perhaps for the first time in years. Although protected and limited by professional restraints, a genuine caring relationship can evolve, helping to restore the individual to human connectivity and hence to sanity.

3. Create and maintain a safe and comfortable relationship.

The therapeutic relationship should be as conflict-free as possible. It should feel comfortable and safe for both the client and the therapist. If either the client or therapist feels disrespected or threatened, that issue should be addressed and resolved. It is impossible for people to receive help—or to provide it—when they feel unsafe or uncomfortable. To repeat, the client and the therapist alike need a safe, nurturing environment.

In the process of working on the creation of a mutually safe relationship, the disturbed client learns, perhaps for the first time, what it is like to feel close to someone without causing turmoil and without feeling endangered.

As a part of creating a safe, comfortable relationship, make your therapy space more like a home than an office, clinic, or hospital. Pleasant pictures, not framed credentials, should create the ambience. When clients are especially frightened, begin by suggesting that they look around your space to see how pleasing and safe it is. Very anxious people often begin relaxing when they realize that they are not in an office as much as in a comfort zone.

Ask if there is anything you can do to make your clients feel more comfortable. Do not be afraid of being solicitous; I guarantee that most patients will immediately sense that there is something different going on in this health care provider's office when you show interest in their creature comfort.

In the interest of focusing on your patients' comfort and creating a good relationship, avoid taking notes during sessions with very disturbed people. Ordinarily, I take notes during the first session with patients to establish a base of information for future reference, but I always apologize for any interference it may cause. If clients are very disturbed, frightened, or suspicious, I put aside the note tablet. If they have a tenuous grip on reality, seeing me take notes may frighten and distract them. They may become fearful of who will read the notes. If nothing else, they will get stuck wondering why I find one thing or another worth writing down. It is best to be able to relax and converse more casually during therapy.

4. Create an ideal, even utopian environment in which both you and your client relate to each other according to the highest ethical and personal standards.

In keeping with the first three guidelines, therapy should be like a mini-utopia, in which you are absolutely at your best as a person and are therefore able to reach people whom others have found impossible to deal with. This mini-utopia is made possible by the limits placed on it such as restricting the relationship to the office, avoiding any outside entanglements, and establishing rules for courteous and rational relating. Within these limits, the therapist should strive to create an ideal relationship, one that will help the client learn how best to relate to all the people in his or her personal life.

5. Do not ignore or enable obnoxious or threatening behavior.

If your client, on the first visit or any other visit, acts in a disrespectful or threatening manner, do not ignore it. As soon as the other person begins making you feel uncomfortable with hostile remarks, gently draw attention to it, express your concern, and ask if you have done something

to contribute to the angry reaction. Your vulnerability will actually reassure most people. Tell the truth; explain that it is hard for you to be at your best if you are feeling defensive.

If a patient retorts, "I thought this is where I could say anything I want" or "I thought I was supposed to say what I feel," you can explain that therapy is intended to be a safe place where people learn how to talk in a respectful and even caring manner toward each other. At times, that will mean restraint on your part and on the patient's part. The object is to develop good communication—not to express anything that comes to mind without regard for the consequences. Always work to create a caring, respectful atmosphere and tone.

Nothing is more frightening to disturbed or out-of-control people than their own out-of-control anger. People, especially disturbed people, need to learn that they will feel safer when they decide to avoid provoking or escalating conflict. Nearly every client I have known has responded well to my encouragement of a mutually friendly, respectful, and even caring attitude.

Through learning how to treat others in a respectful and caring manner, clients also learn how they should be treated. They learn to no longer tolerate or enable bullying, abusive, and controlling behavior on the part of family members and other people in their lives.

6. Notice odd behavior, gently call attention to it, and ask what it is about.

If your client is staring over your head, making odd gestures, or cocking his head as if listening to voices, gently ask about it. Ignoring odd behavior is tantamount to ignoring the person. Taking odd behavior seriously shows your interest for and concern about the patient. Odd behavior always has meaning; it is always carried out for a purpose. It will help both you and your patient to learn what the disturbed behavior is about.

Once you begin to notice odd behavior, it will tend to diminish because the person will feel that you are actually paying attention in an interested fashion. Odd behavior is usually driven by feelings of loneliness and isolation. Sometimes it is aimed at getting attention; sometimes it is aimed at relieving awful feelings; sometimes it is an expression of irrational experience, like hearing voices. By asking about the behavior, you encourage more genuine and direct communication. If you can do it in a caring manner, it is useful to remind the person that odd behaviors distress or scare other people and cause many doctors to implement coercive psychiatric interventions.

