Polypharmacy in Psychiatry

edited by

S. Nassir Ghaemi
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S. Nassir Ghaemi

Cambridge Hospital
Cambridge, Massachusetts
To my father, Kamal Ghaemi, M.D., who taught me to love scholarship by example.
And to my mother, Guity Kamali Ghaemi, who taught me the meaning of dedication.

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Foreword

Polypharmacy is a timely topic. This therapeutic regimen can be an enhancer of successful psychopharmacotherapy for the many people affected with a psychiatric illness. However, besides being beneficial, polypharmacy can also be a hindrance to improvement and remission. Clearly, it is essential that those who prescribe modern psychopharmaceuticals be conversant with the assets and liabilities of drugs that can harm as well as benefit patients. In addition, polypharmacy may be a contributor to noncompliance, since there are data indicating that the more drugs a patient has to take, and the more frequently these drugs have to be taken per day, the higher the incidence of noncompliance.

Enabling prescribers to know when they should resort to polypharmacy, when they should avoid it, and what drugs should or should not be coprescribed, are the important objectives of the erudite contributors to this well-written book, which is loaded with wisdom gained from extensive clinical experience. It will educate readers on the art of polypharmacy that is likely to benefit and not harm patients. To achieve their goal, the chapter authors provide convincing evidence from carefully analyzed and well-chosen published data. Throughout the book, the contributors offer provide readers with cogent answers to such astute questions as: when would antidepressant use be warranted in polypharmacy for bipolar disorder, and when and which drug or drugs are indicated for a candidate for polypharmacy for a particular psychiatric disorder?

This is a superb book written by experienced, knowledgeable, gifted clini-
Foreword

Cian who lucidly and convincingly share their views on the art of polypharmacy for clinicians of all ages and experience. I know of no other book on this important aspect of psychopharmacotherapy. This valuable treasure trove of knowledge provides information that will enhance readers’ practice of the art of psychopharmacotherapy for the welfare of their patients. For many reasons, I recommend this book without reservation to all psychiatrists and other physicians who treat the psychiatrically ill. This book should be in the library of every resident in psychiatry, not only for its content but for what and how it teaches readers.

Frank J. Ayd, Jr., M.D.
Emeritus Director of Research
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Preface

Polypharmacy, the use of multiple medications, has long been controversial in medicine. Conventional wisdom frowns upon it. Yet, gradually, polypharmacy has become more common in psychiatry. Whether this change is welcome is unclear, and, surprisingly, no single source addresses this question in psychiatry. Readers of this book will gain a broad view of the subject, from the historical roots of conventional medicine’s antipathy to polypharmacy, to the psychopharmacological revolution and the rebirth of polypharmacy in psychiatry.

The book begins with the historical background in the 19th century, when medicine consisted of many untested treatments and limited diagnostic methods. Research was in its infancy, and little was known about disease. Physicians were too ready to prescribe for every ailment, especially given the absence of scientific knowledge about their treatments. This led to a fight against polypharmacy. With the help of such medical advances as the discovery of the bacterium and the prevention of illness by sanitary measures, polypharmacy declined in the first half of the 20th century.

In psychiatry, the situation mirrored that of medicine, with some special features. Before 1900, psychiatrists viewed most conditions as variations on one disease, labeled “insanity,” and, like other physicians, used many untested treatments and potions, to little effect. That era of ineffective polypharmacy was replaced after Freud, with a shift toward believing that most psychiatric symptoms were attributable to childhood sources, and psychotherapy thus became the one
Preface

Treatment for all. The psychopharmacology revolution, inaugurated with the discovery of lithium in 1949, gradually reintroduced medications into psychiatry. By the 1970s, new medications forced psychiatrists to more carefully study and diagnose patients, resulting in progress to the DSM-III nosology, identifying many diseases, and many treatments for them. This process accelerated greatly in the 1980s with the introduction of newer, safer generations of antidepressant and antipsychotic agents.

Hence, psychiatry today practices polypharmacy once again. We review clinical aspects of contemporary polypharmacy by disease entity (depression, bipolar disorder, anxiety disorders, schizophrenia), by special populations (children, the elderly), and by drug type (alternative and herbal treatments). We also include a chapter on polypharmacy from the social work perspective, to bring in the viewpoint of non-M.D. mental health professionals on polypharmacy in psychiatry. The authors of this chapter specialize in psychopharmacology for social workers, and one of them has published a textbook on the topic. Each chapter author was instructed to focus on polypharmacy in the treatment of those conditions, with an emphasis on clinical relevance in contemporary treatment. They have reviewed the relevant literature, and also presented their own experience and views. I edited each chapter to remove redundancies and to ensure that these basic guidelines have been met.

This book is intended for practicing psychiatrists in the United States and overseas, as well as other mental health professionals, particularly psychologists, social workers, nurses, medical and graduate students, and other physicians.

S. Nassir Ghaemi
Acknowledgments

I thank Jinnie Kim, Acquisitions Editor at Marcel Dekker, Inc., who first approached me regarding this book project. I had given a lecture at a symposium at an annual meeting of the American Psychiatric Association on polypharmacy of bipolar disorder. She suggested that a book on the larger topic of polypharmacy in psychiatry might prove attractive and I became more and more intrigued by the idea. I soon realized how useful this project was for me, and, in the process of writing and editing it, I learned a great deal that will remain important in my research and practice.

I would like to acknowledge and thank my psychiatric mentors who have influenced my thinking and provided, directly or indirectly, much of the content and background to my work presented here. Frederick Goodwin has been a central figure in my career, both as an example of the creative thinker and as a practical guide in the fields of research and clinical practice. Ross Baldessarini helped train me as a resident and more recently has been an important teacher with whom I am able to discuss psychopharmacology and nosology in a coherent, inquisitive manner. Leston Havens, in his writings and in person, has also helped me think deeply about what we do in psychiatry, and continues to be a source of creative thinking about our field. Besides these mentors, I have also greatly benefited, in writing and personally, from David Healy, Frank Ayd, Daniel Dennett, Jennifer Radden, and Godehard Oepen. I especially would like to thank Frank Ayd for agreeing to write the foreword to this book.
I also thank the chapter contributors. This topic is difficult and complex, and I greatly appreciate their willingness to tackle it in each of their disciplines.

I dedicate this book to my parents. My father, who trained and practiced as a neurosurgeon and a neurologist but is also a humanist in the classical sense, has always served as a role model. Without his constant encouragement toward scholarship, I would not have been able to progress in my work. He also specifically encouraged me in taking up this book project, and many of the ideas I express here were influenced by him. Words are inadequate to recognize my feelings about my mother’s personal support for me and her unqualified dedication to her children.

I also would like to thank my wife, Heather, for tolerating my stints away from her and our baby, for encouraging my work on this book, and for agreeing to coauthor a chapter, all the while juggling the requirements of new motherhood. And I must also acknowledge our daughter, Valentine, whose babbling and laughing punctuated my work, making everything even more meaningful and enjoyable.
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1

“All the Worse for the Fishes”:
Conceptual and Historical Background of Polypharmacy in Psychiatry

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In diseases of the mind . . . it is an art of no little importance to administer medicines properly; but, it is an art of much greater importance and more difficult acquisition to know when to suspend or altogether to omit them.

Philippe Pinel (1)

Presumptions are of vast importance in medicine, as in law. A man is presumed innocent until he is proved guilty. A medicine . . . should always be presumed to be hurtful. It always is directly hurtful; it may sometimes be indirectly beneficial. If this presumption were established . . . we should not so frequently hear . . . that, on the whole, more harm than good is done with medication. Throw out opium, which the Creator himself seems to prescribe, for we often see the scarlet poppy growing in the cornfields, as if it were foreseen that wherever there is hunger to be fed there must also be pain to be soothed; throw out a few specifics which our art did not discover, and is hardly needed to apply; throw out wine, which is a food, and the vapors which produce the miracle of anesthesia, and I firmly believe that if the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind,—and all the worse for the fishes.

Oliver Wendell Holmes (2)

It must have been a dark and damp day—that May 30, 1860—a typical wet Boston spring day, when Oliver Wendell Holmes addressed his medical col-
leagues at the Massachusetts Medical Society. Maybe Holmes was in something of an irascible mood that day, when he made the above statement. I can imagine that many in Holmes’s audience were more preoccupied with the great issues of the day—civil war, slavery, abolition, a vital presidential election—than with seemingly harmless potions. But Holmes, the famous physician and writer and Harvard Medical School professor (later eclipsed in fame by his son the Supreme Court justice), did not toss off those words as a mere peripheral opinion. That day, at the medical society, he gave a lecture that built up to the argument he made, a considered examination of the nature of medication treatments, and his conclusion that aside from certain specific treatments, most medications were worthless or, worse, harmful. Maybe he meant to provoke. And, indeed, his lecture stimulated a great deal of discussion about the topic that continued long afterwards, and Holmes’s statement is still not infrequently quoted in many contexts.

Holmes was a judicious man, well respected by senior physicians. He did not offer his judgment lightly. He felt that the profession of medicine, as well as the public, was harmed by use, and overuse, of inadequately proven medications. In 1860, Holmes went after pharmacology in general, not to mention polypharmacy (2).

In fact, I might hazard to state that medical care before the 1940s consisted of polypharmacy if it consisted of anything at all. This is because physicians rarely prescribed just one treatment; they usually prescribed multiple medications at once. There are many reasons for this, among them beliefs prevalent at the time about homeopathy, which I address later. But one major factor might have been, as Holmes claimed, that almost all medications did not work, and thus physicians tended to use many medications, hoping to elicit benefits not present when used singly. Anton Chekhov, the Russian writer who practiced medicine all his life, once commented that if many medications are used, then the disease is incurable (3). In Holmes’s view, nineteenth-century medicine simply possessed ineffective medications; disease might be curable, but treatments needed to be proven to cure disease before being used.

I take Oliver Wendell Holmes’s credo as my own. Yet in this book we will explore the benefits as well as the limits of polypharmacy in psychiatry.

In thinking about polypharmacy, one might first want to ask the question: What do physicians do? Today, the immediate answer would likely be: prescribe medications or operate. This has not always been the case. Before the nineteenth century, physicians mainly prescribed medications; they did not operate, which was left to surgeons. Surgeons in general were not classified as physicians, nor trained as physicians; in fact, the majority of them took apprenticeships with barbers. Only with time, as knowledge of the human anatomy increased, did surgeons begin to receive medical training with physicians. For the purposes of this book we ignore surgery, since it has little application in contemporary psychi-
Historical Background

So, let us say that what physicians do is prescribe medications. Is that all we do? Immediately, we realize that there is something else that physicians do that helps patients, a nonspecific activity captured to some degree by the catchphrase “good bedside manner.” Physicians provide information to patients about their symptoms, frequently reassuring them that nothing in fact needs to be done and that the symptoms will subside. Physicians also provide psychological support to patients, which often promotes recovery from medical illness. This support to some extent is a likely underpinning of the famous placebo effect. In psychiatry, this aspect of medical care is more formalized in different techniques of psychotherapies.

So, besides prescribing medications, physicians provide technical information and psychological support. These aspects of medical practice may in fact have been more effective and important in the nineteenth century than pharmacology, which, as Holmes suggested, was physiologically ineffective in most cases. In psychiatry, until the last few decades, medications were generally avoided in many quarters: instead, psychotherapy, formalized and highly structured in its psychoanalytic form, was considered the main effective treatment.

Part of the reason there is any question about polypharmacy in psychiatry is the fact that pharmacology has finally established itself. In other words, until recently, any medication use in psychiatry, much less multiple medication use, was controversial.

Thus, to some extent, in telling the story of polypharmacy in psychiatry, I must discuss the story of the rise of psychopharmacology in general.

Before I discuss the origins of psychopharmacology, one other aspect of what physicians do must be mentioned. Again, our source is the inimitable Holmes. While he wrote many popular books, including the highly regarded Autocrat of the Breakfast Table (4), Holmes’s contribution to scientific medicine is mainly limited to his work on puerperal fever, summarized in his 1843 essay, “The contagiousness of puerperal fever” (5). With epidemiological techniques of observation, Holmes showed that puerperal fever, a postpartum infectious disease that led to the deaths of many young mothers, was spread hand to hand from physicians to patients. He showed that by proper handwashing alone, the incidence of puerperal fever could be markedly reduced. This was long before the first microbe was identified* or the germ theory of infection was suggested, much less accepted. And he had many opponents, who could not fathom why handwashing might prevent or cure a disease. What Holmes discovered was that

* In characteristically acerbic fashion, nearly 50 years after first publishing on this topic, Holmes commented: “The whole question I consider now transferred from the domain of medical inquiry to the consideration of Life Insurance agencies and Grand Juries. . . . Of course the whole matter has been looked at in a new point of view since the microbe as a vehicle of contagion has been brought into light, and explained the mechanism of that which was plain enough as a fact to all who were not blind or who did not shut their eyes” (6) (original italics).
doctors could prevent, rather than treat, diseases by certain methods, such as sanitary habits. This is something else physicians do: they give instructions to the public on how to prevent diseases when factors that lead to the disease can be identified. This is really epidemiology, and thus often not considered part of the daily activity of physicians. But, in fact, it might be argued that many more diseases have been prevented by epidemiological methods than cured by pharmacological ones.

Take tuberculosis. Antitubercular antibiotics, developed in the last 50 years, have many side effects and are sometimes ineffective. There is little doubt that the prevalence of tuberculosis began to decline long before those antibiotics became available or widely used. The main factor leading to this decline was the discovery that tuberculosis was much more prevalent in unsanitary, crowded living conditions, and when those conditions were ameliorated the disease began to abate.

Consider poliomyelitis. There still is no cure for this condition. But it almost disappeared after a preventive vaccine was discovered and applied extensively in children. The major diseases that plagued mankind throughout the nineteenth century have been mainly prevented by nonpharmacological means, rather than cured by medications, much as Holmes presaged.

The result is that twenty-first-century medicine is left with many conditions that are less preventable. The medical profession, having exhausted a great part of its epidemiological tools, is left with its three remaining tricks: medications, psychological influence, and surgery. In psychiatry, as mentioned, surgery is not a viable option in most cases. Psychotherapies have been exhaustively used, and while it is not the province of this book to assess this matter in detail, it is probably not inaccurate to assert that psychotherapies have not proven effective alone in treating most psychiatric conditions.* They remain important in psychiatry: sometimes psychotherapies are effective alone, sometimes they are effective with medications, and sometimes they are not effective at all. Granting a role for psychotherapies, medications have become an important aspect of psychiatric practice—partly by default, partly by virtue of apparently real benefit.

Thus, the study of polypharmacy in psychiatry begins with an examination of the context in which medications are used in psychiatry: the story of psychopharmacology.

Medications were poor cousins to psychotherapies in psychiatry until the last few decades. In fact, medications designed for use in psychiatric illnesses were not systematically studied until the 1950s and did not begin to enjoy rela-

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* Psychotherapies alone are clearly ineffective in mania or schizophrenia. They are likely ineffective in severe depression. Some evidence exists for efficacy of certain kinds of psychotherapy alone, such as cognitive behavioral psychotherapy, in mild to moderate acute major depression, but even this evidence is mixed when compared to antidepressant medication (7–10).
Historical Background

It was relatively common use until the 1960s. Yet from these humble beginnings, it is not much of an exaggeration to assert that the birth of psychopharmacology revolutionized the entire field of psychiatry by the 1970s. In the last two decades, psychopharmacology has so grown in stature that some psychiatrists are worried that the entire field of psychiatry is being reduced to psychopharmacology.

This outcome would have been unthinkable four decades ago. In the 1960s, psychopharmacology was still meekly knocking at the door of mainstream psychiatry, seeking to be given some recognition at the hands of psychoanalytically oriented leaders in the profession. One of the psychoanalytic leaders of the age who expressed some open-mindedness to psychopharmacology was Mortimer Ostow (11). In a conference that entertains perhaps more than it intended, Ostow mainly discusses the potential utility of psychopharmacology in terms of how medications might promote the psychoanalytic process.* Medications, he mused, might help defuse certain defense mechanisms, or enhance the transference, and thus allow psychoanalytic treatment to proceed more efficiently. Even Jonathan Cole, the head of the first psychopharmacology research section of the National Institute of Mental Health (NIMH) set up in 1956, suggested that the new drugs might be better understood in the psychoanalytic setting. In an interesting paper, Cole and Seymour Fisher wrote that the psychoanalytic setting may be well suited to examine the interaction between each individual’s personality and drug response: "In orthodox psychoanalysis, the analyst has more intensive contact with his patient and more previous experience with the individual patient receiving drug therapy than have psychiatrists treating patients in other ways or in other situations. The analyst will, therefore, usually know his patients ‘better’ and be able to make both more detailed and more sensitive observations concerning the patient’s personality structure, his current problems, and the changes occurring in the patient’s personality structure, his current problems, and the changes occurring in the patient’s personality structure..."

* A good example is Ostow’s 1960 paper (15), “The use of drugs to overcome technical difficulties in psychoanalysis.” There Ostow begins by describing the various requirements for patients to benefit from psychoanalysis, including needing to recognize that they are ill, being willing to follow the basic rule of saying whatever comes to mind, being able to entertain and examine interpretations of analytic material, being able to engage in a transference, and so on. Ostow then proceeds to provide a few cases where using a neuroleptic or an antidepressant helped patients on one or more of these requirements so as to engage in psychoanalytic work more effectively. “How do the drugs work?” he asks. “I believe that the best hypothesis is that the phenothiazine tranquilizers (and reserpine) decrease the psychic energy available to the ego by retarding its generation in the id, and iproniazid increases the rate of transfer of id energy to the ego.” In 1960, psychoanalysis was still so powerful that psychopharmacology had to be interpreted in analytic terms. One gets the sense of the extent of this psychoanalytic power when one reads the comments of Daniel Freedman at that conference on Ostow’s paper, where criticism had to be couched in profuse praise (keeping in mind that Freedman later became editor of the Archives of General Psychiatry and one of the most powerful figures in mainstream post DSM-III empirically-oriented psychiatry): “Dr. Ostow is to be congratulated... His paper is a tour de force and while all together commendable from some vantage points, it lacks the force of experimentally and clinically validatable argument.”
during drug therapy” (12). Other psychoanalysts were overtly hostile. In another conference in 1966 in Boston (13), Elizabeth Zetzel made some clear comments that, read today, smack of worship of abstractions in the face of concrete realities. She was responding to an earlier exposition of the pharmacological approach by the British psychiatrist, Dr. William Sargant (14). Dr. Sargant, who supported “somatic” treatments in psychiatry, provided, at the time, a minority perspective:

When I came to work at the Massachusetts General Hospital in Boston in 1938, I had already spent several very disillusioning years trying to learn how to treat the nervous and mentally ill at the Maudsley Hospital, London, largely by various forms of psychotherapy, because that was the only method of treatment available at that time. The end result was that so many patients, after months of patient intensive treatment, still had to go on to the chronic wards of mental hospitals, most of them never to come out again. Then suddenly we saw the advent and use of the fast-acting barbiturates . . . the discovery of Sakel’s insulin coma treatment, and Meduna’s drug-induced convulsion therapy. One also began to hear varying reports about . . . prefrontal lobotomy. . . . On trying some of these treatments out many more patients suddenly started to get better, and in a matter of only a few weeks instead of the months or years it took before, if they ever got better at all. The psychotherapy we gave also became so much easier. . . . I had spent three unhappy years at the Maudsley when we only had talk and talk and more talk to help our patients; and what a disaster it all was, until the drug and other physical treatments came along to bring about the present astonishing treatment revolution. . . . I came to Boston . . . in 1938 . . . to sit at the feet of Helena Deutsch and Finesinger in Professor Stanley Cobb’s newly formed psychiatric department at Massachusetts General Hospital. Everything here was totally different again. We were back in the bad old psychotherapy days with a vengeance. Patients were even denied sedatives and were allowed to go sleepless and to suffer agonies of mind for nights on end. When I protested, I was told that if you made your patients better, and especially if you let them sleep comfortably, you would lose your main chance of bringing them to a tortured acceptance of the analyst’s particular brand of Freudian or other insight. . . . Fortunately all these new drug and physical treatments need very little psychotherapy indeed for them to be effective. . . . The dreadful truth must be told even in Boston. Physical treatments are now rapidly replacing psychotherapy in England and in most other countries of the world. . . .

Zetzel (13) began the discussion from the viewpoint of mainstream psychiatry at the time, as a psychoanalyst. She begins by disavowing an extremist Freudian view:

I was happy to accept the invitation to discuss Dr. Sargant’s paper . . . I do not believe that measures which may bring about relief of suffering or social rehabilitation should be withheld without adequate reason. . . . I have never
Historical Background

suffered under the alleged Freudian delusion that psychoanalysis had all the answers, particularly in respect to its curative powers. Where, I wonder, did Dr. Sargant get the idea that this was the sermon preached by the founder of psychoanalysis? . . . Freud, as most of us know, always believed rather more than some of his followers in the ultimate correlation of his psychological findings with physiological and biological knowledge. Jones, in his biography, notes in this context a “half serious prediction made by Freud that in time to come it should be possible to cure hysteria by administering a chemical drug without any psychological treatment.”

But then Zetzel presents a perspective that seems rather uncompromising:

There need be no widespread assumption to the effect that drugs and psychotherapy are incompatible. There are, however, significant differences between the theory and philosophy determining their use advocated by Dr. Sargant and (here). . . . Dr. Sargant is, in his own words, dedicated to a strictly utilitarian approach, seeking to find, if necessary by repeated trial and error, the drug or combination of drugs which will afford the greatest symptomatic relief and related improvement in social behavior. He seems to imply that mental illnesses such as schizophrenia or psychotic depression can be regarded as unfortunate afflictions which can attack otherwise good, healthy, mature individuals.

This is indeed the commonplace view held by mainstream psychiatry today. She later comments:

Schizophrenics must learn that at times being well is less comfortable than being schizophrenic. They must learn ultimately to master anxiety and depression, but in order to do this must be allowed to feel some anxiety and depression. . . .

The 1950s and 1960s were a time when early shots were fired in what would turn out to be a war of almost epic proportions. In a few circles, attempts were made to avoid too large a later conflict. Gerald Sarwer-Foner was a psychiatrist in Canada who began to specialize in the relationship between psychopharmacology and psychotherapy (15). He argued that both could and should coexist, that psychopharmacology was a legitimate form of treatment, but that it also had limitations and psychological components that demanded attention. As mentioned, Ostow toyed with the concept of making medications a handmaiden to more effective psychoanalysis (a view that foreshadowed Peter Kramer’s later observation that serotonergic antidepressants like fluoxetine could help patients better engage in, rather than impede, psychotherapy). Along the same lines, let us consider the famed Boston psychoanalyst, Elvin Semrad, who trained generations of powerful psychoanalysts as well as later psychopharmacologists, one of whom would become a key figure in the transformation of psychiatry in the 1970s and 1980s, Gerald Klerman. In the same 1966 Boston conference alluded to previ-
ously, Semrad and Klerman (16) collaborated on the topic of how to reconcile psychotherapy and psychopharmacology, but still viewed drug treatment as a back-up to psychotherapy:

In our total treatment strategy, drug therapy (like other medical treatments) is used as an adjunct when recovery cannot be initiated or maintained on the basis of a positive object-transference relationship. Chlorpromazine is particularly useful when there is overwhelming affect, psychic pain, which has to be avoided. We are less impressed with the value of the ‘energizers’, the antidepressants. . . . The question arises as to whether drug therapy offers any specific effect on therapy processes over and above the exchange of need, affection, sustenance between doctor and patient. . . . Repeated observation indicates to us that patients under the influence of drugs recite very well but cannot and do not affectively and experientially participate in the content of their recitation.