Contemporary biological psychiatrists tend to treat odd and even bizarre behavior in their offices as a sign of mental illness rather than as a

form of activity that children and adults can learn to control. In effect, these psychiatrists enable the child's self-destructive conduct by labeling it as symptoms of an illness. As a result of being told that their children have disorders, parents also give up trying to teach their children better manners and more socially acceptable behavior. Especially in regard to children, acknowledging odd behavior in a kind and concerned manner, and pointing out its negative consequences, can have a very beneficial effect in a short period of time. Within minutes, the children begin to learn that they can take responsibility for how they conduct themselves and they quickly see how much better other people respond to their improved conduct.

7. Get to know the person as a fully developed human being, not narrowly as a mental patient.

Toward the end of my first session with a new patient, I asked her if she felt that I had gotten to know her during the hour we had spent together. She replied ironically, "Yeah, if you think I'm nothing more than the worst parts of me." I saw immediately that I had spent so much time collecting the history of her problems and difficulties that I had neglected to engage her about her overall life, including the many things she felt good about herself and the many activities she enjoyed.

Focus on the life story of the whole person and do it in a positive light. If a diagnosis comes to mind, such as schizophrenia or panic disorder, expunge your thoughts and start over again. The moment you start thinking of diagnoses, you will lose your sense of the person's uniqueness, and you will stop trying to get to know him or her. People can sense when a mental health professional is squeezing them into a diagnostic category and, conversely, they can tell when you are interested in them as a unique human being.

Therapists should not think diagnostically about their patients; emotionally distressed people do not have illnesses, they have life stories gone awry. If diagnoses must be made for insurance purposes or other practical reasons, discuss the least harmful diagnosis with your patient and reach an agreement on it before writing it down or communicating it to anyone else.

8. Help your patients learn their own life story and help them take charge of how it will unfold in the future.

Instead of diagnosing your patients, learn about their lives, especially what has helped and harmed them along the way. Provided that people are not mired down in helplessness and victimization, an examination of their stories can be very helpful to them. They reconstruct their own

biographies—what happened to them that helped and what happened that harmed; what they did right and what they did wrong in response to life's challenges.

If a person has undergone a very abrupt and acute break with reality, it can be very helpful to examine the precipitating trauma. The trauma may be culture shock for a student visiting from another country. It may be the death of a loved one. It may be an ongoing abusive relationship that restimulated the effects of even worse abuse in childhood. Life stories, and the traumatic events that abound in them, are infinitely varied.

Often, an individual's current problems stem from self-defeating viewpoints learned in childhood. It may have been safer as a child to avoid close contact with an alcoholic, unpredictable father, but in adulthood, avoiding or shrinking from men in authority will become self-defeating. It may have been necessary in childhood to hide your feelings from other people, but this kind of emotional guardedness impedes meaningful relationships in adulthood. It may have been necessary in childhood to remain in a heightened state of suspicion in your dealings with an older, abusive sibling, but in adulthood, this can turn into self-defeating paranoia about your peers. Learning to apply new and better lessons to life is central to therapy.

Each person has a different story, and learning that story can help the individual to overcome feelings of being overwhelmed while encouraging the capacity to make better choices in the future. But it is worth reemphasizing that no attempt to understand the past will be useful as long as the person feels and acts in a helpless fashion. Instead, past emotional injuries will become fuel for increased helplessness, rather than empowerment. Therefore, feelings of helplessness must be addressed and overcome early in the process of therapy.

9. Be optimistic.

The importance of being optimistic may seem so obvious that it need not be stated, but in fact, modern psychiatry is deeply pessimistic, even profoundly negative, in its attitude toward patients. Because psychiatrists nowadays rarely have the knowledge or inclination to build therapeutic relationships with their patients, they have no idea about how to genuinely heal other human beings. In fact, they have been taught that they cannot talk to schizophrenia, and so they pessimistically turn to prescribing drugs and electroshock, despite causing innumerable adverse effects and irrevocably damaging many patients. Commonly, they instruct patients to take their medications for the rest of their lives, sending a clearly pessimistic message. Even the often-expressed myth that patients have a biochemical imbalance is profoundly discouraging. On top of that,

psychiatrists tell their patients that they have genetic disorders, adding to their sense of hopelessness and engendering fears for their biological offspring. Biopsychiatric pessimism about the capacity of human beings to take charge of their lives reinforces their patients' worst view of themselves as helpless in the face of their problems. By being pessimistic, health care providers—including most psychiatrists—make their patients dependent on them and end up doing far more harm than good.