Until the 1970s, so few effective medications and other treatments were available and proven that psychiatric treatment was left to psychoanalysis almost by default. One gets a sense of this by perusing a textbook written by Sargant along with Eliot Slater, another esteemed British academic psychiatrist, on Physical Methods of Treatment in Psychiatry (17). Textbooks are famous for being a few years behind the times, but the fourth edition of this one, published in 1964, seemed all too descriptive of the state of affairs of psychiatry then, with chapters on the following treatments: chemical sedation and stimulation (which included all known drugs, mainly phenothiazines, barbiturates, amphetamines, and monoamine oxidase inhibitors, covered in 40 pages), convulsion therapy (34 pages), prefrontal leucotomy (39 pages), continuous sleep treatment (11 pages), modified insulin therapy (16 pages), insulin sopor and coma (32 pages), the use of drugs in psychotherapy (25 pages), diet, vitamins, and endocrines (36 pages), treatment of the epilepsies (29 pages), and treatment of the alcoholic and other addictions (18 pages).

Over time, the development of tolerable effective medications made psychopharmacology an irresistible force on its own, leading to a wholesale reorganization of psychiatric classification in 1980, the DSM-III, whose effects we still feel today (18). By the 1980s, psychopharmacology was on the ascendant, and when the decade of the brain arrived (1990–2000), new generations of antidepressants and antipsychotic agents placed psychopharmacology on a throne of power it had never held before. In the process, medications became used more and more frequently and in more combinations. Once any kind of medication treatment became acceptable, polypharmacy frequently became the rule.

This book is an attempt to come to terms with this outcome of the development of contemporary psychiatry. To understand how the rise of psychopharma-
Table 1 Factors Associated with the Rise of Psychopharmacology

1. Scientific: Research on biogenic amines conducted in depression and schizophrenia expanded on early clinical evidence on psychotropic medications.
2. Clinical: The advent of medications influenced the move to standardize diagnostic criteria in an “atheoretical” way in DSM-III. This has resulted in many diagnoses with extensive overlap, excellent reliability, but limited validity. To some extent, poly nosology and polypharmacy go together.
3. Economic: The pharmaceutical industry produced and marketed medications and influenced demand for them on the part of the public and clinicians.
4. Political: The Food and Drug Administration imposed certain minimal guidelines for drug approval that became viewed as scientific facts, rather than political rules. One of these was that drugs should be indicated only for specific conditions designated by the FDA.
5. Cultural: Americans have always had a large appetite for pharmacological treatments, dating back to the nineteenth century.

cology led to the ubiquity of polypharmacy, we need to follow in more detail the ascendant path taken by psychopharmacology as a branch of psychiatry (19).*

In general, there are five factors associated with the rise of psychopharmacology (Table 1) that later led to frequent polypharmacy: scientific advances in biochemical research, and the economic (pharmaceutical industry), political (the Food and Drug Administration), cultural (the appetite for medications), and clinical (DSM-III and the revolution in psychiatric nosology) contexts.

The cultural component is large, and I will leave it for a later chapter. The role of scientific advances in biochemical research in psychiatry almost goes without saying. In fact, in 2000, Nobel prizes were awarded for researchers who focused on understanding the biochemical basis of psychiatric conditions (research on serotonin and dopamine function in the brain) (17,20).† It is notable,

* Much of the following material is derived from and indebted to the work of David Healy (19).
† The Nobel Prize in 2000 was awarded to Eric Kandel for his work on the neurobiology of short-term memory. Previously, Julius Axelrod received a Nobel for his work on the biogenic amines, serotonin and norepinephrine, work largely inspired by research on the mechanism of action of tricyclic antidepressants. It is an important historical footnote that of these researchers in psychiatry, Kandel is the first MD psychiatrist to win a Nobel since the 1920s, and only the second in history. The other psychiatrist was the chairman of the department of psychiatry at the University of Vienna, Julius von Wagner-Jauregg, an enemy of Freud, who found that he could produce temporary improvement in general paralysis of the insane with malaria blood injection (20). These patients, who suffered from neurosyphilis, would improve during and after febrile spikes, which temporarily killed some of the spirochete infection. Psychosis seemed so refractory and incurable that even temporary abatement of psychosis with such a drastic measure sparked great attention and led to the award of a Nobel prize. Malaria therapy, left out of Sargent and Slater’s 1964 text (14), was studied in
however, that much of this research would likely not have taken the form it did were it not for the previous, unrelated, discoveries of clinical efficacy with chlorpromazine for schizophrenia, imipramine for depression, and lithium for mania.

The most important factor associated with the rise of psychopharmacology may be the economic context, which heavily influences clinical nosology. It is a simple fact that without medications, there would be no pharmacology and no polypharmacy. It is also a basic fact, granted by most everyone, that many medications are quite helpful to persons with many illnesses and that private enterprise (capitalism) is necessary to research, develop, and distribute many of these medications. Thus, I do not intend for a discussion of the economic context of polypharmacy to imply one-sided criticism of the pharmaceutical industry. Rather, I wish to highlight an obvious point—that economic factors drive pharmaceutical companies, which are, after all, for-profit industries like almost every industry in a modern capitalist economy.* As a result, in a great many instances, economic factors influence the availability and use of medications in medicine, including psychiatry.

It is worth noting that in the 1950s, when the pharmaceutical industry began to be interested in medications for psychiatric conditions, such interest was limited and inchoate. The psychotropic effects of the first psychiatric medications—chlorpromazine for schizophrenia and imipramine and iproniazid for depression—were first noted as side effects of attempts to use those agents to treat other medical conditions. (The only exception was lithium, to which I will return.) Thus, it is not true to assert that the pharmaceutical industry was interested in producing psychiatric medications from the start; in fact, the industry was quite reluctant. But the patients were there, thousands and millions of psychotic and depressed and agitated patients who filled many psychiatric hospitals for decades in wards that sometimes were filthy and degrading. And the doctors were there, trained often in psychoanalysis, but realizing that their training helped them little in the treatment of severe mental illness and that it cured practically no one. It was individual psychiatrists, like Nathan Kline and Ronald Kuhn, who observed the benefits of the first psychotropic agents and pressured the pharmaceutical companies to pursue more research into those medications (19). After a while, individuals in some pharmaceutical companies took note of the fact that there appeared to be many psychiatric patients diagnosed with schizophrenia in particu-

* I once joked to a colleague in the pharmaceutical industry that his industry at least produced medications that helped people, rather than some other industry that might actually harm people, like the tobacco industry; then I learned he had previously worked for the tobacco industry!
Historical Background

lar, and some with depression, and that these medications might not only help those persons but the drugs might also prove profitable. Of course, in that era in the United States, psychiatrists were diagnosing practically all patients with schizophrenia, thus the original focus on that condition as regards medications. With time, clinicians and pharmaceutical companies also began to recognize the importance of depression and, much, much later, bipolar disorder. Lithium, in fact, was not marketed or developed by any pharmaceutical company for mania until a great deal of pressure was brought to bear on the industry from psychiatric researchers, the NIMH, and U.S. Food and Drug Administration (FDA) officials to distribute it for public use in the late 1960s. Thus, lithium is the exception to the rule that I will now suggest: the first step to the transformation of modern psychiatry was the entry of the pharmaceutical industry into the research and practice of psychiatry.

When chlorpromazine and imipramine were introduced, the pharmaceutical industry participated in funding the education of psychiatrists regarding the conditions of schizophrenia and depression. Conferences were held and books distributed that advanced ideas at odds with standard psychoanalytic thinking and more in line with traditional medical models of psychiatry (19). The new psychopharmacologists harkened back to views held by psychiatrists before the rise of psychoanalysis, particularly the observations of Emil Kraepelin, Eugen Bleuler, and their followers, which divided all psychosis into schizophrenia and affective disorders (19). The fact that the pharmaceutical industry provided such support for different views broke the monopoly of psychoanalytic thinking on psychiatry.

Another factor, related to economics, is less well recognized: the regulatory influence of the FDA. I will go into more detail here because I believe the FDA’s role is complex and confusing, and again this history is well described by Healy (19). Obviously, on the positive side, the FDA performs a major service in ensuring, at a minimum, that new medications are safe and effective for the specific circumstances for which they are indicated. The Progressive Movement in the United States influenced the public and politicians to recognize the need to regulate food (unclean meat packing had led to much illness) and drugs (tetanus outbreaks had occurred due to unsanitary preparation of smallpox vaccines). The Food and Drug Act passed in 1906, but a federal agency to enforce the act was not instituted until 1938, during the New Deal, when the FDA was created. The 1938 amendment specified that the FDA needed to declare a drug safe before it could be marketed, and it asserted FDA control over how a drug was to be advertised (banning false statements). Prescription-only drugs, introduced as a category before World War I, were made the province of FDA control in a 1951 amendment. Finally, in the major move that completed the evolution of current rules, a 1962 amendment specified that the FDA had to declare a drug effective, and not just safe, before it could be marketed. This last move came on the heels of the thalidomide disaster, when this drug, marked for sedating properties, was
given to women during pregnancy and resulted in limb deformities in exposed fetuses.

Thus did the current state of affairs evolve: the federal government established an enforcement agency, the FDA, charged with identifying prescription-only medications, which could not be marketed unless they had proven their safety and efficacy to the FDA.

In 1962, the wording of the amendment was loose enough to leave open the details of what kinds of data would be required to prove a drug effective to the FDA’s satisfaction. Over time, these standards have developed and somewhat differed among different branches of the FDA. The branch relevant to psychopharmacology, the Neuroscience branch, has evolved its own requirements over time. It appears that in 1962, the main change brought to the private market by the FDA was that drugs should establish efficacy based on randomized clinical trials. The principle of randomization was rather new and important in medicine.

Introduced in the early 1950s in psychiatry with trials of lithium and chlorpromazine, random assignment of patients to either receive or not receive the study medication became the hallmark of a clinical trial, as opposed to clinical observation. The problem with simple clinical observation, as Holmes and others had pointed out in the nineteenth century, was that it could be biased based on the wishes of the doctor or the patient. Further, a doctor might choose a specific drug preferentially in less ill persons, thus making it seem effective. Randomized assignment to receive a drug or not would appear to take care of those biases. Thus, the randomized clinical trial was born in psychiatry in the 1950s and codified as a necessary component of psychopharmacological research by the FDA in the 1960s.

But that was not all. Two further steps soon followed: randomized trials might still be biased if the doctor or patient knew who was getting the new, and potentially more effective, drug. Thus, the double blind was introduced to hide the active treatment from both. Further, simply being in a clinical trial and knowing that one would receive a potentially exciting new treatment might lead to a placebo benefit for any medication. Thus, the placebo comparison became commonly required. Very quickly, the process of proving the efficacy of a drug and being allowed to market it in the United States went from loose guidelines focusing on a drug’s safety to the requirement of randomized, double-blind, placebo-controlled clinical trials.

Another step, equally important, became more prominent in the 1950s and 1960s. With the new FDA amendments, a consensus arose that the FDA was not in the business of providing general approval for medications. Since efficacy was now required, this meant efficacy for, as Healy put it, “‘indications that medical experts agreed were the indications for which compounds were needed—diseases’” (19). By focusing on diseases rather than symptoms, the FDA was following the tradition of Holmes and Osler, while at the same time, in psychiatry, this
approach led to a presumption in favor of medical models of diagnosis as opposed to other models (such as the Freudian reluctance to diagnose).

This process—requiring proof of efficacy as well as safety, insisting on randomized clinical trials, and wanting a focus on specific diseases—proved rather expensive for pharmaceutical companies. As a result, research data at this level (randomized, double-blind, placebo-controlled) required extensive funding from either pharmaceutical companies or other sources. Other sources were limited, since private foundations were few, and the federal research branches (mainly the National Institutes of Health, NIH) tended to gear most of their funding to basic animal studies rather than clinical human drug studies, partly reasoning that clinical human studies already had sources of support in the pharmaceutical industry, whereas animal studies had fewer other sources of support. Thus, more clinical drug studies have, over the years, been conducted with private pharmaceutical research funding than with NIH funding. And, since the pharmaceutical funding is largely geared to FDA requirements, the FDA’s rules for regulating the pharmaceutical industry have, de facto, comprised almost the entire content of most controlled clinical research in psychopharmacology, as well as the rest of medicine. In other words, what the FDA probably intended to be minimum standards for pharmaceutical research has become almost the entire extent of controlled psychopharmacology (and in general almost all pharmacology) research. Healy describes this process well (19):

The FDA has come to occupy something of a magisterial role on the world stage. As with the magisterium of the Catholic Church, it acts not to say what must be believed but to adjudicate on certain claims that are made, allowing some of those to stand and refusing to legitimize others. In one sense this is a very minimal role, but the strategic position of the FDA in the current world psychiatric economy means that this minimum can be extraordinarily influential. Yet the FDA is in place to regulate an industry, not to arbitrate on science.

In practice, given limited funding resources, it does both.

The FDA story did not end in the 1960s. This whole story is so important to understanding why the psychiatric literature consists of certain controlled studies and not others, as will be seen in chapter after chapter of this book, that it deserves a detailed recounting here.

When the FDA proposed the need for randomized controlled trials in the 1960s, with a preference for double-blind and placebo-controlled methods, many companies responded by providing research that was randomized and double-blind, but frequently did not use placebos, instead comparing a new agent to active controls. In psychiatry, since the 1950s, one could identify one medication for each of the three major mental illnesses, with randomized clinical trial (often placebo-controlled) evidence of their efficacy: lithium for mania, imipramine for
depression, and chlorpromazine for schizophrenia. The United States was a signatory to the Helsinki Declaration of Human Rights, which, in the wake of Nazism, clearly required that no patients should enter research studies in which they fail to receive treatment with an effective medication, if such medication is available. Based on this commitment, regulatory authorities in Germany have refused to allow placebo-controlled trials to this day. Even in the United States, certain university ethical boards (such as at Duke and Johns Hopkins Universities) do not allow psychiatric placebo-controlled studies for the same reasons. Thus, pharmaceutical companies in the United States in the 1960s and 1970s conducted studies in comparison with one of the three standard treatments mentioned above, and if a new drug for one of those conditions was equally effective as the standard treatment, then that drug was judged to be effective. In the case of depression, one would avoid the increased risk of suicide that is entailed if the illness goes untreated (or treated with placebo).

This approach ran into the problem of the “failed study.” A failed study is one in which no treatment is effective, even one that has previously been proven effective, due to a special nonresponsiveness of the sample. Thus, in a study of depression, for instance, new drug X may be as effective as imipramine, both with 33% efficacy over 2 months; however, if there had been a placebo group that also showed 33% efficacy, this study would have been a failed study, rather than one that appeared to show equal efficacy of drug X to imipramine, implying that drug X is effective because imipramine is effective. A truly negative study would be one in which imipramine was more effective than placebo, but drug X was not. A truly positive study would be one in which both imipramine and drug X were more effective than placebo and equal to each other in efficacy.

These considerations, spearheaded by Paul Leber, the head of the FDA Neuroscience section, led the FDA to require the use of placebo-controlled studies (19):

Paul Leber, who had joined the FDA in 1978, pointed out to all concerned that given the numbers involved in a traditional antidepressant trial, the lack of a difference between old and new treatments was not convincing evidence that the new treatment worked. The clearest outcomes from such studies would concern differences in the side-effect profile of the two compounds; therefore all the trials were doing, in one sense, was providing good marketing copy for the companies. Despite general disbelief, Leber pushed through a formula that all submissions must contain evidence of at least two pivotal studies. Though not spelled out in detail, it is understood by all parties that pivotal ordinarily means placebo-controlled. The drug development plans of a number of companies were thrown into turmoil.

This is probably where the FDA’s wish to regulate the pharmaceutical industry most powerfully impacted the larger psychiatric community and the pub-
lic. It is a troubling fact that the FDA requires pharmaceutical companies and university researchers to, in effect, break the Helsinki Declaration’s prohibition on placebo treatment when an active drug is available. Beyond this ethical question, the most discussed end result of this process is that much of the scientific research in psychopharmacology is conducted in such controlled circumstances that it often cannot be generalized to real-world patients. To conduct a double-blind, placebo-controlled randomized trial to prove efficacy in a specific indication, e.g., depression, one would have to exclude many persons: those with substance abuse, serious medical illnesses, histories of mania, and so on. One would also have to exclude those who are so severely ill that they cannot adequately give informed consent or who would likely not reliably come to outpatient appointments. As a result, many patients in the real world, who have some or many of these characteristics, might not respond in the same manner, and thus the randomized data might not be useful to predict response in those complex real-world patients. In the case of polypharmacy, patients treated with multiple medication are frequently nonresponsive to single medications. But clinical trials do not try to identify such patients and will also frequently screen them out.

One later development that Healy did not touch on in his book is the issue of parallel versus crossover designs (Fig. 1). The FDA group in the 1980s insisted that psychiatric randomized clinical trials should not only be placebo-controlled, they should also employ parallel arms for treatment. This means that subjects should randomly be assigned to one drug or another at the very beginning of the study with no changes in assignment later in the study. The crossover design, in contrast, allows for a patient to be switched from one group to another if she does not respond to the first treatment. The crossover design has a number of advantages: first, it begins with randomized parallel treatment, thus providing the same basic information as a simple parallel-designed study; second, if a placebo is used, a crossover design ensures that, at least later, those who receive placebo can be switched over to the active treatment; third, the crossover design would provide clinically relevant information about what percentage of persons who fail to respond to one drug will respond to another. The main disadvantage of the crossover design is that it is statistically more complex to interpret efficacy once one gets beyond the initial parallel phase. The other disadvantage was created by the FDA’s insistence that only parallel design data could be used to establish efficacy in pivotal trials; crossover studies, while not prohibited, would be extra. In the real world, where money is not spent when it does not have to be spent, the FDA’s minimum requirement became a total reality, and pharmaceutical companies rarely sponsored extra crossover design extensions for their studies. Clinically, this has meant that psychiatrists have very little information based on randomized studies that can inform them about how a particular drug may work in those who fail to respond to another. Patients and doctors often decry the apparent trial-and-error nature of psychopharmacology practice today (try
Parallel versus crossover designs: (a) In a parallel design, subjects are randomized to drug A or drug B, with no further changing of groups. If one group is placebo, then subjects randomized to that group will never experience active drug. (b) In a crossover design, subjects are randomized to drug A or drug B but are allowed later changing of groups, for example, if they fail to respond to the first drug. If one group is placebo, then subjects randomized to that group will still have the chance to experience active drug after the crossover. Crossover data also provide information on the likelihood to respond to one drug after another fails, that is, data on refractory illness.

One drug, then another, and another), but this is no accident. The structure of the regulatory process almost ensures such an outcome (19):

Most studies conducted seem as much if not more oriented to the registration of a compound than they are aimed at answering a question of scientific importance. . . . Because companies are not in the business of proving that there are differences among their compounds, the result is a marketplace stuffed full of agents that are biologically quite heterogeneous, but whose clinical differences are minimized, or indeed left blatantly unexplored, for the sake of grabbing a share of the big indication—which in psychiatry since 1980 has been depression.

This brings us to the connection to polypharmacy. Psychiatrists do not know if one medication for an indication, say depression, is better than another. If one does not work, they have little rigorous evidence that instructs them what to do next. They either switch to another agent by trial and error or they add another agent by trial and error. Since the minority of persons respond sufficiently in the real world, both in terms of symptom and function, to one agent for many
conditions, polypharmacy ensues. Part of the reason for this polypharmacy stems from the lack of adequate data to inform clinicians about which specific drugs would be effective in which specific persons in which specific circumstances. Also, polypharmacy, when required, is often haphazard rather than data-based simply because there are no data, and part of the reason for the lack of data is that research and funding is skewed toward registration studies, with their expensive simple design: double-blind, placebo-controlled, parallel group short-term treatment for a specific indication.

One final aspect of the FDA role is relevant to the limited database available for rational polypharmacy. Not only are the designs of the kind of research studies more or less dictated by the FDA and thus influence the type of evidence that is available in the research literature, but the specific aspects of illnesses studied is influenced by FDA rules. Thus, the FDA indicates agents for treatment of acute major depression, acute mania, and acute schizophrenia, to mention the big three. The FDA has also indicated agents for the prevention of relapse in these conditions. To get a drug on the market, one needs to prove efficacy in one of these acute conditions. In practice, once a drug is used for an acute condition, clinicians tend to continue to use the drug for prevention of relapse. Drugs are thus introduced for long-term treatment by the ‘‘back door.’’

Further, prevention studies are by definition long term, more expensive, and more risky if placebos are used. As a result, there are many more studies of these acute conditions than long-term preventive studies. Also, there are very few studies of refractory depression, mania, or schizophrenia, again because companies have little motivation to conduct those difficult and expensive studies: once their drugs are on the market, they will be used for refractory patients. Finally, in the case of bipolar disorder, there are extremely few studies of bipolar depression or rapid-cycling bipolar disorder, mainly because the FDA has never accepted those conditions as separate diseases worthy of separate indications. Since clinical trials need to be conducted in ‘‘clean’’ populations, these difficult subgroups are often excluded.

One last issue is of practical importance. Frequently, clinicians will limit themselves to medications that are FDA-indicated for specific conditions. They do this rightly in part, because FDA indication has come to be a proxy for a certain minimum level of scientific rigor (at least two randomized clinical trials of a specific nature). They do this incorrectly because FDA ‘‘approval’’ or ‘‘indication’’ is often wrongly interpreted by physicians as ‘‘permission’’ to use a drug. This is quite important: the FDA does not approve a drug to tell a physician that it is acceptable to prescribe it for a specific condition; the FDA approves a drug to tell a pharmaceutical company that it is acceptable to market the drug for a specific condition (19). The FDA is regulating drug companies, not physicians. In fact, FDA legislation specifically states that physicians are allowed to

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*I borrow this term from Ross Baldessarini (personal communication).*
use any drug for any purpose once it has been marketed for any indication. Yet
lawyers often convince juries that FDA indication is basically equivalent to
science and that any non–FDA-indicated medical care is unscientific and thus uneth-
cial. As a result, physicians, fearing lawsuits, gear their prescribing patterns to-
ward FDA indications. This process has the unfortunate effect of motivating
pharmaceutical companies even more strongly toward doing registration studies
to get FDA indications, since those indications will drive up usage of a drug.
And of course, research beyond or outside of FDA indications is even more
neglected. Treatment of refractory conditions, the bread-and-butter of polyphar-
armacy, to repeat, is ignored more and more frequently.

In sum, I have discussed issues around the FDA’s influence at length be-
cause I think they are important in terms of understanding why there are limited
controlled data on polypharmacy in specific conditions, on the one hand, and
why clinicians have to resort to polypharmacy so frequently and in a trial-and-
error fashion. I emphasize the FDA because while the profit-based motivations
for pharmaceutical companies are obvious, the implications of federal regulations
are less obvious. In my experience, pharmaceutical companies are well aware of
the limitations of the current state of affairs, and sometimes, despite limited pay-
off, they engage in studies that go beyond the FDA’s standards. But the compa-
nies appear to relate to the FDA quite meekly, and thus a few well-placed govern-
ment officials can have as much, or more, influence on a huge medical field as
the most renowned Ivy League full professors or corporate CEOs.

Now that I have sketched aspects particular to psychiatry, let us return to
the original nineteenth-century critics of polypharmacy, Oliver Wendell Holmes
and William Osler. I engage in this exercise partly to pay homage to the wise
thoughts of our predecessors, and partly to raise issues still relevant today which
I hope readers will bear in mind as they read the clinical chapters of this book.
I also partly want to focus on the drawbacks of polypharmacy, lest I and my
coauthors be accused of simply extolling its virtues in the clinical chapters that
follow.

Polypharmacy has some deservedly pejorative connotations. These derive
partly from the appropriate influence of medical leaders like Holmes and Osler,
who led the field of medicine away from random therapeutics toward a more
scientific approach to understanding, preventing, and treating disease. Let us pick
up Holmes’s 1860 lecture.

Holmes entered that lecture hall filled with his medical society colleagues,
said, seeking to convince them to prescribe less and to observe more. He mainly
sought to inculcate what we today might call a more empirical, or evidence-
based, approach to medicine. He began by criticizing those who felt comfortable
practicing medicine on a day-to-day basis, making little effort to stay conversant
with changes in the field or to critically assess their own practices (2):
There are of course in every calling those who go about the work of the day before them, doing it according to the rules of their craft, and asking no questions of the past or of the future, or of the aim and end to which their special labor is contributing. These often consider and call themselves practical men. They pull the oars of society, and have no leisure to watch the currents running this or that way. . . . In the meantime, however, these currents are carrying the practical men too, and all their work may be thrown away . . . . if they do not take knowledge of them and get out of the wrong ones and into the right ones as soon as they may.

“Practical” clinicians are prone to influences far removed from science:

The truth is that medicine, professedly founded on observation, is as sensitive to outside influences, political, religious, philosophical, imaginative, as is the barometer to the changes of atmospheric density.

Holmes’s view is consistent with my discussion of the rise of psychopharmacology and the influence of the federal government and the pharmaceutical industry. (This does not mean that one must draw an extreme postmodern conclusion that medicine, and science in general, is purely social/political, but that social-political factors, in addition to more purely scientific factors, influence medicine.)

Holmes then contrasts two philosophies of medicine: one emphasizes “Nature” (“trust in the reactions of the living system”) and its ability to heal most illnesses slowly but surely; the other emphasizes “Art” (“an intentional resort to extraordinary abnormal impressions for the relief of disease”) and the need to intervene with drugs or surgery. Holmes argues that Hippocrates was an advocate of the natural approach, conceiving of the physician as an aid, a midwife, to the body’s natural attempts to recover from disease. He symbolized the interventionistic school in the figures of Themison (“who called the practice of Hippocrates ‘a meditation upon death’”) and, in American medicine, perhaps not too surprisingly, Holmes selects the father of American psychiatry, Dr. Benjamin Rush, as a proponent of the interventionistic school.* This association reminds me of the old medical school saying, popular among psychiatrists, that neurologists don’t treat disease, they admire it.† Of course, this saying itself reflects the

* Holmes quotes Rush: “It is impossible to calculate the mischief which Hippocrates has done, by first marking Nature with his name and afterwards letting her loose upon sick people. Millions have perished by her hands. . . .”

† Oddly enough, a variant of the same joke is popular among surgeons, except that internists are its butt. Psychiatrists and surgeons have opposite methods but frequently similar temperaments. Neurologists might with some satisfaction note that their discipline, slow to approach any treatments, is more scientific and more accomplished in both its understanding of disease and its effective treatments than psychiatry. In fact, many new treatments in psychiatry today are derived from medications for neurological disorders, e.g., antiepileptic agents are the main source of new treatments for bipolar disorder.
prejudice psychiatrists have for treatment, whether it be medications or psycho-
therapies. Surprisingly, for a field devoted to almost entirely psychological symp-
toms, most psychiatrists (at least in the United States) are little inclined to spend
much time or energy on pure description (phenomenology). I will discuss the
cultural aspects of polypharmacy later in this book, but the cultural component
is an important one.

Holmes goes on to identify those factors that predispose the “practical”
men of American medicine toward polypharmacy. Two factors are major. “First,
there is the natural incapacity for sound observation, which is like a faulty ear
in music.” Some physicians just do not observe well; they do not understand
what they see, sometimes not even seeing at all. Thankfully, I think this is the
smaller of the two factors “Secondly, there is in some persons a singular inability
to weigh the value of testimony.” More commonly, physicians observe, but they
make “inveterate logical errors” in interpreting the significance of what they
observe. In fact, Holmes here, in my opinion, completely presages today’s trend
toward “evidence-based medicine,” the view that medical decisions should be
based as much as possible on empirical studies, with more rigorous data (random-
ized clinical trials and the like) being more important than data based on limited
forms of evidence. Table 2 provides an adaptation of the five levels of evidence
proposed by the Canadian Medical Association (21–23). This is nothing more
and nothing less than learning how to “weigh the value of testimony.”

Holmes goes on to list those logical errors of physicians (2):

The mode of inference (that counts) only their favorable cases. . . . The nu-
merical system is the best corrective of this and similar errors. The arguments
commonly brought against its application to all matters of medical observa-
tion, treatment included, seem to apply rather to the tabulation of facts ill
observed, or improperly classified, than to the method itself.

The post hoc ergo propter hoc error: he got well after taking my medi-
cine; therefore in consequence of taking it.

The false induction from genuine facts of observation leading to the

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<thead>
<tr>
<th>Table 2</th>
<th>Evidence-Based Medicine: Levels of Evidence</th>
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<tr>
<td>Level 1: Double-blind, randomized trials</td>
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<tr>
<td>Level 2: Open, randomized, prospective, outcome studies</td>
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<tr>
<td>Level 3: Large naturalistic studies ($n \geq 100$); case-control studies</td>
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<td>Level 4: Small naturalistic ($n = 10–100$) studies</td>
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<tr>
<td>Level 5: Case study; case series ($n &lt; 10$) expert opinion</td>
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*Source:* Adapted from Refs. 21–23.
construction of theories which are then deductive applied in the face of the results of direct observation.

And lastly, the error which Sir Thomas Browne calls giving “a reason of the golden tooth”; that is, assuming a falsehood as a fact, and giving reasons for it, commonly fanciful ones . . . (such as) the fabulous effects of the homeopathic materia medica—which consists of sugar of milk and a nomenclature.

I believe that the third logical error (false induction from facts to a theory then imposed on reality) is the most common problem in medicine, due to the natural human desire to theorize. In psychiatry, I think psychoanalysis, broadly conceived, had that kind of effect. As mentioned earlier, in psychopharmacology, an overemphasis on diagnostic specificity and categorization may have produced a similar effect today such that polypharmacy is excessively encouraged. As Holmes put it, this kind of tradition results in “bad practice founded on false doctrine.” And change is slow and difficult: “It is so hard to get anything out of the dead hand of medical tradition!”

Holmes put the blame for these factors that encourage polypharmacy at the feet of physicians. But he also had strong words for patients: “Another portion of the blame rests with the public itself, which insists on being poisoned. . . . The popular belief is all but universal that sick persons should feed on noxious substances.” He identifies, as a cause, certain “old superstitions” such as the one that “disease is a malignant agency, or entity, to be driven out of the body by offensive substances. . . .”

Ultimately, Holmes, like Osler, recommends that medicine shift its focus from drug treatments to understanding diseases. “The causes of disease . . . have been less earnestly studied in the eagerness of the search for remedies. . . . The one prevalent failing of the medical art is to neglect the causes and quarrel with the effect.” Osler would make his great mark by convincing the field to make this shift, thereby inaugurating scientific medicine.

But before we turn to Osler, Holmes must be allowed to make his grand ending, the famous statement that caused much controversy, as he intended, and with which I began this book (2):

Presumptions are of vast importance in medicine, as in law. A man is presumed innocent until he is proved guilty. A medicine . . . should always be presumed to be hurtful. It always is directly hurtful; it may sometimes be indirectly beneficial. If this presumption were established . . . we should not so frequently hear . . . that, on the whole, more harm than good is done with medication. Throw out opium, which the Creator himself seems to prescribe, for we often see the scarlet poppy growing in the cornfields, as if it were foreseen that wherever there is hunger to be fed there must also be pain to be soothed; throw out a few specifics which our art did not discover, and is
hardly needed to apply; throw out wine, which is a food, and the vapors
which produce the miracle of anesthesia, and I firmly believe that if the whole
materia medica, as now used, could be sunk to the bottom of the sea, it would
be all the better for mankind,—and all the worse for the fishes.

This statement is the hallmark of Holmes’s philosophy, quoted repeatedly over
a century afterward by FDA representatives as part of their mission (24,25). To
break physicians of the habit of polypharmacy, Holmes wanted them to make a
presumption, similar to the law, that medications are inherently harmful, and thus
one must have sufficient evidence of proof of efficacy to use them. He suggested
this rule to reverse the opposite view, current in his age and especially fostered
by the Homeopathy movement, that medications were generally harmless and
little evidence of efficacy was need to justify their use. Scientific medicine, after
Osler, as I have said went Holmes’s way, and in fact one might say that the entire
philosophy of the federal government’s regulation of prescription medications is
derived from Oliver Wendell Holmes.

William Osler is often credited with being the father of modern medicine.
He was eminently likable, had remarkable oratorical skill with a taste for the
classics, and published a general textbook of medicine that went into many edi-
tions. Yet his reputation did not rest solely on these factors, nor for any specific
experimental discoveries. Osler’s main mark, in my opinion, was in moving med-
cinal education and practice from the old apprenticeship model, which focused on
experience and treatment, to a newer scientific model, focused on experiment
and understanding disease. Osler, like Holmes before him, felt that his medical
colleagues overemphasized drug treatments, which were largely useless, and
needed to focus instead on the scientific understanding of diseases. He probably
laid out the most accessible version of his philosophy on this subject in a lecture
to his colleagues at McGill University in Montreal in 1895, titled “Teaching and
thinking: The two functions of a medical school” (26).

In that lecture, he first lays out the imperative of studying disease for the
first 2 years of the medical curriculum, before any clinical work or contact with
treatment (26):

A man cannot become a competent surgeon without a full knowledge of
human anatomy and physiology, and the physician without physiology and
chemistry flounders along in an aimless fashion, never able to gain any accu-
rate conception of disease, practising a sort of popgun pharmacy, hitting now
the malady and again the patient, he himself not knowing which.

It is worth emphasizing that these words were still revolutionary in 1895,
as they had been when Holmes intoned similar thoughts a generation earlier.
Today this kind of medical curriculum is taken for granted, but in 1895, most
medical schools did not function along the lines Osler advocated.
The primary function of this department of the university is to instruct men about disease, what it is, what are its manifestations, how it may be prevented, and how it may be cured. . . . The three great advances of the century have been a knowledge of the mode of controlling epidemic diseases, the introduction of anaesthetics, and the adoption of antiseptic methods in surgery (26).

It is instructive to observe the sequence, in time and importance, which Osler lays out. First learn about the nature of a disease and its signs and symptoms, then focus on prevention before finally attempting cure. This emphasis on prevention before treatment also was a hallmark of Holmes’ approach, as was the focus on antisepsis and infectious diseases.

It cannot be denied that we have learned more rapidly how to prevent than how to cure diseases, but with a definite outline of our ignorance we no longer live now in a fool’s paradise, and fondly imagine that in all cases we control the issues of life and death with our pills and potions. It took the profession many generations to learn that fevers ran their course, influenced very little, if at all, by drugs. . . . Of the difficulties inherent in the art not one is so serious as this which relates to the cure of disease by drugs. There is so much uncertainty and discord even among the best authorities (upon non-essentials, it is true) that I always feel the force of a well-known stanza in *Rabbi Ben Ezra*:

Now, who shall arbitrate?
Ten men love what I hate,
Shun what I follow, slight what I receive;
Ten, who in ears and eyes
Match me: we all surmise,
They this thing, and I that: whom shall my soul believe? (26)

Osler, like Holmes, felt that it was a sign of the advance of scientific medicine that fewer medications were being used. Polypharmacy was a characteristic of the prescientific era (26):

With the diminished reliance upon drugs, there has been a return with profit to the older measures of diet, exercise, baths, and frictions, the remedies with which the Bithynian Asclepiades doctored the Romans so successfully in the first century. Though used less frequently, medicines are now given with infinitely greater skill; we know better their indications and contradictions, and we may safely say (reversing the proportion of fifty years ago) that for one damaged by dosing, one hundred are saved. . . . But know also, man has an inborn craving for medicine. Heroic dosing for several generations has given his tissues a thirst for drugs. As I once before remarked, the desire to take medicine is one feature which distinguishes man, the animal, from his fellow creatures. It is really one of the most serious difficulties with which we have to contend. Even in minor ailments, which would yield to dieting
or to simple home remedies, the doctor’s visit is not thought to be complete without the prescription. And now that the pharmacists have cloaked even the most nauseous remedies, the temptation is to use medicine on every occasion, and I fear we may return to a state of polypharmacy, the emancipation from which has been the sole gift of Hahnemann and his followers to the race. As the public becomes more enlightened, and as we get more sense, dosing will be recognized as a very minor function in the practice of medicine in comparison with the old measures of Asclepiades.

The only point on which Holmes and Osler differed was homeopathy, led by Hahnemann, which was a precursor to today’s alternative and herbal treatment movement (see Chapter 11). Holmes excoriated the homeopathy movement for being unscientific, based essentially on level V (see Table 2) anecdotal experience. Holmes argued for the need for quantitative studies with a comparison group, even discussing the use of a placebo. In fact, his attack on homeopathy was, for Holmes, the flip side of his opposition to polypharmacy.* As mentioned earlier, modern FDA regulators like Paul Leber specifically cite Holmes as an intellectual source for current government guidelines on pharmacological research (25). Osler may have cited the homeopathic movement to laud its effect on urging practitioners to use low doses of medications, but Holmes worried that polypharmacy with low doses of medications was as bad, or worse, as higher dosing with fewer medications.

The issue of alternative treatments, alive then as now, deserves some comment, especially as this book devotes one chapter to studies on polypharmacy with alternative and herbal treatments. Holmes, in an 1861 address, proposed that any natural substance, even if used to treat disease, should be viewed as a “food,” not medication, and he felt more sanguine about the risks of such substances (27).

I do not know that we ever apply to a plant any element which is not a natural constituent of the vegetable structure, except perhaps externally, for the accidental purpose of killing parasites. The whole art of cultivation consists in

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* Holmes thought that homeopathy promoted the view that medications cured diseases, and this led to the polypharmacy approach of aggressively using many medications. While he believed that some medications cured some diseases, Holmes generally believed that most diseases improved naturally or with prevention. He expanded on these views in an 1891 preface and appendix: “While keeping up the miserable delusion that diseases were all to be cured by drugging, Homeopathy has been unintentionally showing that they would very generally get well without any drugging at all. . . . A noxious agent should never be employed in sickness unless there is ample evidence in the particular case to overcome the general presumption against all such agents—and the evidence is very apt to be defective. The miserable delusion of Homeopathy builds itself upon an axiom directly the opposite of this; namely, that the sick are to be cured by poisons. . . . It is simply a theory of universal poisoning, nullified in practice by infinitesimal contrivance. . . . To uphold the exhibition of noxious agents in disease, as the rule, instead of admitting them cautiously and reluctantly as the exception, is, as I think, an eddy of opinion in the direction of the barbarism out of which we believe our art is escaping” (italics original) (6).
learning the proper food and conditions of plants, and supplying them. . . .
If the law of the animal cell . . . is like that of the vegetable, we might expect that we should treat all morbid conditions of any of the vital unities belonging to an animal in the same way, by increasing, diminishing, or changing its natural food or stimuli. . . . I see no reason, therefore, why iron, phosphate of lime, sulphur, should not be considered food for man, as much as guano or poudrette for vegetables. . . . They are elements belonging to the body, and even in moderate excess will produce little disturbance. . . . But when it comes to substances alien to the healthy system, which never belong to it as normal constituents, the case is very different. There is a presumption against putting lead or arsenic into the human body, as against putting them into plants, because they do not belong there. . . .

By now, this line of reasoning should be familiar. To emphasize that he does not oppose drugs in principle, Holmes adds, “I trust the youngest student on these benches will not commit the childish error of confounding a presumption against a particular class of agents with a condemnation of them.” In general, Holmes would likely have agreed with the recent congressional law that loosened regulations on alternative and herbal medications, as long as they were not marketed for and claimed to be treatments for specific diseases, and rather were seen as enhancing aspects of normal functioning of the human body. Thus, St. John’s wort can be sold over the counter without any federal regulation of its safety or efficacy as long as it is marketed as “enhancing mood” but not if it claims to treat depression. The potential complications of this line of reasoning are notable when one finds that numerous studies of St. John’s wort in depression suggest that this agent is an antidepressant, and when one considers the evidence that some antidepressants, like fluoxetine (Prozac), may “brighten” mood in nondepressed persons (see Chapters 3 and 11) (28,29). But Holmes’s general point is likely to be valid: as a rule, natural substances, like vitamins and minerals, have fewer side effects than typical synthesized medications. The exceptions to these rules are frequent enough, however, to complicate any simple perspective on this subject.

To summarize, Oliver Wendell Holmes and William Osler exemplify the movement among leaders of medicine in the nineteenth century away from polypharmacy and towards more of an emphasis on understanding and preventing diseases. Meanwhile, the evolution of psychiatry in the twentieth century has been characterized by little understanding of the disease processes underlying major mental illnesses and a plethora of treatments, mostly ineffective or only marginally so. Part of the reason for continued polypharmacy in psychiatry has had to do with the resistance of psychiatric diseases to yielding their secrets to biological research as well as nosological and social/economic factors. There are two major players in psychiatric research, as in all medical research, besides scientists: the government and private pharmaceutical corporations. In psychiatry, due to the limited progress in understanding disease entities, government and pharmaceutical corporations have heavily influenced nosological schemes. As
new medications for target conditions became available, the psychiatric community would turn its attention to those conditions and diagnose them more frequently. Since the federal government has only allowed marketing of a drug for specific diagnoses, and since most treatment research has been funded from pharmaceutical company sources, clinicians have had to rely on scientific data that is largely limited to FDA-based paradigms for specific diagnoses. These paradigms often have not touched on relevant clinical scenarios, and the specific diagnoses frequently have not included the varied and complicated presentations of real-world practice. As a result, extrapolating from drug-disease bodies of evidence, clinicians often combine medications for the complex realities of clinical practice, settings in which little treatment research is conducted. A recent Austrian study found that only 5–22% of patients treated in university-affiliated psychiatric hospital and clinics received just one medication for a range of psychiatric illnesses, while a similar number received five or more medications (30).

One can neither criticize unduly nor laud this state of affairs. It is hard to imagine how things might be different, barring extreme perspectives (31).* It is important, nonetheless, to honestly view this landscape not only clinically, but politically. Polypharmacy is a reality in psychiatry, and often it reflects the unscientific nature of many aspects of the field, just as in medicine in general in the nineteenth century. And in those cases, where possible, psychiatrists would likely benefit from heeding the advice of Holmes and Osler to focus on prevention or nonspecific measures of support (the transference, supportive therapy) and recognize that less is more. In one study at a Veterans Administration hospital, providing regular psychopharmacology education led to a reduction in types of polypharmacy that went beyond the empirical evidence (33). In other cases, polypharmacy in psychiatry reflects the state of research and knowledge in the field, partly driven by the structure of FDA-mandated rules and pharmaceutical companies’ needs. When used in a manner that combines common sense with scientific evidence, polypharmacy can then be useful and effective in treating individual persons with complicated psychiatric syndromes.

In this book, I hope the reader will find specific information on when to employ combination treatments in specific psychiatric syndromes, how to do so safely, and when not to engage in such polypharmacy.

It remains for a working definition for polypharmacy to be given. First, the phrase itself needs to be justified. Some colleagues object to it, arguing that it is pejorative (34). To the extent that it is viewed pejoratively, one is probably

* One need not deny the existence of psychiatric illness altogether, as does Thomas Szasz, while admitting that psychiatric nosologies are influenced by political, economic, and social factors. It is important to remember that long before any pharmaceutical company ever dreamed of a treatment for schizophrenia, the condition had been well characterized and frequently observed by French psychiatrists like Morel and, of course, later by Kraepelin (32).
observing the long-term effects of Osler and Holmes on medical tradition. Pharmacists sometimes argue that it is not their fault that doctors prescribe too many medications, and they suggest using the term “polytherapy.”* Mark Frye, Robert Post, and colleagues have suggested the more accurate but tongue-twisting term “polypharmacotherapy” (35). Still others suggest “cotherapy” or “copharmacy” (36) or “combination therapy” or “combination treatment,” all attempts at trying to differentiate a “skillful” or “rational” approach to combining medications from the presumably more haphazard approach implied by the term polypharmacy. Frye and associates even quote Osler to this effect: “The true polypharmacy is the skillful combination of remedies” (35).

Yet I think it is a bit presumptuous to presume that there is a purely “rational” form of polypharmacy that can be contrasted with an “irrational” form, or that skillful combination contrasts with simply unskillful treatment. Despite the current popularity of bureaucratese, changing the name of something does not change its reality. The reality is that polypharmacy is sometimes skillful and sometimes unskillful, sometimes thought through and sometimes haphazard, and logical and illogical at the same time in different degrees. Thus, I continue to use the term “polypharmacy” in this book and will leave it for clinical reality to change before clinicians produce a consensus on a new term.