So it is especially important for therapists to keep in mind that they can help almost all their clients by starting with a warm, welcoming, and caring relationship. Especially for disturbed patients who have already been overwhelmed by psychiatric pessimism, make clear how optimistic you feel about being able to help them to live better, happier, more productive and loving lives.

10. Be confident.

In keeping with being optimistic about a patient's future success, be confident about your ability to help this very disturbed person and expect that he or she will show signs of being less disturbed, even within a few minutes. You might even remind the patient that success in therapy depends more on the patient than the therapist. A responsible, hardworking client is likely to find help even from a marginal therapist, while a helpless, dependent client is likely to find little help anywhere.

Your goal is to create an environment that allows or encourages people to relate to you without pushing or manipulating them. So while expressing confidence that this person will shortly discover how useful therapy can be, also be humble enough to realize that it is ultimately up to the individual to decide how he or she feels about you and your approach. Trying too hard is one of the worst mistakes a therapist can make. It reeks of desperation and disrespects the autonomy of the other. Yet you want to communicate a quiet confidence that the individual in the room with you can work with you in an understandable and productive manner.

11. Be willing to improve your own attitudes.

If you are finding it difficult to become caring, empathic, optimistic, or confident about a particular client, then it is your job—your professional obligation—to find those resources within yourself. In *The Heart of Being Helpful* (1997b), I call this *empathic self-transformation*—the willingness and ability to find the human-to-human resources necessary for the work of being a psychotherapist with each individual patient. In the job of helping people with their psychological problems, the therapist cannot self-indulge with feelings of helplessness, resentment, or pessimism. These

feelings have to be overcome. Knowing that there are no exceptions to this rule will help you to maintain a positive outlook as a therapist and make your hours of therapy relatively stress-free and satisfying to you and, ultimately, to your client.

12. Avoid using artificial therapeutic techniques, especially with very disturbed persons.

If people have relatively strong egos and feel reasonably secure in themselves, they may be able to tolerate or even benefit from one or another therapeutic technique, whether it is role-playing, dream analysis, free association, cognitive therapy, behavioral therapy, self-hypnosis, relaxation techniques, biofeedback or whatever. But disturbed people will experience anything that is rote, contrived, or repetitive as one more humiliating insult, and even as an assault.

Working with disturbed people requires you to offer them a genuine human relationship, even in the face of their craziness. You, in turn, should not introduce anything out of the ordinary into the session. Your goal is to build a genuine relationship.

Again, what makes this possible with disturbed patients is the utopian quality of the therapy setting, including its limits, its safety, and the skills of the therapist in maintaining a genuine relationship with people who tend to drive others away.

13. Refuse to start patients on medication or to refer them for medication evaluation, especially if they are very disturbed.

The need to keep therapy drug-free is even more imperative with very disturbed or psychotic patients. When people are already feeling emotionally overwhelmed in the extreme, the last thing they need is a big dose of brain dysfunction. Already struggling to control their feelings and to understand them, they do not need the bizarre mixture of apathy and emotional lability that characterizes so many drug effects. They do not need the added burden of trying to figure out from moment to moment and day to day if they are experiencing their own genuine emotions or the emotional effects of adverse drug reactions.

For these already disempowered persons, it is further disempowering for them to be told that their salvation, cure, or restoration depends on a physical intervention, rather than learning to take charge of their lives. They have already given up hope in themselves and in other human beings; do not confirm their worst fears. They already feel helpless in the face of their emotions; do not make them feel even more helpless by

telling them that they have a biochemical imbalance that is out of their personal control. Do not make them feel more dependent and helpless by acting as if you can diagnose a mythical biochemical imbalance or cure them with a pill.

I explain to my patients that I never use psychiatric medications as therapy, but that I will continue to prescribe for them if they cannot manage to withdraw from their drugs. All of my patients are free to obtain medications from other doctors and to continue to see me for therapy and for additional monitoring of how the drugs are affecting them. On rare occasion, some have done this for a while. However, they are likely to discover that taking medications tends to make them preoccupied with tampering with their drugs, rather than with learning to take charge of their lives. They will also find that it is hard to know what they really feel, and how they are really responding to life, when toxic agents are jerking around their brains, minds, and emotions.

Nowadays, when patients come to health care providers, they know that the moment they mention any kind of painful feelings, a drug will be prescribed, or a new drug will be added, or doses will be upped. The modern patient literally lives in a world where conversation consists of the patient expressing feelings and the doctor responding with drugs. This truly bizarre relationship ultimately devolves into a ritual of mutual manipulation, wherein the patient expresses feelings with an eye to controlling the flow of medication, while the doctor prescribes the medication to suppress the patient's feelings. It is, of course, impossible to conduct genuine therapy of any kind under such circumstances.