How will we define polypharmacy? In Chapter 4, Godehard Oepen addresses some of these questions, which are worth repeating here, making some of the distinctions I just mentioned:

First, we have to distinguish between irrational polypharmacy [sometimes seen as the result of intellectual laziness or economic considerations, and often decried as the cause of increased mortality and complications (37)], and rational polypharmacy (based on a theory of both the nature of the condition to be treated and the nature of the proposed treatment, as stated above). . . . Irrational polypharmacy can be seen in part as the result of intellectual laziness, professional incompetence, or just personal prescribing habits. These are doctor-related variables, and rather undesirable. However, there is also a second, patient-related factor to consider: sometimes patients request to receive two neuroleptics or to stay on two or more previously prescribed neuroleptics because of perceived subjective benefits. This cannot be summarily dismissed as just drug-seeking or fear of change: I myself have encountered individual patients in Germany as well as in the United States who got worse when I tried to simplify treatment and discontinue additional neuroleptic drugs and seemed then to improve again behaviorally, perceptually, and in general when put back on selectively combined antipsychotic regimens. Similarly, a study looking at the effect of reducing polypharmacy to monotherapy with neuroleptics found that less than half of the psychotic patients tolerated this change; the remainder had to continue on combined

* This phrase was suggested by Dr. Ross Baldessarini (personal communication).
antipsychotic therapy, as neither dose increase nor change to a different drug was therapeutic (38). These observations are not just "clinical folklore," but true case-based data and deserve clinical and research attention, as they can lead to a better understanding of relevant pathogenetic factors. A third variant of irrational polypharmacy is related to cultural factors. First, we need to notice that we have different subcultures in our own culture: academic psychiatry is quite different from psychiatry in private practice, and again from psychiatric practice in state hospitals. Muijen and Silverstone reported that British hospitals with an associated academic psychopharmacology unit had the lowest prevalence of polypharmacy, while hospitals without such affiliation showed a much higher percentage of polypharmacology, ranging from 45% to 94% (with two or more antipsychotics as the most frequent type) (39). Similar trends have been reported in the United States, with a higher rate of polypharmacy in state hospitals (40). Community outpatient services also appear to have a higher rate of polypharmacy than academic centers, decreasing temporarily from 1970 to 1983 with the availability of depot injections, but since then increasing again (41).

I think Dr. Oepen is touching on some of the major relevant issues here. Polypharmacy is not simply dependent on the decisions of the physician. It can be just as dependent on the nature of the illness the physician is treating. Some conditions that are naturally more refractory to available treatments will require polypharmacy more frequently than other, more responsive conditions. All this assumes that to prevent a reversion to the "heroic" measures of the nineteenth century that Holmes described, polypharmacy for severe illnesses should be data-based, rather than purely speculative. Thus, in this book, I have asked each chapter author, in dealing with a different condition or population, to go about defining what polypharmacy means for that population and to what extent it is and is not justifiable. For instance, bipolar disorder is a difficult-to-treat condition in which complete remission with one mood stabilizer is quite uncommon; thus, clinical trials now frequently focus on combining two treatments for manic symptoms (see Chapter 2). In contrast, remission with a single antidepressant (though not as common as we might think) is more common in unipolar depression, and clinical trials do not tend to provide data on combining two antidepressants for unipolar depression (see Chapter 3). In one case, polypharmacy is more common because of the nature of the illness and available treatments. Thus, one cannot make a general statement that applies definitively across syndromes.

Defining polypharmacy in psychiatry entails understanding the circumstances in which it occurs. In 1975, Hollister (42) suggested a number of scenarios:

The rationale for combining psychotherapeutic drugs is based on several seemingly logical hypotheses, each with rather little proof:
a) When drugs of the same type are given in fractional doses, therapeutic effects are summed but side effects are reduced due to lesser concentrations of single drugs or cancellation of opposing effects. An analogy is made in this instance to the combination of three sulfonamides, in which antibacterial effects were summed, but the decreased urinary solubility of separate drugs at high concentrations was circumvented by lower concentrations of three single drugs;
b) Drugs with different mechanisms of action for controlling the same disorder may have complementary therapeutic effects. Such combinations are widely and wisely exploited in therapeutics: digitalis and diuretics in heart failure; diphenylhydantoin and phenobarbital for controlling seizures; isoniazid and paraaminosalicyclic acid for treating tuberculosis; and so on;
c) Drugs have specific effects on various target symptoms, requiring more than one drug to treat all the symptoms a patient may manifest. As psychotherapeutic drugs are always used symptomatically in our present state of ignorance, this argument is more persuasive than in branches of medicine where the pathophysiological bases for disorders are better known. These hypotheses are often employed to serve frankly commercial goals. They have persuaded many clinicians to use the melange of psychoactive drugs so commonplace today, even though the old axiom that the more effectively a disease or disorder can be managed, the fewer treatments needed, still applies to most of psychiatry.

The first hypothesis is a modern version of the homeopathic principle, which Holmes long ago identified as a risk factor for polypharmacy. All medications have side effects, and therefore sufficient proof of efficacy must exist to outweigh those side effects. I will call this Holmes’s rule: to demand empirical proof that a treatment is effective so as to outweigh the presumption against the use of a medication due to its inherent side effects.* The third hypothesis is less reflective of psychiatry today than it was in 1975, but still is relevant. Especially in less understood conditions, like personality disorder and posttraumatic stress disorder, and in less studied populations (like children and the elderly), psychiatrists still are tempted by the target symptom approach to treatment, as opposed to the syndrome-oriented approach. Since Osler repeatedly warned against this risk factor for polypharmacy, I will call this Osler’s rule: to emphasize the need to treat syndromes (based on underlying disease) not symptoms. Even in that section of adult psychiatry that is syndrome-oriented, there is so much overlap between syndromes, and thus comorbidity, that polypharmacy can be justified on the grounds of treating two or more syndromes (e.g., major depression plus generalized anxiety). The second hypothesis, as Hollister pointed out, remains

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* "A noxious agent should never be employed in sickness unless there is ample evidence in the particular case to overcome the general presumption against all such agents" (6).
the most defensible and is the form of polypharmacy with the most empirical support.

_Holmes’ rule for polypharmacy:_ There must be empirical proof that a treatment is effective so as to outweigh the presumption against the use of a medication.

_Osler’s rule of polypharmacy:_ Treat syndromes (based on underlying diseases), not symptoms.

Readers may still want a general definition of polypharmacy, if for no other reason than as a starting point to refine the definition for specific psychiatric syndromes. One of the few definitions provided in the psychiatric literature ascribes polypharmacy to “the patient who receives two or more psychoactive drugs for the management of behavioral symptoms” (43). To assess this and other definitions, I suggest thinking through some typical clinical scenarios.

The kind of polypharmacy that is often frowned upon involves using two agents of the same class and biochemical makeup for the same condition, e.g., using two typical neuroleptics for schizophrenia or two serotonin reuptake inhibitors (SRIs) for unipolar depression. Polypharmacy is more often accepted when one combines drugs of different classes or different biochemical mechanisms, e.g., a typical plus an atypical neuroleptic for schizophrenia, or an SRI plus bupropion for depression, or a mood stabilizer plus a neuroleptic for mania. Sometimes clinicians will call a drug regimen polypharmacy simply because there are many drugs of whatever variety, e.g., an antidepressant for depression, a benzodiazepine for insomnia, an antihypertensive pill, and a medication for diabetes (all of these being common conditions and thus frequently overlapping in the same individual). Sometimes polypharmacy occurs briefly, as when an antidepressant is started for depression and a benzodiazepine is used to give immediate relief for sleep and anxiety symptoms, with the goal of tapering off the benzodiazepine after the delayed antidepressant benefit occurs. Drug interactions vary from drug to drug, but clinicians tend to worry more when the number of drugs is four or five as compared to two agents.

Some have opposed as too broad the liberal definition of polypharmacy as the use of two or more medications, and instead advocated the simple conservative definition of polypharmacy as the use of three or more medications (44). This would allow the exclusion of the scenario where one might simply use a benzodiazepine as a sleep aid on an infrequent basis in addition to another medication on a regular basis for a long-standing condition. On that basis only 7% of 1579 oncology patients were reported to experience polypharmacy (44). Others have been quite critical of this definition, seeing it as too strict and seriously underestimating the true prevalence of polypharmacy (34). In a survey of 41 psychiatric inpatients, polypharmacy rates were only 4.9% if defined as three or more drugs and excluding drugs not used for a primary psychiatric diagnosis (e.g., benztropine for neuroleptic-related side effects), 9.8% if defined simply as
Historical Background

three or more psychotropic drugs given for whatever purpose, and 56.1% if defined as two or more psychotropic drugs given for whatever purpose (34). Thus, there was a leap from around 10% to over 50% when moving from two or more drugs as the definition of polypharmacy to three or more drugs.

I think it is fair to state that the main drawback to polypharmacy is side effect burden. If one were to take five placebos or one placebo, there would seem to be no difference of clinical or ethical importance. But one should remember Holmes’s rule: All medications have some risks; thus, proof of efficacy is essential. A corollary to this rule is that multiple medications will entail more side effects, and thus even more proof of efficacy is required for polypharmacy. At the same time, safety becomes a larger concern with polypharmacy: How much more are the side effects of the multiple agents? What are the drug-drug interactions? The issue of drug interactions in particular is unique to polypharmacy; it does not exist, by definition, in monotherapy. Thus, in each of the clinical chapters that follow, specific attention will be given to drug interactions and the side effect burden of polypharmacy.

Hence the salient features one wants to capture with a definition of polypharmacy include the following ideas: that excessive combinations of treatments can lead to increased side effects and drug interactions, that combining medications without empirical evidence to support it is to be discouraged, that adding more medications for each symptom noted is generally unhelpful, but also that sometimes individuals will have more than one disease each of which needs treatment with one medication, and also that sometimes persons with refractory diseases will need treatment with two or more medications (based on empirical research) for that condition. Further, sometimes persons may be treated with one medication regularly for a disease, and another very infrequently for symptomatic purposes. I attempt to capture the concept of polypharmacy as potentially hurtful but sometimes helpful, while not applying the term to simple situations where two diseases are being treated appropriately with two medications (e.g., a person receiving an antihypertensive and an antidepressant appropriately for two common and basically unrelated conditions).

Given these observations, I would suggest the following general definition of polypharmacy in psychiatry: Polypharmacy in psychiatry is a state of multiple drug treatment that occurs when two psychotropic agents are used to treat the same psychiatric condition (e.g., bipolar disorder) or two commonly associated conditions (e.g., bipolar disorder and generalized anxiety disorder). The term also applies to any combination of three or more medications for whatever purpose. I think this definition is broad enough to encompass variations based on specific psychiatric diagnoses, and complete enough to capture the basic clinical scenarios in which the term is used. It goes beyond the controversy between defining polypharmacy as two versus three drugs by accepting the more conservative definition of three drugs or more in general, but also using the term
polypharmacy for two drugs when they are used to treat the same condition or associated conditions. It remains to be fleshed out and tested in the clinical chapters.

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INTRODUCTION

Bipolar disorder is generally considered less responsive to medication treatments than unipolar depression. Thus, it would not be surprising to observe an increased prevalence of polypharmacy. However, there are varied approaches to polypharmacy of bipolar disorder, some based on more evidence than others. One of the features that makes bipolar disorder particularly prone to polypharmacy of an ineffective and even dangerous variety is the fact that drugs from different psychotropic classes are frequently utilized. This kind of polypharmacy seems, at face value, less objectionable than combining medications from the same class, as with, for instance, two neuroleptics for schizophrenia. Thus, it is commonplace for patients with bipolar disorder (which is generally characterized by mania and depression) to be treated with both mood stabilizers and antidepressants and/or neuroleptics. This kind of polypharmacy, though sometimes necessary, is, in our opinion, a particularly insidious and problematic variant in bipolar disorder.

The problem is that monotherapy is not generally a real alternative; it is ineffective in most cases. Thus, in the treatment of bipolar disorder, polypharmacy is the rule, but one must be quite careful to avoid certain kinds of polypharmacy that may actually worsen the course of bipolar illness. The purpose of this chapter will be to explain the issues involved, review the data that pertain to them, and provide clinical guidelines for safe and effective polypharmacy in bipolar disorder.
THE UNACCEPTABLE STATUS QUO

Polypharmacy is the rule rather than the exception in the treatment of bipolar disorder. Unfortunately, it is too often a woefully unscientific and ineffective polypharmacy. It is a basic recommendation of almost every psychiatric textbook that the treatment of bipolar disorder begins with the utilization of a mood-stabilizing agent, such as lithium. Unfortunately, it appears that many patients never start with a single mood stabilizer; instead, they usually begin with a combination of an antidepressant or a neuroleptic along with the mood stabilizer. In a recent empirical study, we found that only about one third of patients with bipolar disorder had ever been treated with a single mood stabilizer alone (1). The majority received polypharmacy from the very beginning of their psychiatric care, usually with antidepressants.

Sometimes patients do not receive mood stabilizer treatment at all. In another study by our group, fully two thirds of patients we diagnosed with bipolar disorder upon admission to hospital were not taking mood stabilizers at all at the time of admission (1). Part of this lack of mood stabilizer use may have to do with noncompliance on the part of the patient, but part is also likely due to the failure of clinicians to insist on the need to prescribe mood stabilizers for individuals with bipolar disorder. This suggestion is supported by a recent study of 457 patients with type I bipolar disorder treated in the Stanley Center for the Innovative Treatment of Bipolar Disorder located at the University of Pittsburgh. Even in that academic setting, 18% of patients were not prescribed mood stabilizers at all (2). Furthermore, over two thirds of patients were prescribed antidepressants and more than one third received neuroleptic medications. These findings are consistent with a large outpatient psychiatric prescription database utilized by the pharmaceutical industry (3), which shows that until 1998 the most commonly prescribed medication for the treatment of patients diagnosed with bipolar disorder was fluoxetine. Divalproex caught up with fluoxetine in 1998, but the next two most commonly prescribed drugs were sertraline and paroxetine, in that order. Lithium came in a distant fifth, followed by atypical neuroleptic medications. Clearly, clinicians are practicing a polypharmacy in bipolar disorder that consists of heavy antidepressant use and light mood stabilizer use. The poor outcomes associated with this kind of treatment have often been attributed to mood stabilizers (like lithium) (4), rather than the poor quality of the polypharmacy used. We recommend a polypharmacy that is the reverse of this pattern: heavy mood stabilizer use, common atypical neuroleptic use, and light antidepressant use.

BASIC CONCEPTS

As with unipolar depression, there is no consensus on a definition of polypharmacy in bipolar disorder. However, given that monotherapy response to a mood
stabilizer for bipolar disorder seems much less common than monotherapy response to an antidepressant for unipolar depression, it would seem that a somewhat more liberal approach to polypharmacy would be appropriate for bipolar disorder. The prescription of two medications at the same time, for instance, is quite frequent and is, in fact, generally the rule in the treatment of acute mania. Thus, while we would propose that a working definition of polypharmacy for bipolar disorder would be similar to that used for depression, i.e., the use of two or more agents for the treatment of phases of bipolar disorder, we suggest a greater willingness to accept as necessary a higher frequency of polypharmacy in bipolar disorder than in unipolar depression.

Another factor that complicates the treatment of bipolar disorder, as compared with unipolar depression and schizophrenia, is that there are many phases of illness that need to be treated in bipolar disorder, as compared to only one phase in the other conditions. With schizophrenia or unipolar depression, one is either well or ill (psychotic, depressed). In bipolar disorder, there is only one way to be well (euthymic) but five ways to be ill (pure mania, pure depression, mixed mania, hypomania, and rapid-cycling alternations between episodes). Thus, it is very easy for clinicians to end up with polypharmacy regimens. For example, a patient might first be diagnosed with mania and treated perhaps with just lithium. Then, the patient may become depressed and an antidepressant will be added; this might be followed by a mixed episode, which would be treated with an added neuroleptic. The next phase can be depression, and soon the psychiatrist is trying to catch her tail, as the patient is cycling back and forth through this complex mood disorder. This is the kind of polypharmacy one must avoid in treating bipolar disorder.

In our opinion, the key concept in treating bipolar disorder is to focus on the long term. One should not focus on the acute episodes, consistently responding to them with antidepressants for depression and neuroleptics for mania. The only long-term treatment proven effective in bipolar disorder is the class of mood stabilizers. Furthermore, mood stabilizers also have appreciable acute efficacy for depression and mania. Thus, to avoid the tail-chasing dilemma, a clinician would be wise to aggressively utilize mood stabilizers in the treatment of bipolar disorder and be more cautious with antidepressants and neuroleptics. We will review the evidence for these views later in this chapter.

We mentioned in the previous chapter that unipolar and bipolar depression can be difficult to distinguish and that it is important to make this distinction. The reason for this is that antidepressants are safe and effective in the treatment of unipolar depression, but they have not been proven to be safe and effective in the long-term treatment of bipolar disorder. Antidepressants not only can cause mania but they can cause rapid cycling and a long-term worsening of the course of bipolar illness. This is a key clinical point, which we will review in detail below.

While the polypharmacy of bipolar disorder can result from an attempt to
treat treatment-resistant illnesses, such as refractory mania or bipolar depression, it should also be kept in mind that many patients with bipolar disorder never experience monotherapy, and it is sometimes appropriate to begin treatment from the very start with two or more agents. One might distinguish between the two forms of polypharmacy in bipolar disorder, calling them "stratified" and "sequential" treatment approaches (G. Sachs, personal communication). In the stratified approach, one would treat an acute episode of hospitalized mania with a mood stabilizer and a neuroleptic at the same time, from the very beginning of treatment. In that case, polypharmacy would be indicated at the very start of treatment. Similarly, although we do not recommend this approach, most clinicians tend to treat acute bipolar depression from the very beginning with a mood stabilizer and an antidepressant in almost all cases. While we would agree that this approach is sometimes necessary, as we describe later, it is better avoided when possible. There are some notable cultural differences on the issue of stratified treatment. In Europe it is customary to treat acute mania initially with neuroleptic monotherapy, later introducing a mood stabilizer for prophylaxis (5), whereas in the United States the two medications tend to be combined from the start. Thus, the stratified approach, perhaps more prevalent in the United States than Europe, often commits patients with bipolar disorder to polypharmacy from the very beginning of treatment. This contrasts with the sequential approach, which tends to be the one quoted from textbooks, where patients with bipolar disorder are supposed to begin treatment with one mood stabilizer alone, with other agents only added later. As noted, the stratified approach frequently results in the scenario where mood stabilizers never are given a fair trial by themselves.

CLINICAL DESCRIPTIONS

Bipolar disorder is a difficult condition to diagnose because although current manic symptoms, if noted, establish the diagnosis, the absence of current manic symptoms does not rule out the diagnosis. If current manic symptoms are absent, bipolar disorder, like schizophrenia, becomes a longitudinal diagnosis: a manic or hypomanic episode at any point in the past qualifies for the diagnosis (no matter how many depressive episodes one experiences). Conversely, to say that someone does not have bipolar disorder means asserting that an individual has never experienced a manic or hypomanic episode at any point in the past.

We will discuss this point in detail because bipolar disorder can be so easily misdiagnosed as many other conditions. In the past, the main confounding diagnosis was schizophrenia, where the classic 1970 United States–United Kingdom study revealed how American psychiatry had taken to diagnosing almost any mental symptom as schizophrenia (6). This problem has not been completely resolved, despite clear evidence of the need to diagnose bipolar disorder more
aggressively (7) and the narrow definition of schizophrenia introduced with DSM-III. In a recent Spanish study, 24% of 38 patients with bipolar I disorder had been misdiagnosed with schizophrenia (8). A larger problem in current American practice may be the misdiagnosis of bipolar disorder as unipolar depression. Two recent studies (1,9) indicate that about 40% of persons with bipolar disorder (total \( n = 104 \)) were misdiagnosed as having unipolar depression, and this misdiagnosis led to a lag in the diagnosis of bipolar disorder of 6–12 years. Another finding of these recent studies is that it took even longer to diagnose type II than type I bipolar disorder. This may relate to a lack of consensus among clinicians about how to define hypomania, as well as a persistent tendency to diagnose personality disorder. In the Spanish study, personality disorder was the most frequent diagnosis mistakenly made in individuals with bipolar II disorder (\( n = 22 \)) (8).

Given that, at least from the standpoint of current DSM-IV nosology, the entire bipolar diagnosis hinges on one’s ability to identify current or past manic or hypomanic episodes, we will review what constitutes the manic syndrome and some factors that may impede its recognition.

**APPLYING MANIC CRITERIA: THE DIGFAST MNEMONIC**

The DIGFAST mnemonic aid, initially devised by Dr. William Falk at Massachusetts General Hospital in 1988, may promote more careful assessment of manic criteria and is based on DSM-IV criteria.

The diagnosis of mania is made when euphoric mood is present for one week with three of the DIGFAST symptoms, or irritable mood is present for one week with four of the DIGFAST symptoms, and there is significant social or occupational dysfunction. If there is no significant dysfunction, and the symptoms last at least 4 days, the diagnosis of hypomania is made. If the symptoms last less than 4 days, or if they are only present with antidepressant medications, a diagnosis of bipolar disorder, NOS, may be made.

The DIGFAST symptoms are as follows:

- Distractibility—the inability to maintain one’s concentration, as opposed to the decreased concentration of depression, where one is unable to initiate concentration. In mania this leads to multiple tasks, none of which are finished—in depression, no task can be started easily.
- Insomnia—decreased need for sleep, as opposed to the decreased sleep of depressive insomnia. The patient sleeps less, but has intact or increased energy the next day.
- Grandiosity—can be inflated self-esteem as well, need not be delusional.
- Flight of ideas—observed flight of ideas or the subjective experience of racing thoughts.
Activities—increased goal-directed activities (social, sexual, school, work, home activities); these are goal-directed and thus not dysfunctional. Increased libido is either not expressed in activity or associated with increased activity with one’s usual sexual partner.

Speech—pressured; this is an objective sign observed on the mental status examination. A subjective alternative is increased talkativeness, which is determined by asking the patient or others whether the patient has been more talkative than when euthymic.

Thoughtlessness—refers to increased pleasurable activities with potential for painful consequences. Four behaviors that should be routinely assessed are sexual indiscretions, spending sprees, impulsive traveling, and reckless driving.

A few comments arise from this diagnostic method. First, strict reliance on euphoria would lead to gross underestimation of bipolar illness. Clinical studies report that mixed episodes are the most common type of manic episode, more common than pure manic episodes. Thus, lack of recognition of mixed episodes might lead to misdiagnosis of bipolar disorder with unipolar depression, since mixed patients have depressed mood and often meet criteria for major depression. Many clinicians may cut short the diagnostic process after confirming the presence of depressive symptoms and not assess current manic criteria, thus misdiagnosing mixed bipolar episodes for unipolar depression. Also, even pure manic episodes can be characterized by solely irritable mood, rather than euphoric mood. Since about one half of unipolar depressed patients also have irritable mood (10), the presence of irritability is a nonspecific symptom that should lead to a careful assessment of manic symptoms. Clinical studies also suggest that atypical features of a major depressive episode (e.g., hypersomnia, hyperphagia) as well as psychotic symptoms are more associated with bipolar disorder than typical or nonpsychotic depression, and thus should lead to careful manic criteria assessments (11). Family history should always be carefully considered, and the presence of manic-depressive illness should again lead to a detailed assessment of manic criteria in the patient.

Also, it should be noted that according to current diagnostic criteria, hypomania mainly differs from mania in the issue of social or occupational dysfunction, not in specific manic symptoms. Since it is precisely this assessment of interpersonal dysfunction that patients often underestimate, family report becomes particularly important. In truth, it is worth repeating that it is very difficult to rule out bipolar disorder without family or other third person report. This is one aspect of team-oriented treatment that calls for more attention to be paid by psychiatrists to the reports of nursing staff, social workers, and halfway house staff; the clinical interview counts for little, and contradictory data should be decided in favor of outside report from other clinicians or staff rather than the patient’s self-report in the clinical interview.
The diagnosis of bipolar disorder type II is particularly important, since clinical and genetic data suggest that milder parts of the bipolar spectrum (type II, NOS, or cyclothymia) may be more common than classic type I manic-depressive illness (12). While these conditions are milder in the sense of less severe symptoms of mania, they are not less severe in depressive symptoms, which lead to a great deal of morbidity and a serious mortality risk by suicide. Further, patients with these other less classic forms of bipolar disorder often have unstable lives, with failed careers, a high rate of divorce, and other stormy aspects to their often impulsive biographies (13). Thus, the entire bipolar spectrum needs to be just as aggressively diagnosed and treated as classic manic-depressive illness or unipolar major depressive disorder.

THE CLINICAL INTERVIEW

An important figure in psychiatry who focused on improving diagnostic abilities of difficult psychotic conditions was Harry Stack Sullivan (14). His emphasis was on the difficulties inherent in the clinical interview of paranoid patients (thus making it difficult to diagnose some types of schizophrenia, schizoaffective disorder, psychotic depression, and borderline personality disorder). Sullivan has provided many unique techniques for accurately eliciting signs and symptoms in these patients. As Leston Havens has remarked (15), perhaps diagnosis in psychiatry is in a stage similar to medicine before the advent of auscultation. Sullivan’s techniques may be similar to auscultation, allowing us to see and hear what we otherwise would miss. This level of subtlety in the clinical interview is often difficult to achieve, much less standardize and teach for research purposes. As van Praag notes, “one can witness a standardized interview degenerating into a question-and-answer game: answers being taken at face value, not caring for the meaning behind the words, disregarding the as-yet-unspoken and oblivious to the emotional content of the communication” (16). Thus, in sum, we are not simply suggesting that a structured clinical interview is sufficient to accurately and reliably diagnose bipolar disorder. Van Praag (16) has noted that the advent of biological psychiatry has resulted in a move from overly subjective approaches in research and practice to more objective methods. While initially salutary, this process may now become an obstacle to further progress.

SOME FACTORS THAT IMPEDE DIAGNOSIS OF BIPOLAR DISORDER

The assessment of manic or hypomanic symptoms is impeded by a number of factors (Table 1). Of these, lack of insight is probably the most clinically important. In studies of acute mania, we and others have shown that about one half of
Table 1  Factors That Impede the Diagnosis of Bipolar Disorder

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impairment of insight into mania but not depression</td>
</tr>
<tr>
<td>Poor memory for past manic/hypomanic symptoms</td>
</tr>
<tr>
<td>Unreliability of hypomanic diagnosis by clinicians</td>
</tr>
<tr>
<td>Antidepressant view of the world</td>
</tr>
<tr>
<td>Stigma of the bipolar diagnosis compared with depression</td>
</tr>
</tbody>
</table>

Patients do not recognize that they are experiencing manic symptoms (17,18). The implication is simple: If one does not know that one is manic when it is actually happening, how much less likely will it be that a person will be able to report such past manic symptoms in the future? Thus, it is not surprising that family members will report manic symptoms about twice as frequently as patients will (19). On other hand, in the same study of prodromal and residual manic and depressive symptoms, patients and families agreed on and equally reported the presence of depressive symptoms. This is because, unlike mania, depressed patients are all too aware of their depressive symptoms (20).

This imbalance of insight into depression and mania introduces a major bias against the diagnosis of bipolar disorder (21). Patients tend to seek help when they are depressed; they are familiar with antidepressants; they see advertisements for them (when was the last television advertisement for a mood stabilizer?); and depression is obviously a quite psychically painful condition. By contrast, manic patients can be euphoric (though usually they are not, being mainly irritable), and until recently lithium was the only mood stabilizer that was available. Given its frequent confusion with schizophrenia, bipolar disorder also has a more severe connotation in the public mind: it is more associated with being “crazy” than is unipolar depression. The reality—that both bipolar and unipolar mood disorders consist mostly of depressive symptoms—is a reality that is often lost on patients and clinicians alike.

Thus, clinicians need to do a good deal of explaining and educating when confronted with depressed bipolar patients, explaining to them the nature of the two forms of depression, and why it is important to distinguish between the two.

Other factors are also important. When patients are depressed, they frequently have impaired cognition and memory, and thus, even if they previously possessed insight into manic symptoms, their ability to recall those symptoms might be impaired. Also, when it comes to diagnosing bipolar II disorder, even clinicians cannot seem to agree on how to diagnose hypomania, much less patients. DSM-IV, which introduced hypomania for the first time into the official nomenclature, left the matter deliberately vague. As noted above, the key distinction between hypomania and mania is in function rather than symptoms. With
Polypharmacy of Bipolar Disorder

hypomania, there is not “significant” social or occupational dysfunction; in mania, there is. Everything hinges on the definition of the term “significant,” and this is where clinicians diverge. Further, bipolar II disorder is the only major DSM-IV syndrome not associated with significant social or occupational dysfunction; not only that, one has to rule out significant social or occupational dysfunction before making the diagnosis! This obviously makes its recognition more difficult, as laypersons are not accustomed to viewing periods of normal or even improved activity as pathological in any sense.

There is also the impact of the antidepressant view of the world, which was discussed in the first chapter, that is, the influence of the marketing, success, and availability of treatments for depression. The lay public learns more about depression and demands antidepressant treatment; it knows little about bipolar disorder, and there is little clamor for mood stabilizers.

Now we can proceed to the empirical literature, asking ourselves the question, once we have accurately diagnosed bipolar disorder, when should we engage in polypharmacy, when should we avoid it, and which agents should or should not be combined?

EMPIRICAL STUDIES OF POLYPHARMACY IN BIPOLAR DISORDER

We may divide empirical studies of polypharmacy in bipolar disorder into three main categories: depression, mania, and prophylaxis.

Polypharmacy of Bipolar Depression

The key issue here, alluded to a few times thus far, is the role of antidepressants. Do antidepressants work in the treatment of bipolar depression? Do they treat the acute episode? Do they prevent future episodes of depression in someone with bipolar disorder? Are we justified in using antidepressants along with mood stabilizers, that is, in polypharmacy?

To answer these questions with a basis in evidence, we need to look at research studies of antidepressant use in bipolar disorder. Those studies may be divided into two categories: short-term studies of acute depression and long-term studies of depression prophylaxis.

Short-Term Studies of Acute Bipolar Depression

There are six studies of standard antidepressants in acute bipolar depression (total n = 376), usually combined with lithium (Table 2). By and large, these
Table 2  Controlled Short-Term Studies of New Antidepressants in Acute Bipolar Depression

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>n (BP diagnosis)</th>
<th>Drug</th>
<th>Efficacy</th>
<th>Mania risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohn et al., 1989 (115)</td>
<td>89 (I)</td>
<td>Fluoxetine</td>
<td>FLU &gt; IMI &gt; PLA</td>
<td>FLU = IMI</td>
</tr>
<tr>
<td>Sachs et al., 1994 (116)</td>
<td>19 (I&amp;II)</td>
<td>Buproprion</td>
<td>BUP = DMI</td>
<td>BUP &lt; DMI</td>
</tr>
<tr>
<td>Young et al., 1997 (117)</td>
<td>137 (I)</td>
<td>Paroxetine</td>
<td>PAR = IMI &gt; PLA</td>
<td>PAR &lt; IMI</td>
</tr>
<tr>
<td>Amsterdam et al., 1998 (118)</td>
<td>80 (II)</td>
<td>Fluoxetine</td>
<td>FLU alone &gt; PLA</td>
<td>FLU = PLA</td>
</tr>
<tr>
<td>Young et al., 2000 (119)</td>
<td>27 (I)</td>
<td>Paroxetine</td>
<td>PAR + stabilizer = 2 mood stabilizers</td>
<td>PAR + stabilizer = 2 mood stabilizers</td>
</tr>
<tr>
<td>Amsterdam et al., 2000 (120)</td>
<td>15 (II)</td>
<td>Venlafaxine</td>
<td>VEN alone &gt; PLA</td>
<td>VEN = PLA</td>
</tr>
</tbody>
</table>

FLU = Fluoxetine, IMI = imipramine, BUP = bupropion, DMI = desipramine, PAR = paroxetine, VEN = venlafaxine, PLA = placebo.
studies find that antidepressants can be helpful in the treatment of acute depressive symptoms in bipolar disorder, but only marginally more than lithium used in full therapeutic doses. On the other hand, antidepressants used along with lithium may allow a lower overall lithium dose, which can be better tolerated than full-dose lithium monotherapy. These studies also demonstrate that standard antidepressants cause acute mania to a greater extent than placebo, and this risk seems highest with the tricyclic antidepressants. In type I bipolar depression, the only two antidepressants that have been shown to have a low risk of causing mania are paroxetine and bupropion.

Long-Term Studies of Antidepressants in the Prophylaxis of Bipolar Depression

There have been only seven randomized controlled studies of long-term outcome with antidepressants in bipolar depression (Table 3).

In an early 1973 study (121), lithium was compared to imipramine alone (125 mg/d) and placebo, and not surprisingly from today’s perspective, the tricyclic antidepressant alone was quite ineffective in 122 patients with recurrent affective illness ($N = 44$ previously manic, and 78 with unipolar depression). Recurrence rates for mania or depression at months 5–24 were 18% for lithium-treated subjects vs. 67% in both the imipramine and placebo groups (Fisher exact $p = 0.02$), suggesting that the antidepressant was simply ineffective.

This early report was followed up by another study (122), which asked the question: What would the result be if all bipolar I patients were given a tricyclic antidepressant in addition to lithium, rather than lithium alone? Seventy-five patients were followed for 18.8 months, following at least 6 months of stable mood during treatment with lithium alone. Risk of at least one recurrence of a manic episode in subjects treated with imipramine + lithium was about twice that with lithium alone (significant only in women), with no difference in a low risk of new depressive episodes ($10\%$ overall).

The same group that conducted the first study (121) examined the question of polypharmacy a decade later (124), comparing polypharmacy with lithium + imipramine versus lithium alone versus imipramine (double-blind, placebo-controlled). A novel aspect of this protocol, in contrast to the Quitkin et al. study (122), was that all patients were initially stabilized for at least 2 months on lithium plus imipramine. Thus, the study essentially was a discontinuation paradigm: What happens in patients stable on lithium plus an antidepressant when the antidepressant is removed (or when lithium is removed and the antidepressant maintained)? In 117 patients followed for up to 2 years, relapse rates with lithium alone were 29% depressive and 26% manic, and with lithium + imipramine, corresponding rates were 22% and 28%, suggesting that addition of imipramine had no effect. Kaplan-Meier survival analysis indicated that imipramine + lith-
<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Diagnoses (N)</th>
<th>Treatments</th>
<th>Duration (months)</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prien et al., 1973 (121)</td>
<td>BP-I (44), UP (78)</td>
<td>Li vs. IMI vs. PBO</td>
<td>Up to 24</td>
<td>Hospitalized or new treatment</td>
<td>Efficacy: Li &gt; IMI = PBO in BP</td>
</tr>
<tr>
<td>Wehr et al., 1979 (22)</td>
<td>BP-I (5)</td>
<td>Li vs. Li + DMI</td>
<td>27 (mean)</td>
<td>Nurse ratings</td>
<td>Efficacy: Li + DMI &gt; Li</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Switch &amp; cycling rate: Li + DMI ≫ Li</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Efficacy: Li = IMI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mania: IMI &gt; Li (women)</td>
</tr>
<tr>
<td>Quitkin et al., 1981 (122)</td>
<td>BP-I (75)</td>
<td>Li vs. Li + IMI</td>
<td>19 (mean)</td>
<td>RDC episodes</td>
<td>Efficacy: Li = IMI</td>
</tr>
<tr>
<td>Kane et al., 1982 (123)</td>
<td>BP-II (27), UP (22)</td>
<td>Li vs. IMI vs. Li + IMI vs. PBO</td>
<td>11 (mean)</td>
<td>RDC episodes</td>
<td>Efficacy: Li &gt; PBO; IMI = PBO</td>
</tr>
<tr>
<td>Prien et al., 1984 (124)</td>
<td>BP-I (117), UP (150)</td>
<td>Li vs. Li + IMI vs. IMI</td>
<td>Up to 24</td>
<td>RDC episodes</td>
<td>Efficacy: Li = Li + IMI; IMI more mania</td>
</tr>
<tr>
<td>Sachs et al., 1994 (116)</td>
<td>BP-I (15) (19 treatment trials)</td>
<td>BUP vs. DMI</td>
<td>Up to 12</td>
<td>DSM-III-R episodes</td>
<td>Efficacy: Li + BUP = Li + DMI; Mania: DMI &gt; BUP</td>
</tr>
<tr>
<td>Amsterdam et al., 1998 (125)</td>
<td>BP-II (80), matched UP (79), unmatched UP controls (661)</td>
<td>FLX vs. PBO</td>
<td>Up to 14</td>
<td>DSM-III-R episodes</td>
<td>Efficacy: FLX similar in BPII &amp; UP; switch rate: BP &gt; UP</td>
</tr>
</tbody>
</table>

*Source:* Adapted from Ref. 126.
ium did not lead to better outcome than lithium alone, although both lithium-treated groups outperformed imipramine alone (see Fig. 1).

Only two studies have looked at long-term antidepressant outcome in bipolar II disorder. The first assessed outcome with imipramine in 22 bipolar II and 27 unipolar depressive patients stable for at least 6 months with clinically determined treatments and for another 6 weeks given imipramine alone (up to 150 mg daily) prior to randomization. Unfortunately, in this small sample four treatment arms were designed: imipramine with lithium carbonate, imipramine + placebo, lithium, or placebo alone, for an average of 11 months. Treatment with lithium (with or without antidepressant continued) reduced depressive relapses three- to eight-fold (20% with lithium vs. 76% with placebo). Among unipolar depressives considered separately, relapse rates were 20% with lithium vs. 91% with placebo. In the bipolar II cases, depressive recurrence rates on lithium were similarly lower (20%) than with placebo (60%), though this difference was nonsignificant \((p = 0.12)\). It is impressive that lithium was more effective than imipramine even in the recurrent unipolar sample in this study.

The second study to look at bipolar II disorder, and the only long-term study with a serotonin reuptake inhibitor (SRI), involved retrospective analysis of 80 DSM-III-R bipolar II patients treated with fluoxetine vs. placebo up to 62

![Fig. 1](image)

**Fig. 1** Survival analysis for likelihood of relapse with lithium vs. imipramine vs. both \((n = 117)\). (Adapted from Ref. 124.)
weeks, included with 661 unipolar major depressives (125). These patients were treated as part of unipolar depression clinical trials (apparently, in some of those trials, bipolar I disorder was an exclusion, but bipolar II diagnoses were not exclusionary). Thus, this consists of a post hoc analysis of what happened to the bipolar II subgroup of patients included in those studies. There was no difference in depression recurrence between the groups (50% in the bipolar II group and 69% in the unipolar group). However, hypomania occurred in 5.0% (4/80) of the bipolar II subjects (3 within 8 weeks), compared to 0.30% (2/661) of “unipolar” cases (chi-square 1 df = 8.03; \( p = 0.005 \)). Unfortunately, this post hoc analysis was based on trials in which fluoxetine-treated patients were switched to placebo after a certain period of treatment. Thus, only 35% of the bipolar sample were available for analysis at 6 months, and only 10% at 62 weeks. One cannot draw many conclusions from such a post hoc analysis with limited statistical power.

The other two studies listed in the table are small and of limited interpretability.

**Summary of Controlled Antidepressant Studies**

In summary, controlled studies of antidepressants in bipolar depression, whether short or long term, fail to provide much evidence of efficacy beyond that obtainable from therapeutic mood stabilizer doses. Some antidepressants, such as tricyclic antidepressants, appear particularly risky, though the newer antidepressants have not been studied, and one should not presume that they are particularly safe. The only definite data on the newer agents to date are that paroxetine and bupropion may have a lower short-term mania switch risk.

Given this evidence that antidepressants are not particularly effective in the short- or long-term treatment of bipolar depression, the decision to use them demands safety at the very least. Yet, naturalistic studies at least throw into doubt the safety of antidepressants in the long-term treatment of bipolar disorder.

This literature began with the recognition in the late 1970s, based on the first comparison of lithium and imipramine (121), that antidepressants might not provide as much benefit as expected in treating bipolar depressive symptoms. Wehr and Goodwin’s controlled though small study (22) suggested that antidepressants increase mood cycling. Wehr and Goodwin then reported that antidepressants were associated with rapid-cycling episodes in 57% of an NIMH sample of refractory bipolar patients. (22). Further, in a subgroup, double-blind replacement of the antidepressant with placebo led to resolution of rapid cycling. This report was followed by a similar finding from Italy in a large outpatient population (23). The subject remained somewhat dormant, despite the attention brought to it by Goodwin and Jamison in their classic text in 1990 (13). The 1990s was the decade of antidepressants, which have become the most commonly prescribed class of medications for bipolar disorder. This practice pattern completely re-
versus the evidence basis. As shown above, lithium has been repeatedly shown to be effective in multiple double-blind studies, short-term and long-term, of bipolar depression.

In the mania (so to speak) to use antidepressants, few clinicians seemed to pay attention to the concerns previously raised by Wehr and Goodwin and Kucopolos. In 1995, another NIMH group headed by Robert Post revisited the topic and found evidence of antidepressant-induced rapid cycling in 26% of bipolar patients examined (24). This referred to the fact that these patients appeared to have their rapid cycling in association with antidepressant use. When they were taking antidepressants, they experienced rapid cycling. When they stopped the antidepressants, they were not rapid cycling. Further, antidepressant use seemed to have a mood-destabilizing effect, contributing to treatment resistance. Again, off the antidepressants, patients seemed more unstable and less responsive to mood stabilizers; on the antidepressants, they appeared more responsive to mood stabilizers.

Of course, such naturalistic associations are not definitive. They could be accounted for by natural history. In another outcome study (25), this one being prospective and designed to gather more detailed information, the natural history factor seemed more prominent. This report was based on the NIMH-sponsored Depression Collaborative Study, a 5- to 10-year outcome study begun in the late 1980s in a number of academic centers. In the 10-year outcome analysis, the investigators examined the question of whether antidepressants were associated with rapid cycling or poor outcome in their sample of patients with bipolar I disorder. Indeed, they found this to be the case. However, they conducted a logistic regression analysis and reported that the preexisting depression was statistically associated with poor outcome and that when preexisting depression was controlled as a separate factor, antidepressants had no specific directional effect on outcome. While this finding did not support the other observations, it too was based on naturalistic data, and thus the statistical analysis could not be used to definitively prove or disprove the reports of antidepressant-related poor outcome.

We and our collaborators have provided two naturalistic datasets over the last few years which did support the earlier evidence for antidepressant-induced poor outcome. In the first study (1), we reported on 48 inpatients with bipolar I disorder, and we noted that about one third were taking antidepressants and only one third were taking mood stabilizers. Over an average of about 10 days of naturalistic inpatient treatment, we were able to get almost all patients on mood stabilizers, and almost all patients off antidepressants, with significant clinical improvement. In other words, it appeared to us that antidepressants were not needed to treat these patients, and indeed might have impeded benefit with mood stabilizing agents.

In that study, we also were able to assess treatment benefits comparing mood stabilizer monotherapy to polypharmacy with multiple mood stabilizers
The mood stabilizer plus other treatment group consists of those treated with two or more adjunctive agents (including clonazepam) added to at least one mood-stabilizing agent. Differences between risperidone + mood stabilizer and typical NL + mood stabilizer were statistically significant (p = 0.04, Fisher’s exact test). (Adapted from Ref. 1.)

(Fig. 2). In a retrospective analysis using Clinical Global Impression rating scales, and including all phases of bipolar illness (manic, mixed, depressed), we found that polypharmacy with two mood stabilizers (divalproex + lithium) or a mood stabilizer plus an atypical neuroleptic agent (risperidone) was more effective than monotherapy with a mood stabilizer (divalproex or lithium or carbamazepine). Interestingly, we also found that polypharmacy with a typical neuroleptic added to a mood stabilizer did not give any further benefit in this naturalistic sample to using a mood stabilizer alone.

Thus, our inpatient study suggested that polypharmacy with an atypical neuroleptic or two mood stabilizers was useful in the treatment of bipolar disorder, but polypharmacy with a typical neuroleptic plus a mood stabilizer or polypharmacy with an antidepressant plus a mood stabilizer was not beneficial.

In a second study (9) we replicated these findings in an outpatient bipolar disorder sample (n = 56), and we were also able to demonstrate that antidepressants were associated with rapid-cycling episodes in 24% of our bipolar sample. We had some evidence that antidepressants might have some utility in bipolar...
Fig. 3 Effect of antidepressants (ADs) on rapid cycling and duration of illness. Mood episodes per year increased more than twofold with antidepressant use, but this was not statistically significant ($z = -1.29, p = 0.20, n = 16$, Wilcoxon signed rank test). There was a statistical trend toward a decrease in percent of time ill ($z = -1.80, p = 0.07, n = 16$, Wilcoxon signed rank test). (From Ref. 126.)

depression, in that they reduced the severity of depressive episodes somewhat, but they still led to more frequent episodes (Fig. 3). This marginal benefit was mainly seen in bipolar II depression.

Thus, the thrust of the evidence tends to highlight three findings:

1. Antidepressants have not been shown to be more effective than therapeutic levels of lithium in the treatment of acute bipolar depression and are associated with a risk of acute mania.
2. In controlled studies, antidepressants have failed to prevent major depressive episodes in the treatment of bipolar disorder any better than lithium alone.
3. The bulk of the naturalistic literature suggests that antidepressants may have a long-term mood-destabilizing effect, with associated rapid cycling.

Based on these findings, we would not recommend frequent polypharmacy with antidepressants in the treatment of bipolar disorder.

When would antidepressant use be warranted? In our opinion, two circumstances seem appropriate for polypharmacy with antidepressants. First, for acute, severe, non–rapid-cycling bipolar depression with severe suicidal ideation and/or plan, getting the severity of the depression and suicidality under control is the first priority, and since lithium and other mood stabilizers may not work in any
particular case (or may have a slow onset of action), one would be justified in using polypharmacy with an antidepressant to maximize the chance of immediate treatment response. Second, in the hospitalized bipolar depressed patient with economic limitations on length of stay, a rapid treatment response may require antidepressant use. However, this is best conducted when the antidepressant can be tapered after discharge on an outpatient basis; frequently, such continuity of care does not exist in the current U.S. medical economy.