I believe that my refusal to start patients on drugs is one reason why, since approximately 1970, I have not had any suicide *attempts* in my practice where I have been the primary therapist, and only one where I have been consulting on medication withdrawal in a criminal case where a man was anticipating going to jail. My patients work with me with unencumbered brains and with the knowledge that they will not be drugged in response to sharing their most desperate feelings with me. On the other hand, our patients have ultimate responsibility for themselves, and any good therapist could experience an occasional suicide attempt or even a completed suicide among his clients.

The more disturbed the person, the more the therapy must focus on empowerment. It enormously undermines personal confidence to be diagnosed with a mental illness or biochemical imbalance and to be told that you cannot manage your life without drugs. But it is enormously uplifting to learn that you can learn to manage your feelings, to straighten out your thoughts, and to relate to people and life in an effective, satisfying manner.

14. Refuse to take any kind of threatening, bullying, or coercive actions, especially against vulnerable, disturbed people who cannot resist or fight back effectively.

Coercion in the mental health system comes in many forms, from authoritative assertions that the person cannot do without drugs to outright involuntary commitment and forced treatment. For patients who have already experienced coercion in the mental health system, I quickly mention that I never commit patients or treat them against their will. Especially if the patient has already had bad experiences, I will explain that since finishing my training in 1966, I have never signed commitment papers or participated in locking up anyone, even people who have had self-destructive thoughts and fears.

There is no law that specifically requires a doctor to lock up patients against their will. However, the law in most states does require doctors to take preventive measures of some kind if they have reason to believe that a patient is likely to commit violence against a specific person. It is called "the duty to warn." I can recall exercising this option on only one occasion many years ago and the outcome was most remarkable. I was afraid that a man was going to assault his wife that very night after the session was over, so I discussed my legal duty to warn his wife of the danger. I did not want to do anything behind my patient's back and, somewhat to my surprise, he gladly went along with my calling his wife while he sat in the office with me.

When I got my patient's wife on the phone and explained to her that I was afraid her husband was growing dangerously violent toward her, she angrily told me to stop interfering in her life and hung up. The man continued successfully in therapy without perpetrating violence.

Most severely disturbed patients will have seen numerous other mental health professionals before finding their way to me. If mental health professionals have already seen them, then they have already experienced coercion (Breggin, 1964, 1991c). All or nearly all patients who display serious mental problems are quickly pressured to take drugs and are threatened, bullied, or locked up if they display too much reluctance.

Tragically, people who already feel emotionally overwhelmed are especially sensitive to and demoralized by any kind of authoritarianism or manipulation, let alone outright physical coercion. Therefore it provides enormous relief to disturbed persons when the therapist promises to behave differently and never to threaten or bully them, and never to force them into treatment or a hospital. In addition to feeling safer, they may feel, for the first time in their checkered experience with doctors and therapists, that they have met someone who feels competent and confident about *offering* help to them, rather than *imposing* it on them.

As they begin to trust your word about not committing them, they will usually become more open and forthright in discussing their feelings with you so that you can deal more openly with suicidal or violent feelings.

In addition to not giving drugs, I believe that not coercing patients has also contributed to my relative success as a therapist. If patients become suicidal in my practice, for example, they do not have to hide it from me for fear of my prescribing drugs or locking them up. Instead, they can freely talk with me.

From my viewpoint as a psychiatrist and psychotherapist, it has been an enormous help to me to entirely reject the idea of coercing my patients. It means that I must rely on my ability to *offer* my patients, even my most disturbed patients, quality help that they will voluntarily accept and benefit from. When the going gets rough, it means I sometimes have to worry more, care more, think more, and be more available than doctors who commit their patients, but it has made me a better and happier therapist.

Therapy must be voluntary for the patient; otherwise, it becomes something else, such as indoctrination, intimidation, or brainwashing. As mentioned earlier in the chapter, this was obvious to Tuke in 1813, but it continues to elude the modern psychiatrist, who refuses to let go of the power to force patients into "treatment."

In reality, there is no such thing as involuntary therapy. Involuntary treatment is not treatment; it is incarceration, forced drugging, forced electroshocks to the head, and so on.

It is commonplace for psychiatrists to claim that a patient's irrational or self-destructive behavior demonstrates that he or she is asking for someone to take over his or her life. Because I am unequivocally against involuntary treatment, I get to hear what patients really think about it. Most of them resent the humiliation and loss of freedom for the rest of their lives, and many join organizations to oppose it such as MindFreedom (www.Mindfreedom.org). But even if some individuals seek oppressive treatment, psychiatrists should view it as a self-defeating pattern that should not be enabled.