In general, due to the long-term risks of antidepressant use, we would recommend gradual taper of the antidepressant after the resolution of the acute major depressive episode. This agrees with a recent published expert consensus guideline (26). Although some people may need long-term antidepressant treatment, it is our belief that the evidence warrants giving all patients a trial off antidepressants in order to see if they have sufficient prophylactic benefit with one (or more) mood stabilizers. In a large naturalistic study of our experience, only 19% of patients with bipolar disorder needed long-term antidepressant treatment (27).

**Polypharmacy of Mania**

As stated previously, it is standard practice in the United States to combine neuroleptics and mood stabilizers in the treatment of acute mania. This kind of “stratified” treatment is justified on the basis of the need to quickly control an agitated and often aggressive condition like mania. This initial polypharmacy need not entail long-term polypharmacy, however, since it has been the official recommendation for years that neuroleptics be tapered off after resolution of the acute manic episode. This recommendation was largely based on the side effects of typical neuroleptics, particularly the highly increased risk of tardive dyskinesia with these agents in bipolar disorder (28). However, in practice, most clinicians have tended to keep patients on typical neuroleptics even after resolution of the acute manic episode (29). In fact, it has been estimated that in the early 1990s, before the widespread use of the atypical neuroleptic agents, around 30–40% of patients with bipolar disorder were chronically treated with typical neuroleptic agents (30). This cannot be justified based on the presence of psychotic symptoms, which, though common, are brief and time-limited in bipolar disorder and thus do not require chronic treatment (13).

This kind of polypharmacy is unwelcome since there is evidence that typical neuroleptic agents are not only unsafe in the long-term treatment of bipolar disorder, but, like antidepressants, they have no evidence of preventive benefit. In other words, while they clearly are effective in treating acute mania, they have not been shown to be effective in preventing mania or depression. In fact, they seem to be associated with causing depression in the long run. Let us look at this literature.
Polypharmacy of Bipolar Disorder

Controlled Long-Term Studies of Typical Neuroleptic Medications in Bipolar Disorder

We will skip over short-term studies in acute mania, merely commenting that multiple double-blind studies have shown typical neuroleptics to be effective in treating acute mania (13). There have been only two controlled long-term studies of typical neuroleptic agents in the prevention of manic symptoms for bipolar disorder (Table 4). In a 2-year double-blind crossover study that compared the neuroleptic flupenthixol + lithium to lithium alone (31), patients receiving flupenthixol experienced more episodes of depression than lithium-treated patients, while the frequency of manic episodes was not significantly different. In a smaller double-blind crossover study (n = 11), Esparon and colleagues also found that patients given supplemental flupenthixol had more symptoms on the Affective Morbidity Index (32) than patients receiving lithium (p < 0.05) (33).

In contrast to this rather pitiful literature on traditional neuroleptic agents, there is a burgeoning literature on atypical neuroleptic agents that strongly indicates that these agents may have a major role in the treatment of bipolar disorder.

The Role of Atypical Neuroleptic Agents in the Treatment of Bipolar Disorder

This is a large topic, reviewed in detail elsewhere (34). Some of the major points are that atypical neuroleptic agents, though still possessing extrapyramidal side effects (EPS), have them to a lesser degree than typical neuroleptic agents, and this feature makes these medications much more tolerable in the treatment of persons with bipolar disorder, who tend to be particularly sensitive to such EPS. Further, atypical neuroleptic agents appear to have minimal risk of tardive dyskinesia and neuroleptic malignant syndrome, again reviewed in more detail elsewhere (34), supporting the safety of these agents in longer-term treatment of bipolar disorder.

There are now five double-blind studies of olanzapine in acute mania, three with risperidone, one with ziprasidone, and a number ongoing with quetiapine (34). These data are rapidly changing. Again, as reviewed previously (34), the main finding of these studies is that all of these agents appear to be effective in treating acute mania, either alone or in combination with standard mood stabilizers. This is not too surprising, as typical neuroleptic agents also had been proven effective for acute mania. What is somewhat different is that atypical neuroleptic agents do not tend to cause postmanic depression (34), that is, a depressive episode does not seem to follow the manic episode, which seemed relatively common with typical neuroleptic agents (13). Thus, atypical neuroleptics may have some mood-stabilizing effects, as opposed to simply antimanic effects, unlike typical neuroleptics. This would be the case if we hypothesize that atypical neuro-
### Table 4  Controlled Long-Term Studies of Typical Neuroleptics in Prophylaxis of Bipolar Disorder

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>n</th>
<th>Design</th>
<th>Treatment</th>
<th>Depression</th>
<th>Mania</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahlfors et al., 1981 (31)</td>
<td>93</td>
<td>DB, crossover</td>
<td>Li vs. Flupenthixol + Li</td>
<td>Flu + Li &gt; Li</td>
<td>Li = Flu + Li</td>
<td>Flu + Li led to a statistical trend for more depression</td>
</tr>
<tr>
<td>Esparon et al., 1986 (33)</td>
<td>11</td>
<td>DB, crossover</td>
<td>Li vs. Flupenthixol + Li</td>
<td>Flu + Li &gt; Li</td>
<td>Li = Flu + Li</td>
<td>Flu + Li leads to more symptoms on Affective Morbidity Index</td>
</tr>
</tbody>
</table>

DB = Double-blind.
leptics not only treat mania but might also have antidepressant properties. There is some evidence to support this notion (34).

This leads to the question of whether atypical neuroleptics are mood stabilizers, and thus might be used in place of standard mood stabilizers like lithium, rather than in polypharmacy. This partially depends on one’s definition of mood stabilizer (34), but the question has come up mainly because the FDA has approved olanzapine in the treatment of acute mania. Clinicians sometimes interpret this to mean that the FDA has “approved” olanzapine as a “mood stabilizer,” a term that the FDA does not use as an indication for approval. However, it seems to have become a marketing strategy to use FDA approval for mania to market a drug as a “mood stabilizer,” whereas these are not one and the same thing. If they were exactly the same, then haloperidol and other typical neuroleptics would be mood stabilizers. As we have seen, the long-term data with these agents do not support this notion. What is needed is long-term data on whether atypical neuroleptics, by themselves (in monotherapy), are effective in the prophylaxis of bipolar disorder. We will review the available long-term data in a moment.

Before looking at the long-term evidence available, it is important to mention that the short-term acute mania studies with many of these agents consist of monotherapy paradigms (e.g., olanzapine vs. placebo for acute mania) because that is the kind of protocol required by the FDA for registration (see Chapter 1). Such protocols do not answer the clinically relevant question of whether monotherapy is better than combined therapy. Three studies have examined this issue. In one with olanzapine and two with risperidone, large double-blind, placebo-controlled clinical trials of hospitalized acute mania were conducted in which all patients were already taking lithium or divalproex. Those studies all showed major benefit when combining the atypical neuroleptic with the mood stabilizer versus the mood stabilizer + placebo (i.e., mood stabilizer alone) (34).

These acute polypharmacy studies would suggest that “stratified” polypharmacy, whether with typical or atypical neuroleptic agents, seems to be the most effective approach.

Long-Term Studies of Atypical Neuroleptic Medications in Bipolar Disorder

There is only one controlled study (and it is open, not double-blind) of an atypical neuroleptic agent in the long-term prevention of bipolar disorder, but two other uncontrolled studies will be discussed due to their clinical relevance. All of these studies involve polypharmacy, rather than monotherapy, with atypical neuroleptic agents. Again, this is a rapidly moving field, and soon controlled data will no doubt become available.

In the only randomized study so far (35), clozapine \( n = 19 \) was studied in 1-year prospective randomized outcome compared to treatment as usual \( n = \)
in severe bipolar or schizoaffective illness. Overall improvement on psychiatric rating scales, such as the Brief Psychiatric Rating Scale (BPRS), was statistically better with clozapine than with treatment as usual. When assessing categorical response based on 30% improvement on BPRS scores, somewhat more response was seen with clozapine (65% at 3 months, 82% at 6 months) than with treatment as usual (48% at 3 months, 57% at 6 months). Dropouts were greater in the treatment-as-usual group ($n = 9$) than the clozapine group ($n = 3$). This study was not double-blind or placebo-controlled, and the use of treatment as usual as a comparator raises a variability in treatments that makes the control group difficult to standardize. Nonetheless, the results are encouraging and have the advantage of being more than short-term findings, instead providing evidence for a longer-term mood-stabilizing effect. Since clozapine was used as an adjunct to mood stabilizers, definitive evidence for activity as a stand-alone mood stabilizer is still lacking.

Two almost identical long-term studies have been presented at research meetings with risperidone and olanzapine, with strikingly similar results. In the study with risperidone, Vieta and associates (36) openly followed 305 patients with bipolar and schizoaffective disorders for 6 months while they were taking risperidone as add-on treatment to standard mood stabilizers. All patients entered the study manic, hypomanic, or mixed (DSM-IV criteria) with inadequate response to standard mood stabilizers. They were followed prospectively with standardized ratings scales. Interim analyses were made at 4–6 weeks. Young Mania Rating Scale scores improved from acutely manic at baseline (24.8) to residual levels (5.2). Hamilton Depression Rating Scale scores improved from subthreshold depressive levels (12.7) to residual symptoms (5.6). All improvements were statistically significant. Further 6-month outcome data are pending, and if consistent with the initial results, would argue for long-term adjunctive mood-stabilizing effects with risperidone.

In the study with risperidone, Sanger and associates (37) reported the 49-week open extension of a previous 3-week double-blind study of olanzapine in acute mania. One hundred and thirteen patients received olanzapine (13.8 mg/d) with prospective assessment of response for a mean duration of 201 days (6.6 months). YMRS scores improved from 25.5 at baseline to 7.5 at endpoint, and HDRS scores improved from 12.2 to 6.4. Both improvements were statistically significant. Adjunctive lithium or fluoxetine was required in the majority of patients to treat breakthrough manic or depressive symptoms, however, thus making these results, like the risperidone study, reflective mostly of the long-term adjunctive mood-stabilizing effects of the atypical agent.

In terms of long-term tolerability, a naturalistic study (38) completed by our colleagues at Massachusetts General Hospital found that risperidone and olanzapine polypharmacy with mood stabilizers seemed equally effective. The
main difference in side effects was with weight gain, which is a major problem in the polypharmacy of bipolar disorder, to which we will return. In that study (n = 42 patients, 50 treatment trials), weight gain was greater with olanzapine (16 lb) than with risperidone (8 lb, p < 0.03), and this difference was more marked in patients who remained on those polypharmacy treatments for at least 3 months (24 lb weight gain with olanzapine vs. 3 lb with risperidone). The greatest weight gain was associated with the divalproex-olanzapine combination, the least with the lithium-risperidone combination.

**Polypharmacy in the Prophylaxis of Bipolar Disorder**

We have touched on the prevention of depressive and manic symptoms in our discussion of antidepressants and neuroleptic agents. In this section, we will discuss prevention of such symptoms with combinations of standard or novel mood stabilizer agents.

Until recently, the most common polypharmacy supported by experts was the combination of mood stabilizers, such as lithium + valproate, or lithium + carbamazepine. However, the research literature on such polypharmacy is surprisingly sparse. Most of the literature on combination treatments of mood stabilizers is uncontrolled (39). However, these studies seem to provide increasing evidence for the utility of combining lithium with either valproate or carbamazepine or both. In Post’s review of this literature, there were 15 uncontrolled studies of valproate augmentation of lithium in bipolar disorder, which, when combined, yielded a 62% (246/400) success rate in acute treatment, and a 48% (183/380) success rate in prophylaxis (39).

A few more recent studies shed further light on mood stabilizer combination therapy. In one study, 75% (47/63) of patients with refractory affective disorders (mostly bipolar disorder) responded when valproate was added to either lithium or carbamazepine (40). A few reports have also noted the efficacy and relative safety of combining valproate and carbamazepine in the treatment of refractory bipolar disorder (41,42).

There is only one randomized prospective study of the combination of lithium and valproate in the treatment of bipolar I disorder. In that double-blind study, 12 patients followed for one year were randomly assigned either placebo or valproate added to lithium. The combination treatment was associated with less relapse (p = 0.01) but more side effects (p = 0.04) (43).

In another report, 6 of 18 (33%) patients responded to valproate + lithium to a moderate to marked degree in open one-year prospective treatment, and 4 of those 6 had been resistant to other mood-stabilizing treatments in the past. In 3 of 7 patients, triple therapy with lithium, carbamazepine, and valproate was
the only effective treatment, although marked benefit was seen in only one case (44). In another study from the same group assessing lithium + carbamazepine combination therapy, 52 patients were followed in an open randomized manner on either lithium alone, carbamazepine alone, or the combination for up to 3 years. While treatment response (based on moderate to marked improvement on the CGI) was higher on the combination treatment (55%) than lithium (33%) or carbamazepine (31%) monotherapy, this difference was not statistically significant, possibly due to the small sample sizes. However, statistically significant benefit to combination therapy was clearly present in patients with rapid-cycling bipolar disorder (56% combination therapy response vs. 28% lithium response and 19% carbamazepine response, \( p < 0.05 \)) (45).

In most of these studies, each mood stabilizer was used in full dose. There are minimal, if any, research data on using reduced doses of lithium and an anticonvulsant in combination. After all, this is what would test the hypothesis of a synergy between them: Does a low dose of lithium work in the presence of an anticonvulsant, and vice versa? Taking into account the additive side effects in combination treatment, we sometimes use the agents in this manner, one in full dose and the other at a low (‘‘subtherapeutic’’) dose.

New anticonvulsants may also be useful in the treatment of breakthrough episodes. While a number of double-blind studies suggest efficacy for lamotrigine in monotherapy for acute bipolar depression (46) and for prophylaxis of rapid-cycling mood episodes in type II bipolar disorder (47), these studies did not involve polypharmacy. In a large open naturalistic study, lamotrigine response, mainly as add-on therapy, was 50% for depressive symptoms and 48% for manic symptoms (based on 50% or greater decline in YMRS or HDRS scores) in 40 rapid-cycling bipolar I patients (46). In the double-blind placebo-controlled clinical trial of acute bipolar depression, there was not statistically notable increased risk of mania (46).

Another alternative is gabapentin, which has gained in popularity. Gabapentin’s advantages in safety are counteracted by its lack of evidence for efficacy, however. In two double-blind studies of treatment refractory mania (48) and bipolar depression (49), gabapentin was not more effective than placebo. While it may have antianxiety effects, its mood-stabilizing effects, at least in refractory bipolar illness, have not been established. Naturalistic data suggest it may possess efficacy in nonrefractory type II bipolar illness (50).

Topiramate has important potential benefits in treating bipolar disorder. Monotherapy with topiramate has not yet been studied sufficiently. Preliminary results from two controlled studies suggest that it may be effective in acute mania in monotherapy (double-blind comparison with placebo) in the absence of concurrent antidepressant use (Ortho-McNeil, data on file), and it may be effective as add-on therapy (single-blind comparison to bupropion) to standard mood stabilizers in acute bipolar depression (51).
POLYPHARMACY OF BIPOLAR DISORDER AND SIDE EFFECT BURDEN

The main argument against polypharmacy in the treatment of bipolar disorder is the increased side effect burden that occurs with it. This has been an especially major issue when available mood stabilizers were limited to lithium, divalproex, and carbamazepine, all of which have significant side effect profiles.

With newer anticonvulsants and atypical neuroleptic agents, however, the side effect burdens of mood-stabilizing agents are reducing, and the prospects for tolerable polypharmacy is increasing. In this section we will assess the major side effect problems seen in polypharmacy and the methods of managing them.

Weight Gain

The problem of weight gain is probably the most intractable dilemma in the polypharmacy of bipolar disorder (52). This is not only a cosmetic issue of concern to patients, but also a medical issue that should be of concern to all clinicians, since weight gain is associated with increased risk of cardiovascular morbidity and mortality, cancer, diabetes, and hypertension (53). A recent study found that increased mortality from all causes was correlated with greater weight (54). Cardiovascular disease in particular appears to be a major cause of mortality in bipolar disorder (55), perhaps second only to suicide, and possibly related to iatrogenic obesity. Thus, as clinicians, this problem is one we must take seriously (56). As of publication of this text, we think it is still accurate to say that lithium and divalproex are the mood stabilizers with the most research evidence and clinical experience in support of their use. Unfortunately, they share many side effects, including weight gain and cognitive effects (57). In the United States, many clinicians, including us, would use either lithium or divalproex as part of the treatment regimen of most patients with bipolar disorder. This means that almost all patients are exposed to the problem of weight gain. As will be noted in our algorithm, we recommend adding atypical neuroleptic agents to lithium or divalproex as the second step in treatment. In general, atypical neuroleptic agents are associated with weight gain, with clozapine and olanzapine having the highest weight gain liability (58,59). This step in our algorithm occurs, in our experience, in about two thirds of patients with bipolar I disorder, since only about one third are sufficiently responsive to lithium or divalproex monotherapy (60). Others might combine lithium and divalproex, which in our practice is a third step. Any of these combinations increases the weight gain burden, however, first and foremost. In a recent study of atypical neuroleptic use in bipolar disorder (38), olanzapine was associated with much more weight gain than risperidone when combined with lithium or divalproex (Fig. 4). Specifically, the combination of divalproex and olanzapine was associated with the most weight gain, and the
combination of lithium and risperidone the least. Thus, in general, to minimize weight gain with these agents, one might lean to combinations of lithium + risperidone, or potentially ziprasidone (61) as well. It is worth noting that in a head-to-head comparison in two double-blind studies, olanzapine produced more weight gain than divalproex in acutely manic patients (62,63). Previous studies have also shown that clozapine produces even more weight gain than olanzapine (59). Thus, of these agents, the two most problematic in terms of weight gain are clozapine and olanzapine, followed by divalproex. To minimize weight gain, one could lean toward the other alternatives.

Nonetheless, all of these agents seem to cause weight gain, some more than others. Sometimes this problem is so acute that entire classes of agents must be discarded, and then we move to the only other likely mood stabilizers with double-blind evidence of some efficacy in bipolar disorder: carbamazepine or lamotrigine (46,47). We view carbamazepine and lamotrigine as rather similar agents, both of which have high rash risks (discussed below). But they do have the advantage of not causing weight gain. Lamotrigine is generally better tolerated than carbamazepine on other grounds, as long as serious rash does not occur. The addition of lamotrigine to lithium is particularly well tolerated and is not likely to exacerbate weight gain. The combination of divalproex and lamotrigine is best avoided in general due to increased risk of skin rash (64). Gabapentin does not affect weight, but it has not been shown effective in monotherapy of bipolar I disorder in double-blind studies (65,66). Topiramate tends to cause weight loss (about 10–15 lb on average in bipolar disorder) and thus may be an alternative as an add-on to agents that might be effective but have led to too much weight gain (67).

**Fig. 4** Weight gain in pounds in polypharmacy of atypical neuroleptics plus standard mood stabilizers. *RI-12 wks* and *OL-12 wks* refer to use of those agents for 12 weeks or longer. The other two columns include the entire sample, including dropouts before 12 weeks. (Adapted from Ref. 38.)
We find it helpful to also distinguish between type I and type II bipolar disorder when assessing the need for polypharmacy and side effect burden. While we think one should still recommend lithium or divalproex as first-line treatments for bipolar II disorder also, it is important to note that most of the research on these agents is conducted in bipolar I disorder. Although such studies may extrapolate to bipolar II disorder, one cannot assume that this will be the case. In fact, in some of the limited studies of milder aspects of the bipolar spectrum, some differences have been noted compared to studies of bipolar I disorder. For instance, in one report on patients with cyclothymia, divalproex was effective for depressive symptoms at much lower levels than is typically used in bipolar I disorder (mean valproate level 32.5) (68). Thus, one might be able to use low doses of lithium and divalproex in bipolar II depression and thus limit side effects like weight gain or cognitive problems. However, if these medications are ineffective, or if patients adamantly refuse to try them, we think it is reasonable, in the case of bipolar II disorder, to use a novel anticonvulsant by itself as the next step. Lamotrigine in fact seemed more effective in bipolar II than bipolar I rapid-cycling disorder (47). Again, while gabapentin was not shown effective in monotherapy of refractory bipolar I disorder, this does not necessarily mean that it is ineffective in bipolar II depression. In fact, some naturalistic data suggest that it indeed may be more effective in bipolar II than in bipolar I disorder (50).

By using novel anticonvulsants or low-dose standard mood stabilizers in bipolar II disorder, one can enhance tolerability and limit the side effect burden in that sensitive subgroup.

**Sedation/Cognitive Effects**

Similar considerations as those just described largely hold for sedation and cognitive side effects. Lithium and divalproex both tend to cause sedation or cognitive side effects (57). Sometimes these cognitive effects can be subtle, but it must be remembered that many patients with bipolar disorder (especially type II) can be quite high-functioning individuals. In the workplace, or in relation to creativity required for music or artistic activity, any level of subtle cognitive dysfunction can be quite impairing and often leads to noncompliance. Thus, as above, these symptoms must be carefully assessed. Among the atypical neuroleptic agents, one would expect somewhat less cognitive side effects with those agents that do not have significant anticholinergic effects, such as risperidone, quetiapine, and ziprasidone (69). All three of these agents can cause some antiadrenergic effects (69), however, which sometimes can also produce cognitive impairment. Studies in schizophrenia in general indicate relatively limited cognitive side effects with all the atypical neuroleptic medications (70), but, again, patients with bipolar disorder, due to their higher level of functioning, are likely more sensitive to cognitive effects than are patients with schizophrenia.
The novel anticonvulsants again are less likely to cause cognitive side effects in general, although this appears to be a problem in some patients with topiramate (67). To limit this side effect, one would probably benefit from using lamotrigine in bipolar I disorder and either lamotrigine or gabapentin in bipolar II disorder.

Extrapyramidal Symptoms

When atypical neuroleptic medications are used in bipolar disorder, one runs into the problem of extrapyramidal symptoms (EPS). Most studies of EPS are conducted in schizophrenia, and the earlier typical neuroleptic literature suggests that patients with bipolar disorder may be more sensitive to EPS than patients with schizophrenia (71). Thus, we are probably justified in extrapolating from the schizophrenia literature and being prepared for the likelihood that EPS will be a problem in patients with bipolar disorder.