If involuntary treatment seems to work, it is because the client has become submissive in response to authority. Involuntary treatment teaches the victim to become docile and to manipulate to avoid and escape punishment, and it motivates the so-called therapist to rationalize abusive acts. As I describe in detail in *Beyond Conflict* (1992a), victims of coercion hide their true feelings from those who exercise arbitrary power over them.

Meanwhile, people who exercise that arbitrary power never want to know what their victims are truly feeling. As a result, involuntary treatment alienates the victim from the oppressor—the patient from the doctor—and substitutes a charade for a genuine relationship.

Despite hundreds of years of implementation, there are no studies showing that involuntary treatment helps people, protects them from suicide, or protects the public from violence.

If you decide that it is necessary and right in principle to lock up and drug any of your patients, including the disturbed ones, it will handicap you as a therapist. To be successful as a therapist for very disturbed people, you have to be convinced that all human beings can learn to take control of their emotions and their behavior and go on to live useful and happy lives. You will have to welcome emotional suffering as a sign of life and an indicator that the person inside is alive and well, if screaming in pain, and ready to find a better way to live. You also have to respect and treasure each individual's freedom and responsibility sufficiently to believe that no human being has a right to lock up another for their own good. To me, locking up people or giving them drugs is quitting on them by saying, in effect, "You can't handle your life, and I can't handle you either."

Many well-meaning professionals attempt to provide therapy to individuals who are incarcerated against their will in mental hospitals or prisons. In theory, it might be possible to do this on a voluntary basis. But the therapist must remain acutely aware of institutional pressures on how he conducts his therapy and attempt at all times to serve the client, rather than the institution. Unfortunately, as I have learned from many colleagues, aligning oneself with the clients, rather than with the authorities, in an institution inevitably leads to getting fired. For this reason, it is probably impossible to conduct genuinely voluntary therapy within an involuntary institution.

Increasingly, it is also impossible to conduct genuine therapy in public outpatient clinics, because nearly all of them are under the control of biological psychiatrists who will not put up with any opinions that deviate from their own. I have seen highly competent professionals fired from mental health clinics for opposing the use of drugs. I always encourage mental health professionals to have at least a part-time private practice where they can conduct therapy more as they wish.

15. Welcome your patients' most painful feelings.

You will not be able to welcome your patients' most desperate feelings if you plan to drug the feelings into oblivion or to lock them up for their own safety. Even if you say you want to hear all their most desperate feelings, your patients will hesitate to communicate them, unless they want to push you to give drugs or to lock them up.

When clients tell me that they are feeling suicidal, I explain to them, in effect, "If you didn't have a sense that life can and should be better,

you wouldn't be so despairing over how bad it's gotten. How much you want to die—that's how much you want to love your life and how much you really want to live. I'd be more worried if you were indifferent about life. Life matters to you, and as long as that's so, I know you can learn to live an especially wonderful life."

I also give suicidal or desperate patients a phone number where they can reach me and arrange to see me as often as necessary. Since I do not give drugs, I have to give more of myself. If my patients have a caring family, I will work with them as well.

16. Share your most important values with your patients because new and better values are key to an improved life.

Values matter. In our personal lives—our relationships with family and friends, and in our choice of work and recreation—I believe in individual liberty. People should not accept emotional or physical bullying or coercion in their personal or professional lives. In the political realm, the problem of individual freedom obviously becomes more complicated, but in our personal lives, it can be straightforward. In our personal lives, we should respect each other's freedom. As therapists, we respect the freedom of our patients, and we encourage them to respect the freedom of others (see my discussions of liberty, love, and oppression from an individual and societal perspective in Breggin 1988, 1988–1989, and 1992a).

For many good reasons, adults may choose to take care of less able children or adults. Responsible adults may also decide to tolerate unpleasant or difficult people to help them or to achieve important goals. But in our personal lives, helping people should be a choice rather than the result of being physically or emotionally bullied.

I also believe that a life without love is more akin to death than to life and that people thrive to the extent that they love other people, nature, life itself, or God. So my therapy promotes liberty and love.

I also believe that we must take complete responsibility for our actions, moving beyond viewing ourselves as victims. Ultimately everything I do in therapy takes place in the context of promoting liberty, love, and personal responsibility.

While there is a great deal of room for disagreement about values, I have tried to get to the rock bottom of those that matter in adult relationships and have summed them up to my own satisfaction with the ideas of personal responsibility, liberty, and love (Breggin, 1988–1989; 1992a). My clients know or quickly learn my values, and of course, they can read my books. I believe that clients have a right to know their therapists' basic values because those values will inevitably affect them.

Beyond the right to know what kinds of values are being implemented in the therapy, learning new values is among the most important aspects of insight therapy. My patients tend to perk up from the moment that I tell them that I believe in promoting their right to live life as they choose. They perk up even more when I explain that I believe in love and want to help them lead more love-filled lives.

Having said that, I must admit that some patients, and even acquaintances outside of therapy, get nervous when I then speak about personal responsibility, fearing that it means something onerous. But often, that fear or resentment of personal responsibility is precisely how and why these people have ruined their lives, and they need eventually to face this reality if they are going to prosper. Therapy can help people overcome the guilt they feel about pursuing their own interests, including the expression of love for others, and it can help them overcome their self-defeating resentment of taking responsibility for their lives, including the pursuit of love in their lives.

17. Make clear your last resort, both to yourself and to your patients.

Other professionals often beg me to admit that there are some people I would drug. I make no exceptions, but they sometimes seem desperate to make me admit to at least one exception. Why is that? Because drugs have become their last resort, their fallback position, their default position. They cannot believe that a therapist can function without sharing that same faith—without believing in drugs as a last resort. They feel driven to hope that sometimes I will also turn to prescribing psychiatric medications, if only on rare occasions. Otherwise, I am wholly denying their version of God—the Almighty Drug As the Last Resort.

Other human beings and a personal relationship with God are far better last resorts than drugs. In fact, life itself, with all its varied ways of healing, is the alternative to a medication-impaired brain. Your clients will do much better if they understand that the restoration of their mental balance or sanity can best occur from a combination of their own internal resources and the people in their lives as well as from their most profound values and devotion to community and to a higher power, if they believe in one.

18. Address psychological or learned helplessness early in the therapy, especially with very disturbed or emotionally disabled people.

People become overwhelmed when they give up in the face of enormous stress, conflict, disappointment, or trauma. Psychosis and other deep disturbances are personal surrenders. The failing individuals succumb to

feeling helpless and overwhelmed. Their will is broken, and in the extreme, they give up trying to manage their mental lives or their daily activities.

It is important, in a caring but consistent manner, to address feelings of helplessness because therapy or any other intervention will prove ineffective until individuals believe that they can learn to control their emotions, behavior, and lives. Make clear that *feeling* helpless is not the same as *acting* in a helpless fashion. Help them understand that even the most urgent signals of helplessness must not be obeyed and, if they are not obeyed, they will eventually weaken. Explain that reason, personal responsibility, respect for the rights of others, and love must become the final guidelines for action. Explain that some people survive and even triumph over the worst kinds of stresses, from multiple loses, to physical paralysis, to years of incarceration, and that their job is to survive and then to triumph by going on to live an even better life based on sounder principles.

I am not talking about giving lectures to patients. I have already written more about helplessness in this chapter than I will talk about it in most therapies. Usually, a few words at appropriate moments will get the point across that helplessness cannot be indulged without destroying one's own life. The actual therapy work involves learning where helplessness was engendered in childhood and then choosing and learning to overcome it in adulthood.

Once the person begins to grasp the importance of rejecting helpless, victimized feelings, the additional work of therapy can begin, including the investigation of how the individual learned to react helplessly to stress and conflict.

19. Be willing to offer practical advice and guidance, especially with disturbed persons who lack successful experiences.

Many clients—including those who are not deeply disturbed—can benefit from guidance in how to go about making decisions and resolving conflicts with loved ones. In couples therapy, for example, I observe how my clients interact with each other and give them direct advice on how to communicate in a more respectful and loving manner. In the process, I emphasize the centrality of love to all personal relationships.

Obviously, therapists will vary in their ability and interest in providing guidance, but it can be a helpful aspect of the therapeutic relationship. In my older years, people seem to benefit a great deal from my advice, and in retrospect, I am glad that I offered less of it when I was young.

Very disturbed people who require a protective milieu also require a great deal of guidance, even about the most simple acts of everyday survival, but it must always be provided free of authoritarianism or coercion. Keep in mind how vulnerable to humiliation people feel when

they are struggling with disturbed feelings and helplessness and offer any guidance with the utmost respect for their autonomy.

20. Graciously recognize that you have no monopoly on helping people.

Therapists will naturally vary in how much they emphasize relationship, insight, historical reconstructions, and learning new principles or behavior. Similarly, patients will vary in how they feel about different therapists and their therapeutic approaches.