First, it is important to define EPS. Most experts include in the term “extrapyramidal syndrome” the following conditions: parkinsonian tremor, rigidity, acute dystonia, and akathisia (73,72). Some persons think of akathisia separately since its presumed pathophysiology is different from tremor and rigidity, but this is all rather speculative. If one thinks about the term EPS as relating to abnormalities that involve the basal ganglia and lead to acute reversible movement-related side effects, then akathisia would seem to be included in that definition. In fact, Ayd’s review of the early neuroleptic literature found that akathisia represents about half (21%) of the cases of EPS (39%) identified in a large population (n = 3775) with typical neuroleptic agents (73). This study would suggest that to ignore akathisia as an extrapyramidal syndrome would be to miss half of the cases. A recent study (74) of 120 long-term hospitalized patients with schizophrenia found a rate of akathisia (24%) similar to the earlier report three decades previously. On the other hand, tardive dyskinesia (TD) would not meet the definition of EPS, because it is not acute but slow in onset, and frequently (though not invariably) it is irreversible. Again, some persons include TD as part of the extrapyramidal syndrome, but it depends on how loose one wants to be with one’s definition. EPS, defined narrowly as the acute symptoms mentioned above, has not been shown to predict increased or decreased risk of TD (76). TD seems to be a separate issue, and, in fact, TD occurs spontaneously in schizophrenia (at a rate of about 0.5% per year, about 10–20% by age 70) in patients who have never experienced EPS and never been treated with neuroleptics at all (77). For this reason I think we are justified in discussing EPS and TD separately.

Regarding TD first, it is important to note that the highest risk period for TD is the first 5 years or so of treatment. In a number of studies of TD incidence with typical neuroleptics, the incidence rate is highest in the first 5–10 years of treatment, and tapers off afterwards (78). Thus, one can expect that about 20%
of patients with typical neuroleptics will develop TD in the first 5 years of treatment. Given that the TD prevalence rate after 20–30 years of treatment with typical neuroleptics is thought to be 40–50%, there appears to be a slowing down of TD incidence per year after the first few years of treatment. This means, contrary to popular assumptions, the highest risk of TD is actually in the first 5 years or so of treatment. After that high-risk period, one has selected out a TD-resistant cohort, which seems to develop TD at a rate of about 1% per year, slightly above the spontaneous rate of 0.5% per year (79). This contrasts with the first few years of treatment, where the TD rate with typical neuroleptics is about 5–8% per year. Thus, again contrary to some common assumptions, we have about 3–5 years of experience with the atypical neuroleptic agents, which indicate quite low TD rates. Few cases have been published of TD with atypical neuroleptic agents, and most of these were in individuals previously exposed to typical neuroleptic agents (80). In the clinical trial studies, the reported TD rates for risperidone and olanzapine have been 0.3% and 0.5%, respectively, in the first year of treatment, which means they are at or below the spontaneous rate in schizophrenia (81,82). Thus, the potential risk of TD with atypical neuroleptic medications appears minimal (76). Nonetheless, further data in patients with bipolar disorder are required.

In contrast, EPS, such as akathisia, appear to be more than minimal in the treatment of bipolar disorder with atypical neuroleptic medications. In our experience, akathisia tends to be the major problem. Somewhat surprisingly, it has been shown to occur with agents that frequently have the reputation of low EPS liability, like clozapine and olanzapine. This may be related to the fact that the intrinsic anticholinergic effects of these agents, which reduce parkinsonian tremor and rigidity, are less protective against akathisia (83). Again, we wonder whether this confusion partly has to do with the inclination among many to ignore akathisia as an EPS. Van Putten has clearly shown that this is commonly the case and that akathisia often goes undiagnosed or misdiagnosed as merely agitation (84) or even misinterpreted as mania or psychosis (85)! These scenarios are probably not uncommon; for instance, in a careful study of 80 patients with schizophrenia, 9 (11%) were determined to have worsening of psychosis as a result of subtle akathisia, with improvement with biperiden treatment (86). Unlike other EPS, akathisia is primarily a subjective side effect of an intense inner experience of restlessness and dysphoria, often, though not always, accompanied by observable agitation and restless legs. It is often misdiagnosed; when assessed systematically, van Putten et al. observed it in up to 75% of patients receiving haloperidol (85).

It is important to recognize that akathisia rates in clinical trials may be extreme underestimates. This is mostly due to the special nature of clinical trial designs: the extra-clean nature of research subjects (generally required to have no psychiatric or medical comorbidities, be willing to participate in double-blind research, and be compliant, reliable, and engage in no substance abuse), often...
short periods of follow-up, likely due to inadequate assessment of subtle akathisia symptoms, and lack of assessment of other psychiatric diagnoses like bipolar disorder. The short period of acute clinical trials (usually about one month) is particularly relevant, given that it is estimated that only about 50% of cases of akathisia occur in the first month of treatment, although about 90% occur by 3 months (73). Thus, it will be important throughout this review to keep in mind the limitations of clinical trials and the relevance of naturalistic studies.

Clozapine is widely considered to have a low EPS rate, and indeed it infrequently causes parkinsonian tremor, rigidity, or akinesia; in fact, clozapine is the treatment of choice for psychosis in patients with idiopathic Parkinson’s disease (87). However, it is far from free of akathisia risk. In fact, in one of the early major double-blind studies (88) that established its efficacy in patients who had experienced EPS with typical neuroleptics, clozapine caused akathisia at a rate similar to chlorpromazine (5/75 with clozapine vs. 4/76 with chlorpromazine in 1 month of treatment). In a blind survey of a naturalistic sample of hospitalized psychiatric patients, where researchers systematically and carefully looked for akathisia, they found a 39% prevalence of akathisia with clozapine (n = 23) vs. 45% with typical neuroleptics (n = 29), essentially no difference (89). All patients had been receiving clozapine for at least one month, though at higher doses than is sometimes used today (mean 574 mg/d). Just as with earlier studies with typical neuroleptic agents, akathisia with clozapine heralded a poor prognosis, being associated with greater symptom severity on the Brief Psychiatric Rating Scale (r = 0.55, p < 0.01). In another naturalistic comparison of risperidone (n = 23), clozapine (n = 41), and typical neuroleptic agents (n = 42), akathisia rates were 7.3%, 13%, and 24%, respectively, in over one year of follow-up (90). This study has the benefit of long-term follow-up, but also the disadvantage of excluding those who took these agents for less than 3 months of treatment (some of whom likely developed akathisia). In clinical trials with olanzapine (n = 1796), that agent was reported to have an akathisia rate of 7.0% vs. 21.5% with haloperidol (n = 810) (91). In another report of an apparently different clinical trial, double-blind akathisia rates (based on one side effect rating scale) were 14% with olanzapine (n = 1336) and 35.5% with haloperidol (n = 660) over 6 weeks (92). Overall EPS, including akathisia, were reported in 18.0% with olanzapine and 46.5% with haloperidol. Even in “clean” double-blind conditions, these akathisia rates are not much different than the conservative 20–25% figure reported over three decades with typical neuroleptic agents (73,74,93).

In general, we feel that akathisia is the major EPS of concern with atypical neuroleptics, and it remains a major source of noncompliance or intolerability. *

* Nonetheless, the akathisia rates are lower with atypical than with typical neuroleptic agents, which manifests in many patients as improvement in chronic akathisia when transferred from a typical to an atypical agent, like clozapine (94), though frequently this is not the case (95).
Polypharmacy of Bipolar Disorder

Further, akathisia seems to occur with all atypical neuroleptic agents, regardless of their biochemical differences. Especially in polypharmacy, clinicians should pay close attention to akathisia, and whenever the patient appears more anxious or agitated, akathisia should be the first etiology to be ruled out. Akathisia is associated also with an increased risk of suicide (96), and it is extremely psychologically painful, thus patients should not be allowed to experience it, if possible, for any longer than a few days. Akathisia can occur with serotonin reuptake inhibitors (SRIs) also (97,98); thus, if the combination of a SRI and an atypical neuroleptic is used, even closer attention to the potential risk of akathisia should be given. Treatment of akathisia has been examined in 9 studies of anticholinergic agents, 15 studies of beta-blocking agents, and 6 studies of benzodiazepines, with the beta-blockers evidencing the greatest efficacy (83). In our experience, propanolol remains the most effective option to reduce akathisia, after reducing the neuroleptic dose if possible.

Drug Interactions

Clearly the most problematic mood stabilizer for drug interactions is carbamazepine. It induces most hepatic cytochrome P450 enzyme systems, especially 1A2 and 3A4, thus markedly reducing effective drug levels of other agents metabolized in those systems (57). As a rule of thumb, we assume that the addition of carbamazepine to other agents metabolized by the liver will tend to reduce the effective levels of those drugs by one third to one half. Thus, one would need to increase doses of the other agents correspondingly. In the polypharmacy of bipolar disorder, this is quite a problem since neuroleptics and antidepressants and other mood stabilizers (except lithium, which is excreted unchanged by the kidney) all tend to be affected by carbamazepine’s hepatic induction (57). Oxcarbazepine, an analogue of carbamazepine, has less potent hepatic effects and is likely to be a more useful agent in polypharmacy (99).

Other anticonvulsants cause fewer drug interactions. Divalproex is a mild inhibitor of the hepatic cytochrome P4502D6 system (57). This effect is usually not clinically noticeable, with some exceptions, such as concomitant use of lamotrigine. Divalproex markedly increases blood lamotrigine levels and also increases the risk of rash with lamotrigine (from about 10–15% in lamotrigine monotherapy to closer to 20% in cotherapy with divalproex) (73,74,93). Thus, this combination should be generally avoided, although there is no absolute contraindication to the combination. The concern has to do with the potential for a serious rash, like Stevens-Johnson syndrome.

The novel anticonvulsants have far fewer drug interactions. Gabapentin has none of consequence. Topiramate, when used with carbonic anhydrase inhibitors, possesses an increased risk of producing renal stones. Lamotrigine, as noted, leads to rash more frequently in cotherapy with divalproex (67).
Lithium has a number of potential drug interactions, which are generally well known. Drugs that increase lithium levels, and thus pose a risk of causing lithium toxicity, include nonsteroidal anti-inflammatory drugs (NSAIDs), thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, and some antibiotics (metronidazole, tetracyclines). Theophylline and acetazolamide can decrease lithium levels (57). In our experience, the most common scenario that leads to high lithium levels and toxicity is dehydration, not exactly a drug interaction, but an important clinical concern.

Other side effects that can become burdensome in polypharmacy of bipolar disorder include rash, lipid dysfunction, diabetes, and prolactin effects.

Rash is most often related to the anticonvulsants carbamazepine and lamotrigine. The concern has to do with the potential for a serious rash, like Stevens-Johnson syndrome (SJS). While well-tolerated, lamotrigine has a reported 1/1000 (0.01%) risk of SJS (100). This generalized toxic epidermal rash can be fatal in some individuals. Lamotrigine also has a 10–15% reported risk of a nonserious rash in all individuals. However, any rash is cause for concern and the safest course is to discontinue the drug if any rash occurs. The risk of rash increases in combination treatment with valproate; however. Thus, the former combination needs to be cautiously used; valproate reduces lamotrigine’s hepatic clearance, raising lamotrigine levels, and thus leading to a lower necessary dose. Valproate also increases the half-life of lamotrigine from 25 to 70 hours. In the large open study, the mean dose of lamotrigine used was 287 mg/d in monotherapy and 105 mg/d with valproate (101). The risk of rash is also lower if the drug is titrated slowly; the method used in that study appears reasonable: 25 mg/d for the first 2 weeks, then 50 mg/d for weeks 3 and 4, then increasing 25 mg/week until clinical effect. This titration should be halved in dose with valproate. Some clinicians recommend an even slower titration with an increase in daily dose of only 12.5 mg/week. This more conservative approach may be particularly useful in situations when the urgency of the clinical need for mood stabilization might allow a slower titration. In recent years, using the slower titration, rates closer to 1:6000 have been reported (102). At this rate, the serious rash risks of carbamazepine and lamotrigine are similar. Thus, combination with divalproex should be avoided, and probably the combination of carbamazepine and lamotrigine should also be avoided to minimize their additive rash effects.

The other side effects mentioned again relate to atypical neuroleptic medications. Recent studies suggest that the atypical neuroleptic agents may increase the risk of diabetes mellitus and may adversely alter lipid profiles. In one study over 5 years of treatment in state hospitals with atypical neuroleptics, a 10% rate of new onset diabetes was identified (103). In another study of 25 inpatients with
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Olanzapine was associated with an increase in fasting triglyceride levels from 162 to 222 mg/dL (104). In another evaluation of 14 patients with psychosis, 10 (71%) had elevated insulin levels, 3 (21%) demonstrated increased fasting blood glucose, 8 of 13 (62%) had elevated triglycerides, and 11 of 13 (85%) developed elevated cholesterol levels after a mean of 7.2 months of treatment with olanzapine. These risks seem highest with clozapine and olanzapine (105), which are structurally related molecules. The risk is not secondary to weight gain alone but happens in the short term even in individuals who do not gain weight. There have been cases of fatalities in previously healthy persons who experienced diabetic ketoacidosis with olanzapine (62,106–108). These issues need to be kept in mind in persons with other risk factors for diabetes, and these drugs should probably be avoided in diabetic individuals. The altered lipid profile risk should also be carefully evaluated in persons with hypercholesterolemia and/or coronary artery disease. The prolactin effect has been described more often in relation to risperidone and appears to be associated with clinical symptoms of amenorrhea, galactorrhea, menstrual irregularity, and sexual dysfunction (109). These clinical symptoms are reported to occur in less than 10% of clinical trial subjects with schizophrenia (109), and this rate is consistent with the naturalistic literature in bipolar disorder to date (38). An association between long-term elevated prolactin levels and carcinogenesis has been reported in animal studies (110), but no human data bearing on this topic are available. Osteoporosis, however, is associated with long-term amenorrhea secondary to elevated prolactin use (111). Thus, concerns about prolactin should likely focus on perimenopausal females and childbearing-age females who have some of the clinical symptoms noted above. In general, our practice now is to assess fasting blood sugar, lipid profiles, and prolactin levels in all patients receiving atypical neuroleptic medications and to make dose or drug adjustments according to abnormal findings and patients’ other medical and psychiatric risk factors.

Some agents used to treat bipolar disorder have their own specific risks, like lithium’s renal effects and divalproex’s hepatic effects, but these are not specific to polypharmacy and are well described in the literature. One topic that relates to polypharmacy, however, is lithium’s thyroid effect. Lithium is an antithyroid drug; frequently this leads to a need for thyroid replacement. Thyroid abnormalities are known risk factors for depression and rapid cycling. Not only frank hypothyroidism, but subclinical hypothyroidism (normal thyroid-stimulating hormone, low normal free T4, no physical hypothyroid symptoms) is associated with worse outcome in the treatment of bipolar disorder (13). In a recent study, better outcome in bipolar disorder was associated with free T4 levels in the upper quartile of the normal range, compared with the lower quartile of the normal range, regardless of other medications used (112). With lithium, one often gets in the scenario where the drug may be effective, but it may lower free T4 levels sufficiently to undercut its own benefit. Thus, we have a low threshold to
add thyroid hormone to patients taking lithium, seeking to obtain free T4 levels in the upper quartile of the normal range.

THE ROLE OF POLYPHARMACY IN BIPOLAR DISORDER

In summary, bipolar disorder is one of the psychiatric conditions in which it is very important to distinguish between useful and unhelpful types of polypharmacy. In our opinion, the worst kind of polypharmacy for bipolar disorder tends to commonly combine antidepressant, typical neuroleptic agents, and mood stabilizers. In this ineffective form of polypharmacy, antidepressants are used aggressively, neuroleptics moderately, and mood stabilizers cautiously. We are proponents of the opposite form of polypharmacy, which we believe is supported by the empirical literature. In this approach, mood stabilizers would be used aggressively, atypical neuroleptics frequently, novel anticonvulsants moderately as adjuncts, and antidepressants cautiously. Either way, polypharmacy is employed, and two to five agents are likely to be required, but to improve symptoms and function sufficiently in most patients, we believe that empirically supported polypharmacy is likely to produce better results. In a recent review of NIMH treatment results using approaches similar to those we recommend (only 19% were treated with antidepressants, n = 131 for bipolar subgroup), polypharmacy was associated with higher discharge rates from hospital and a 78% moderate to marked improvement rate overall. The use of three or more medications increased from 3.3% in the 1970s to 9.3% in the early 1980s, 34.9% in the late 1980s, and 43.8% in the early 1990s (113). Thus, polypharmacy based on maximizing mood stabilizers and minimizing antidepressants seems to be an effective approach to treating bipolar disorder.

SUGGESTED GUIDELINES FOR CLINICIANS

In Figures 5 and 6 we have summarized a sequential approach to polypharmacy in bipolar disorder types I and II.

In bipolar disorder type I (Fig. 5), where acute mania may be extreme, Stages I and II may be combined in the stratified approach, using a standard mood stabilizer and an atypical neuroleptic agent together from the start. In less severe manic, mixed, and rapid-cycling states, one can begin with a standard mood stabilizer alone. We then move to atypical neuroleptic medications as our next line of treatment, added to standard mood stabilizers. We are aware that many clinicians would first combine two standard mood stabilizers rather than combine an atypical neuroleptic with a standard mood stabilizer. However, we
can now say that the controlled research literature is more extensive for our approach, and our clinical experience suggests that it is more tolerable for patients and easier to administer (e.g., fewer drug levels to monitor). Novel anticonvulsants are the next line of treatment, followed by electroconvulsive therapy and clozapine, lower down the line due to their risks. At any point, if side effects become intolerable, we recommend that the clinician discontinue whatever agent seems least effective and most likely to contribute to the side effect. Weight gain and cognitive side effects are the most troublesome types in our experience.

In bipolar disorder type II (Fig. 6), where acute mania by definition does not occur spontaneously, we feel that lower doses of standard mood stabilizers like lithium and divalproex can be offered, consistent with some of the current

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**Fig. 5** An algorithm for the polypharmacy of bipolar disorder, type I. Stages II and III can be reversed in order, depending on the clinical setting. (Adapted from Ref. 1.)

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**Fig. 6** An algorithm for the polypharmacy of bipolar disorder, type II.
available research. This may enhance tolerability and acceptability of these agents in this reticent population. If these medications are rejected, we recommend use of novel anticonvulsants, like gabapentin or topiramate, prior to use of antidepressants. Lamotrigine is also an effective option here. As mentioned previously, most research with mood stabilizers occurs in type I bipolar disorder and thus may or may not be generalizable to type II illness. Thus, whereas gabapentin should strictly be used as adjunctive treatment in type I illness, it may have some viability in monotherapy in type II illness. We prefer to use antidepressants, where needed only after having tried at least a novel anticonvulsant alone, or perhaps, if tolerable, a novel anticonvulsant plus an atypical neuroleptic agent. As with bipolar I disorder, it is our preference to taper off an antidepressant, if effective, after 2–3 months of euthymia.

**SUMMARY**

Polypharmacy in bipolar disorder is generally necessary because standard mood stabilizers are too infrequently effective in monotherapy. However, standard mood stabilizers remain the mainstay of the treatment of bipolar disorder and should be the backbone of any polypharmacy regimen. We recommend aggressive use of mood stabilizers (lithium, divalproex, carbamazepine, and probably lamotrigine), augmented by frequent addition of mood-stabilizing adjuncts (atypical neuroleptic medications, other novel anticonvulsants), and infrequent temporary use of standard antidepressants in cases of severe, suicidal depression, or when multiple combinations of mood stabilizers prove insufficiently effective to treat depressive morbidity (preferably paroxetine or bupropion). Our approach to polypharmacy in bipolar disorder can be summarized in the following formula: maximize mood stabilizers, minimize antidepressants. This is the reverse of what appears to be the most common approach to treating bipolar disorder, an ineffective polypharmacy that frequently involves mixtures of antidepressants, neuroleptics, and insufficient doses or combinations of mood stabilizers. Thus, polypharmacy is quite a double-edged sword in the treatment of bipolar disorder: it can lead to improvement, but it usually is practiced ineffectively. Even when expertly applied, however, this approach to polypharmacy suffers from an often difficult side effect burden, primarily related to weight gain and cognitive impairment.

The key to the successful polypharmacy of bipolar disorder is to focus on the long term, stabilizing mood swings and preventing episodes by using mood stabilizers. A major mistake is to focus on acute symptoms, now depression, now mania, which leads to a chasing of one’s tail as antidepressants and neuroleptics alternately cause mania and depression. Bipolar disorder, perhaps more than any other psychiatric condition, brings home the dictum of Phillipe Pinel: “In dis-
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eases of the mind . . . it is an art of no little importance to administer medicines properly; but, it is an art of much greater importance and more difficult acquisition to know when to suspend or altogether to omit them” (114).

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INTRODUCTION

It is often optimistically estimated that 60–80% of persons with depression will respond to an antidepressant. The reality of treating depression is much more complex and often entails polypharmacy. The estimate of up to 80% response rate with depression is based on randomized clinical trials, which frequently are not generalizable to the real-world setting. In the real world, the treatment of depression can be complicated by substance abuse, medication noncompliance, and anxiety comorbidity, all conditions screened out of clinical trials. Further, clinical trials are usually of short duration (less than 2 months), and patients sometimes lose some or all of their benefit with an antidepressant medication over time. Clinical trial definitions of response with an antidepressant are also usually based on 50% or more improvement in depression rating scale scores. In clinical practice, such individuals, though improved, continue to have significant symptoms or may not have recovered functionally (at work and interpersonally).

Though at first glance polypharmacy would seem to be relatively unnecessary in treating depression, clinical experience suggests that it is not uncommon. In this chapter we will review studies of combination treatments for depression and discuss the clinical scenarios in which polypharmacy of depression occurs.
BASIC CONCEPTS

A few basic concepts need to be clarified. First, there is no consensus on a definition of polypharmacy in depression. However, for the purposes of this chapter, the definition offered in the first chapter of this book will be used: polypharmacy will be defined as the use of two or more agents specifically for the treatment of depression. An example would be the combination of two antidepressants, such as serotonin reuptake inhibitor (SRI) and a tricylic antidepressant (TCA). However, would it be considered polypharmacy if a clinician were to use a medication for sleep (such as trazodone in low dose) along with an SRI? Or if a clinician were to use a benzodiazepine for comorbid anxiety along with a TCA? For our purposes, we will not define a treatment to be polypharmacy if only one agent is used primarily for depression and if only one other agent is used primarily for short-term treatment of depression-related symptoms, such as insomnia or anxiety. However, if three or more medications are used for whatever purpose, then the term polypharmacy would seem appropriate.

Thus, in this chapter we will review studies of two antidepressants combined in the treatment of depression. We will also include studies of augmenting agents, where the second agent is added specifically to treat the entire depressive syndrome, such as lithium or thyroid hormone. This raises a second basic concept.

It is important to recognize that “depression” comes in two flavors: unipolar and bipolar. In fact, we like to view unipolar depression as a diagnosis of exclusion, once one has ruled out bipolar depression. This is because bipolar depression is frequently misdiagnosed as unipolar depression, whereas the reverse scenario seems infrequent. Since even (and only) one manic or hypomanic episode at any point in one’s life is sufficient to diagnose bipolar depression, the patient who presents with depression needs to have an extremely careful assessment of past manic or hypomanic symptoms. In other words, one cannot diagnose unipolar depression until one has ruled out bipolar depression. Empirical studies suggest that about 40% of patients with bipolar disorder are initially misdiagnosed as having unipolar depression (despite seeking help from mental health professionals after their first manic episode) (1,2).