Starting with the importance of the empathic relationship, I practice a mixture of approaches, depending on what my individual client seems to want or need. Often, I will discuss what seems more useful to the client. I try to guide people through an examination of how self-defeating patterns—bad principles and flawed strategies—developed in childhood. As they recognize and become liberated from these self-defeating patterns, they can explore new and more self-fulfilling strategies.

Some clients reap great benefit from looking at the origins of their irrational, self-defeating personal policies of life. Some benefit more from looking at how best to apply good principles to current issues. Some seem to benefit more when their emotions are touched; others when they gain intellectual clarity. But they all benefit from whatever capacity I have to take a real, genuine, caring interest in them. From that they learn and gain the courage to care more positively for themselves.

If one of my clients wishes to seek another form of therapy while seeing me, I have no objection. Instead of feeling competitive or possessive, I support my clients' efforts to obtain all the help they need or want. I am not concerned that they will get different or conflicting ideas from another therapist; that is what a successful life is about—freely selecting for yourself among life's myriad opportunities and alternatives.

Keep in mind that if you or I as therapists cannot seem to help some of our patients, the alternative answer is not drugs. The alternative could be another therapist or no therapy at all. No treatment at all is better than being subjected to toxic chemicals that cross the blood–brain barrier and interfere with higher human functions. With a clear brain and mind, people can take advantage of all the healing opportunities afforded by life, from support groups and workshops to community activities and religious worship.

This point is so important and so misunderstood that it needs emphasizing. It is the height of arrogance for therapists to think and say, "My client wasn't benefiting enough from therapy, so I suggested medication." That implies that clients have only two alternatives in life: their professional relationship with you or prescribed drugs. In effect,

the recommendation of drugs covers up the real problem: the therapist's failure to help the patient. It is far better to recommend that the client shop around for another therapist or another type of therapy while you continue to offer your therapy to the individual and try your best to improve your approach. Every therapist should remember, "If I cannot help someone, then another therapist may be able to do so."

It is foolish and self-serving for therapists to believe that any particular patient must benefit from their relationship and their kind of therapy or accept being medicated. Yet the grip of drugs is so powerful in the mental health field that it is a common delusion among therapists that the patient's choice lies between their particular therapy or a drug.

## CONCLUSION

In many ways, the principles for helping deeply disturbed persons are not substantially different from the principles required for relating well to anyone, especially those nearest and dearest to us. But if we choose to help people who are feeling overwhelmed by their own emotions and by life, then we must be dedicated to conducting ourselves in the most principled, caring, and empathic manner possible. That is the essence of these guidelines for helping deeply disturbed persons.

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APPENDIX

# Psychiatric Medications by Category

## I: ANTIDEPRESSANTS[1]

### Selective Serotonin Reuptake Inhibitors (SSRIs)

Celexa (citalopram)
Lexapro (escitalopram)
Luvox (fluvoxamine)[2]
Paxil (paroxetine)
Prozac and Sarafem (fluoxetine)
Zoloft (sertraline)

### Other Newer Antidepressants

Cymbalta (duloxetine)
Effexor (venlafaxine)
Remeron (mirtazapine)
Symbyax (Prozac plus Zyprexa, a newer antipsychotic)
Wellbutrin and Zyban (bupropion)

### Older Antidepressants (Partial List)[3]

Anafranil (clomipramine)
Asendin (amoxapine)[4]
Elavil (amitriptyline)
Norpramin (desipramine)
Pamelor (nortriptyline)
Parnate (tranylcypromine)[5]
Sinequan (doxepin)
Surmontil (trimipramine)
Tofranil (imipramine)
Vivactil (protriptyline)

## II: STIMULANTS

### Classic Stimulants[6]

Adderall, Adderall XR (amphetamine mixture)
Desoxyn (methamphetamine)[7]

Dexedrine (dextroamphetamine)
Focalin, Focalin XR (dexamethylphenidate)
Ritalin, Concerta, Daytrana (methylphenidate)
Vyvanse (lisdextroamphetamine)

**Others**

Cylert (pemoline; no longer available)
Strattera (atomoxetine)

## III: SEDATIVE, HYPNOTIC, AND ANXIOLYTIC DRUGS (TRANQUILIZERS AND SLEEPING PILLS)[8]

**Benzo Tranquilizers**

Ativan (lorazepam)
Klonopin (clonazepam)
Librium (chlordiazepoxide)
Serax (oxazepam)
Tranxene (chlorazepate)
Valium (diazepam)
Xanax (alprazolam)

**Benzo Sleeping Pills**

Dalmane (flurazepam)
Doral (quazepam)
Halcion (triazolam)
ProSom (estazolam)
Restoril (temazepam)

**Non-Benzo Sleeping Pills**

Ambien (zolpidem)
Lunesta (eszopiclone)
Rozerem (ramelteon)
Sonata (zaleplon)

**Barbiturate Sleeping Pills**

Butisol (butabarbital)
Carbrital (pentobarbital and carbromal)
Seconal (secobarbital)

## IV: ANTIPSYCHOTIC DRUGS (NEUROLEPTICS)[9]

**Newer (Second- or Third-Generation or Atypical) Antipsychotics[10]**

Abilify (aripiprazole)
Clozaril (clozapine)[11]
Geodon (ziprasidone)
Invega (paliperidone)
Risperdal (risperidone)
Seroquel (quetiapine)
Symbyax (olanzapine plus Prozac, an SSRI antidepressant)
Zyprexa (olanzapine)

**Older Antipsychotic Drugs**

Etrafon (antidepressant plus Trilafon)
Haldol (haloperidol)
Loxitane (loxapine)
Mellaril (thioridazine)
Moban (molindone)
Navane (thiothixene)
Prolixin (fluphenazine)
Serentil (mesoridazine)
Stelazine (trifluoperazine)
Taractan (chlorprothixene)
Thorazine (chlorpromazine)
Tindal (acetophenazine)
Trilafon (perphenazine)
Vesprin (triflupromazine)

### Neuroleptics Used for Other Medical Purposes

Compazine (prochlorperazine)
Inapsine (droperidol)
Orap (pimozide)
Phenergan (promethazine)[12]
Reglan (metoclopramide)

## V: LITHIUM AND OTHER DRUGS USED AS MOOD STABILIZERS

Depakote (divalproex sodium; antiepileptic drug)
Equetro (extended-release carbamazepine; antiepileptic drug)
Lamictal (lamotrigine; antiepileptic drug)
Lithobid, Lithotabs, Eskalith (lithium)

### Off-Label or Unapproved Mood Stabilizers

Catapres (clonidine; antihypertensive drug)
Neurontin (gabapentin; antiepileptic drug)
Tegretol (carbamazapine; antiepileptic drug)
Tenex (guanfacine; antihypertensive drug)
Topamax (topiramate; antiepileptic drug)
Trileptal (oxcarbazepine; antiepileptic drug)

## NOTES

1. The new Food and Drug Administration (FDA) black-box warnings apply to all antidepressants but in fact were developed based on the SSRIs and newer antidepressants, and not on the older ones.
2. The brand name Luvox has been withdrawn from the market, but the drug is still available in the generic form.
3. All the older antidepressants can cause psychiatric adverse drug reactions, including mania and psychosis, but they much less commonly come up in my clinical and medical-legal experience. A more complete list can be found in various textbooks, especially *Drug Facts and Comparisons* (2007), a readily available annual publication.
4. Metabolized into a neuroleptic and should be treated as a neuroleptic in regard to its adverse effects, including tardive dyskinesia.
5. A monoamine oxidase inhibitor with special adverse reactions and dangerous dietary interactions.
6. All are Drug Enforcement Administration (DEA) Schedule II narcotics, indicating the highest risk of tolerance and dependence (addiction).
7. Few people realize that doctors can prescribe methamphetamine, the deadly drug of addiction, to children for attention-deficit/hyperactivity disorder.
8. All are DEA Schedule IV narcotics, indicating a risk of tolerance and dependence (addiction), except Rozerem.
9. All drugs listed in *Part IV: Antipsychotic Drugs (Neuroleptics)* can cause extrapyramidal symptoms (EPS) and tardive dyskinesia (TD), although Clozaril and Phenergan are weaker dopamine blockers with less of a tendency to cause these adverse effects.

10. Sertindole is another atypical neuroleptic currently going through the FDA approval process.
11. Actually an older European drug that was revived as an atypical in the United States.
12. Usually classified as an antihistamine but has weak neuroleptic qualities and can cause tardive dyskinesia.

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This lengthy bibliography has accumulated over 25 years, starting with the initial 1983 edition titled *Psychiatric Drugs: Hazards to the Brain*. Instead of pruning out older citations from the text and the bibliography, nearly all of them have been kept. Most of the older citations remain scientifically valid and in general have been confirmed by subsequent research. In addition, they provide a historical perspective on the growth of knowledge about adverse drug effects on the brain and mind. Since many of the older studies are more detailed and sometimes more frank in their observations, they also provide the clinician or researcher with the opportunity to delve more deeply into the subject matter.


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