It is important to make a distinction between unipolar and bipolar depression because the treatments are radically different (3). We discussed the polypharmacy of bipolar depression in Chapter 2. In this chapter, the entire discussion will relate only to unipolar depression. Nonetheless, it is the responsibility of the clinician to accurately and meticulously make the diagnostic distinction, otherwise all the relevant treatment data will be of no use. Another basic concept is that polypharmacy of depression, at least in terms of controlled studies, mainly involves the treatment of refractory depression. In other words, controlled studies of polypharmacy in depression are essentially studies of treatment-resistant de-
Polypharmacy of Depression

pression. Thus, there will be a great deal of overlap between the literature reviewed here and reviews of the treatment-resistant depression literature.

STUDIES OF COMBINATION AND AUGMENTATION TREATMENTS IN UNIPOLAR DEPRESSION

The main research studies on combination and augmentation treatment of unipolar depression have involved combining SRIs and TCAs, adding lithium, thyroid hormone, or buspirone to standard antidepressant agents. We will mainly highlight controlled studies of these agents (i.e., studies which have a drug or placebo comparison arm), but if clinically relevant we will also review uncontrolled or nonrandomized reports.

SRIs + TCAs

There have been five studies of the combination of SRIs and TCAs in unipolar depression (n = 79) (Table 1). Though the majority of research conducted on SRI/TCA combinations has been uncontrolled, the evidence nevertheless suggests it may be an effective approach to take in treating refractory depression.

In the first clinical study of a SRI/TCA combination (4), 30 patients refractory to various non–monoamine oxidase inhibitor (MAOI) antidepressants (mainly TCAs), were given fluoxetine in addition to their medication regimens. Retrospective analysis showed that 26 patients showed improvement in amelioration of depressive symptoms. This first study suggested that combined antidepres-
sant treatment might be particularly effective in improving positive response in refractory patients (4).

In a small, preliminary, open trial, other investigators (5) described a similar response of 8 patients to a TCA/SRI augmentation strategy. Fluoxetine, sertraline, or fluvoxamine were added to ongoing nortriptyline treatment in patients who had been previously resistant to other medication trials and/or electro convulsive therapy (ECT) intervention. In each case this approach produced appreciable improvement where other strategies had yielded ineffective results in treating depressive symptoms (5). Taken together, both studies (4,5) provide evidence, though uncontrolled, that a TCA/SRI combination strategy may be an efficacious choice in treating refractory depression.

In the first controlled (though nonrandomized) study of a TCA/SRI combination in treating refractory depression (6), 14 patients received a combination of desipramine plus fluoxetine during a 4-week open-label trial. These 14 patients were compared retrospectively to 52 other patients who had received desipramine alone. Though this study was not randomized, all patients were inpatients and were rated prospectively with similar instruments. Overall, the investigators (6) found that depressed patients who received the combination of desipramine and fluoxetine experienced shorter latency to antidepressant effect than did subjects in the desipramine alone group. In another recent open-label study (7) of patients who had failed a TCA (desipramine or imipramine) and fluoxetine separately, 7 of 13 responded to the combination.

Recently, results from the only randomized study examining the TCA/SRI combination in patients suffering from refractory depression were reported (8). After failing to respond to 8 weeks of fluoxetine treatment, 41 patients were randomly assigned to one of three blinded treatment conditions: high-dose fluoxetine, fluoxetine + desipramine, or fluoxetine + lithium. Overall, the patients who were treated with high-dose fluoxetine experienced a higher rate of depressive symptom amelioration than the two other augmentation groups. Neither desipramine nor lithium when added to fluoxetine significantly decreased depressive symptoms in refractory patients. In contrast to previous research and anecdotal evidence, TCA augmentation to fluoxetine in this randomized study did not yield a clinically significant improvement.

In summary, surprisingly few controlled studies of TCA/SRI combinations have been conducted, and the one available randomized study failed to find much benefit with the combination. However, clinical experience suggests it may still have some validity, and further controlled research is warranted.

**Lithium Augmentation**

There have been 11 controlled studies of lithium augmentation in unipolar depression ($n = 321$) (Table 2). All of these studies have involved adding lithium to
## Table 2 Controlled Studies of Lithium Augmentation in Unipolar Depression

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>n</th>
<th>Design</th>
<th>Response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Montigny et al., 1983 (11)</td>
<td>39</td>
<td>DB/H11001</td>
<td>+50% improved w/in 48 hours</td>
<td>Highlighted rapid response of lithium augmentation</td>
</tr>
<tr>
<td>Heninger et al., 1983 (12)</td>
<td>15</td>
<td>DB, placebo</td>
<td>5 responded w/in 24–48 hours, others at day 6</td>
<td>Highlighted lack of universal rapid response</td>
</tr>
<tr>
<td>Kantor et al., 1986 (15)</td>
<td>7</td>
<td>DB, placebo</td>
<td>1 response w/in 48 hours, later relapsed</td>
<td>No significant difference b/t lithium and placebo</td>
</tr>
<tr>
<td>Delgado et al., 1988 (17)</td>
<td>28</td>
<td>DB/H11005</td>
<td>29% lithium plus fluvoxamine responded</td>
<td>Early SRI/lithium combo strategy</td>
</tr>
<tr>
<td>Zusky et al., 1988 (16)</td>
<td>16</td>
<td>DB, placebo</td>
<td>No improvement noted</td>
<td>No significant difference b/t lithium and placebo</td>
</tr>
<tr>
<td>Schopf et al., 1989 (13)</td>
<td>27</td>
<td>DB, placebo</td>
<td>22% improved w/in 48 hours</td>
<td>Therapeutic effect increased toward end of 1-wk DB period</td>
</tr>
<tr>
<td>Stein et al., 1993 (14)</td>
<td>33</td>
<td>DB/H11005</td>
<td>18% responded to 250 mg, 44% to 750 mg, 22% to placebo</td>
<td>Helped establish lithium dosing parameters</td>
</tr>
<tr>
<td>Fava et al., 1994 (8)</td>
<td>41</td>
<td>DB/H11005</td>
<td>29% responded to lithium, 53% to high-dose fluoxetine</td>
<td>Lithium augmentation not superior to high-dose fluoxetine alone</td>
</tr>
<tr>
<td>Katona et al., 1995 (18)</td>
<td>62</td>
<td>DB, placebo</td>
<td>52% improved, no rapid response observed at all</td>
<td>Adjunct lithium effective, regardless of antidepressant class</td>
</tr>
<tr>
<td>Baumann et al., 1996 (19)</td>
<td>24</td>
<td>DB/H11005</td>
<td>58% responded (lithium plus citalopram)</td>
<td>Subjects resistant to SRI treatment</td>
</tr>
<tr>
<td>Bauer et al., 2000 (20)</td>
<td>29</td>
<td>DB, placebo</td>
<td>0% relapse with continuous lithium treatment</td>
<td>Examined long-term treatment for adjunct lithium responders</td>
</tr>
</tbody>
</table>

DB = Double-blind.
TCAs or SRIs as an adjunct intervention for nonresponders and partial responders. Lithium augmentation has been one of the most popular strategies for treating refractory depression. In terms of literature and research, this approach appears to be the best established out of all polypharmacy tactics for treatment resistant depression. Over time, the efficacy of lithium augmentation helped enhance the legitimacy of augmentation strategies in the field as a whole (9).

De Montigny and colleagues are generally credited with the initial report of eight TCA-resistant patients responding positively to lithium augmentation (10). In that study, the investigators reported a remarkably rapid alleviation of depressive symptoms in TCA-resistant patients within 48 hours of taking lithium. Though uncontrolled, this study gave rise to further investigation into the therapeutic effect of adjunct lithium intervention. De Montigny and associates (11) went on to look at lithium augmentation to TCA-resistant depression under controlled conditions. They reported that lithium augmentation of TCA medications in refractory patients resulted in greater than 50% improvement of depressive symptoms within a 48-hour period compared with no improvement in patients taking adjunct placebo.

In another double-blind placebo-controlled study of 15 TCA nonresponders with unipolar major depression, TCA treatment was continued (desipramine, amitriptyline, or mianserin) and patients were randomized to receive either a placebo or lithium addition (12). Adding lithium to ongoing antidepressant therapy did in fact produce a statistically significant and meaningful improvement in depressive symptomatology (according to nursing reports of depressive ratings). However, this improvement was slower (6 days for mean onset) than in the previous report (48 hours) (11). In another study (13), 27 endogenous TCA-resistant depressed patients again responded to lithium augmentation compared to placebo. However, only 22% of patients improved in 48 hours.

Another study (14) reported on varying doses of lithium in treatment-resistant depressives. Thirty-three TCA nonresponders were randomly assigned to the adjusted-dose treatment group (n = 16) or to the placebo/low-dose group (n = 18). Subjects in the treatment group received 250 mg of lithium in addition to ongoing TCA medication. After 3 weeks the lithium dose was increased to 750 mg taken daily for 6 weeks. Subjects in the placebo/low-dose group received placebo for 3 weeks, followed by 250 mg of lithium for the remaining 6 weeks of the study. Using the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS), the investigators (14) found that improvement in treatment-resistant depression is significantly greater with 750 mg than 250 mg of lithium. Further, results indicated that a low dose of 250 mg of lithium was no better than placebo in alleviating symptoms of depression.

Two small studies did not find benefit with lithium augmentation of TCAs. In the first study, 4 subjects received lithium and 3 subjects received placebo.
added to their ongoing TCA therapy (amitriptyline, amoxapine, imipramine, or doxepin). Within 48 hours, only one subject had significantly responded to the adjunct lithium administration, but subsequently relapsed within one week (15). In the second study, 16 patients judged to be refractory to a TCA medication (amitriptyline, trazodone, imipramine, desipramine, maprotiline, doxepin, nor-tripryline, or phenelzine) were randomly assigned to lithium (n = 8) or placebo (n = 8) augmentation over a period of 2 weeks (16). Overall, no significant difference was found in speed or degree of improvement between individuals in the adjunct lithium group and placebo group. These two studies are far from conclusive, however, since their small sample sizes elevate the risk of type II error due to inadequate statistical power.

With the advent of the SRIs, interest grew in using lithium to augment SRI effects. An early SRI study (17) examined the role of fluvoxamine in treatment-resistant depression in conjunction with lithium and neuroleptic agents. Twenty-eight refractory patients completed a blinded protocol in one of three conditions: fluvoxamine alone, fluvoxamine + lithium, or fluvoxamine + lithium + perphenazine. After 4–6 weeks of treatment, 29% (8 patients) responded to fluvoxamine alone, 29% (8 patients) responded to lithium augmentation of fluvoxamine, and 7% (2 patients) responded to fluvoxamine + lithium + perphenazine (17). Response rates in this study were rather low and not any better with lithium added to fluvoxamine than with fluvoxamine alone.

As discussed in the previous section, Fava and colleagues (8) compared efficacy of various augmentation strategies in patients who failed to respond to 8 weeks of 20 mg/day fluoxetine treatment. Forty-one patients were randomly assigned to one of three blinded treatment conditions: high-dose fluoxetine (40–60 mg/day), 20 mg/day fluoxetine plus 25–50 mg/day desipramine, or 20 mg/day fluoxetine plus 300–600 mg/day lithium. Overall, the patients who were treated with high-dose fluoxetine experienced the highest rate of depressive symptom amelioration compared to the two other augmentation groups as judged by the Hamilton Depression Rating Scale. Neither augmentation agent was found to be particularly effective in decreasing depressive symptoms.

Conflicting results were found in another study, however (18). Sixty-two patients who had failed a previous controlled trial of fluoxetine or lofepramine (a TCA) were treated with either adjunctive lithium or placebo for 6 weeks. Improvement in depressive symptoms was seen more frequently in patients receiving adjunct lithium carbonate (15/29) than in those receiving antidepressant plus placebo (8/32). HAM-D scores were significantly lower in the lithium group than in the placebo group, yet no differences in efficacy of lithium augmentation were noted between fluoxetine and lofepramine. This study suggests that lithium augmentation may be a useful strategy in treating refractory depression, regardless of the classification of antidepressant (TCA or SRI).

In another study (19), of 69 depressed patients treated with citalopram daily
for 4 weeks, 24 were judged to be nonresponsive. The nonresponsive patients were then randomized under double-blind conditions into a citalopram + lithium group or citalopram + placebo group. After one week lithium augmentation was found to be superior to placebo in alleviating depressive symptoms. Adding lithium to citalopram-resistant patients resulted in improvement in 58% of initial nonresponders.

While most of this research has focused on acute response rates, there has been little investigation into prophylactic benefits in preventing relapse into major depression. One of the few such studies (20) involved 29 patients deemed resistant to individual antidepressant medications, all of whom received lithium augmentation for 6 weeks. Responders to lithium/antidepressant therapy were randomized under double-blind conditions to continuous lithium treatment + antidepressant or antidepressant + placebo. After 4 months of treatment, relapse in depressive symptoms occurred in 47% (7/15) of patients who received antidepressants + placebo. None of the 14 patients who continued to receive the lithium/antidepressant medication combination suffered a relapse (20). After taking lithium in conjunction with an antidepressant for over 5 months, formerly refractory patients were able to achieve and maintain remission. Though further research is necessary to validate and replicate these important findings, continuous lithium augmentation appears to hold promise in preventing relapse of major depression in otherwise refractory patients.

In summary, most of the controlled evidence, though not all, suggests that lithium may possess efficacy in augmenting the acute effects of antidepressants as well as preventing relapse.

**Thyroid Hormone Augmentation**

There have been four randomized placebo controlled studies of thyroid hormone augmentation in treating unipolar depression ($n = 117$) (Table 3).

Goodwin and colleagues (21) gave adjunctive triiodothyronine to 12 inpatient subjects judged to be resistant to either imipramine or amitriptyline (150–300 mg/day) after 26–112 days in this double-blind augmentation study of L-triiodothyronine (T3). After the addition of 25 µg/day (10 patients) or 50 µg/day (2 patients) of T3, 9 patients showed statistically significant improvement in depression scores. Eight of these patients were found to be markedly improved. Goodwin and colleagues (21) described improvement in these TCA nonresponders as occurring within 1–3 days of initiation of T3 augmentation. Individual patient improvement occurred across all areas of depressive symptomology, and overall side effects were low.

Conflicting results were found in another report (22). Sixteen depressed individuals who were unresponsive to imipramine therapy after 4 weeks partici-
Table 3  Controlled Studies of Thyroid Hormone in Unipolar Depression

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>n</th>
<th>Design</th>
<th>Response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goodwin et al., 1982 (21)</td>
<td>12</td>
<td>DB, placebo</td>
<td>75% improved</td>
<td>None</td>
</tr>
<tr>
<td>Gitlin et al., 1987 (22)</td>
<td>16</td>
<td>DB, placebo, crossover</td>
<td>No significant improvement</td>
<td>None</td>
</tr>
<tr>
<td>Joffe et al., 1990 (23)</td>
<td>38</td>
<td>DB</td>
<td>53% response to T3, 19% to T4</td>
<td>T3 somewhat superior to T4</td>
</tr>
<tr>
<td>Joffe et al., 1993 (24)</td>
<td>51</td>
<td>DB, placebo</td>
<td>10/17 responded to T3, 9/17 to lithium</td>
<td>T3 = lithium &gt; placebo</td>
</tr>
</tbody>
</table>

DB = Double-blind.

itated in this study. Subjects were randomly assigned to either a T3 treatment group or a placebo group. After 2 weeks of intervention, the patients were crossed over to the other treatment regimen for an additional 2 weeks. All of the subjects improved over time, regardless of whether they received placebo or T3.

In addition to triiodothyronine (T3), thyroxine (T4) has also been studied for antidepressant effect. Since thyroxine (T4) is converted to triiodothyronine (T3) physiologically, it seems reasonable that T4 would have a similar antidepressant effect as T3. One study (23) pitted these two thyroid hormones against each other in a randomized, double-blind evaluation. Thirty-eight outpatients with unipolar major depression who were judged to be resistant to imipramine or desipramine received 3 weeks of thyroid hormone intervention. Significantly more patients responded to T3 than T4.

In another study (24), a direct comparison of triiodothyronine (T3) and lithium augmentation was conducted. Under double-blind, placebo-controlled conditions, 51 subjects entered the study who had previously failed to respond to either desipramine (n = 46) or imipramine (n = 5) in a previous 5-week antidepressant trial. Nonresponding subjects were randomly assigned to receive T3, lithium, or placebo as augmentation. Both lithium and triiodothyronine were significantly superior to placebo, and equal to each other, in augmenting antidepressant response in TCA nonresponders.

In summary, thyroid hormone augmentation appears to be an effective strategy in the polypharmacy of refractory depression. There is some indication that T3 may be somewhat more effective than T4, and thyroid augmentation may be equally as effective as lithium augmentation. Further research on thyroid augmentation with SRI agents is needed, since the controlled literature to date is limited to TCAs.
Other Combination and Augmentation Studies

In more recent years, other combination and augmentation strategies in treating refractory depression have been employed. Each study offers further insight into underlying mechanisms involved in treatment resistant depression and possible intervention strategies. Pindolol, a beta-adrenoceptor/5-HT receptor antagonist, has been reported to accelerate the antidepressant action of serotonin reuptake (25). In a controlled study (25), investigators found that a greater number of depressed patients improved with fluoxetine + pindolol (75%) than with fluoxetine + placebo (59%). This study agrees with other open (26) and double-blind studies (27,28). No particular predictor of pindolol response has been identified (29).

Although pindolol appears to improve initial response rate of depressed individual when administered in conjunction with a SRI, the question remained whether pindolol could augment the antidepressant response in nonresponsive patients. Consequently, Perez et al. (30) examined whether the addition of pindolol to ongoing SRI therapy could induce a rapid response in patients with treatment-resistant depression. Eighty outpatients with major depression who did not respond to SRI treatment (clomipramine, fluoxetine, fluvoxamine, or paroxetine) after a minimum of 6 weeks were included. Subjects were randomly assigned to receive placebo or pindolol for 10 days in addition to their respective SRI medication. Pindolol was not found to elicit a therapeutic response in treatment-resistant patients at the end of the trial (30). Most placebo-controlled studies of pindolol agree that it does hasten antidepressant effect in treating major depression. In treating refractory depression, however, this study and others suggests that pindolol may not be an effective augmenting agent to SRI therapy (31,32).

Buspirone has also been used as an adjunct agent to SRI therapy in treating refractory depression. Many case reports and open studies report therapeutic effects of buspirone augmentation to various SRIs in treating refractory depression. In the only placebo-controlled study (33), 119 patients who had failed to respond to a minimum of 4-week SRI intervention (citalopram or paroxetine) were randomly assigned to either an SRI + placebo group (n = 61) or a SRI + buspirone group (n = 58). Of patients from the SRI/buspirone group, 50.9% responded, compared with 46.7% in the placebo group, a statistically nonsignificant difference. Though adding buspirone to a SRI appears to be a well-tolerated treatment regimen, this controlled study failed to demonstrate any efficacious difference between the buspirone group and the placebo group (33).

Because refractory depression affects so many patients taking antidepressant medication, it is necessary to continue to try novel, adjunct approaches to treatment. Antipsychotic medications have been shown to exhibit antidepressant activity, both alone and in conjunction with an antidepressant medication (34). Using typical antipsychotic agents in treating refractory depression raises con-
Polypharmacy of Depression

cerns because of the increased risk of extrapyramidal symptoms and tardive dyskinesia. Newer atypical antipsychotic medications, however, pose a lesser risk of these side effects (35).

In a recent randomized double-blind trial (36), 28 nonpsychotic unipolar depressed patients were identified who had prospectively failed to respond to a therapeutic trial of fluoxetine. They were then randomly assigned to one of three double-blind groups: olanzapine/placebo, fluoxetine/placebo, or olanzapine/fluoxetine. After 8 weeks, the combination group achieved a greater improvement in ameliorating depressive symptoms over each agent alone, as judged by the MADRS. All three treatments were well tolerated with a relative absence of acute extrapyramidal symptoms. Weight gain, however, was a significant treatment effect of the olanzapine, both alone and combined with fluoxetine, with subjects gaining an average of 6 kg.

Other approaches to polypharmacy in refractory depression, such as the combination of bupropion and SRIs, are common and have been recently reviewed elsewhere (37). We could identify few other controlled studies of polypharmacy, however.

PSYCHOTIC UNIPOLAR DEPRESSION

Psychotic unipolar major depressive disorder is a condition in which polypharmacy has been the recognized standard of care. Current reviews of this evidence continue to support polypharmacy for this condition (38). In this section we will review some of this evidence.

There have been four randomized clinical trials of antidepressants and antipsychotic agents for psychotic depression and one nonrandomized comparison. A number of recent meta-analyses have also been conducted.

In the first controlled study of the topic (39), Spiker and associates examined 51 patients who were randomized to receive either amitriptyline, perphenazine or the combination. The authors made the classic observation that the antipsychotic agent alone was less effective (19%) in psychotic depression than the antidepressant alone (41%). However, antidepressant monotherapy was much less effective than the combination of the two agents (78%). Later, Anton and Burch (40) showed that amoxapine, a tricyclic antidepressant with antipsychotic effects, was equally effective to the combination of amitriptyline and perphenazine in a double-blind trial of 38 subjects. A recent study (41) of the SSRIs sertaline and paroxetine reported that both agents were effective in monotherapy in 46 psychotic depressed patients. However, this study included 14 bipolar subjects and also had a high dropout rate, and thus is difficult to interpret.

Two recent meta-analyses conclude that ECT is the most effective treatment for psychotic depression, with the largest effect size and overall 82% re-
response rate, followed by the tricyclic antidepressant/typical antipsychotic combination (77% response rate) and typical antipsychotic agent alone (51% response) (42,43).

Recently, many reports have suggested that atypical antipsychotic agents may possess more mood-stabilizing and/or antidepressant benefits than typical antipsychotic agents (44). For this reason, interest in studying these agents in mood disorders has increased greatly. Numerous studies have shown efficacy for these agents in mania and have suggested longer-term mood-stabilizing benefits (45). Fewer studies have been conducted in depression (46). As noted previously, one double-blind study of olanzapine found evidence of adjunctive, but not monotherapy, efficacy in treatment-resistant nonpsychotic unipolar depression (36). In psychotic depression (n = 30), a retrospective nonrandomized comparison study indicated that olanzapine + antidepressants (67%) produced higher response rates than typical neuroleptics + antidepressants (27%) (47).

The only published double-blind randomized clinical trial of an atypical antipsychotic agent in psychotic depression involves risperidone (48). In that German multicenter study, risperidone monotherapy was compared with the combination of amitriptyline + haloperidol. The study included 123 subjects with psychotic unipolar major depressive disorder (n = 38), schizoaffective disorder (n = 66), or schizophrenia with depressive symptoms (n = 19). Ninety-eight subjects completed the study, with a 51% response rate in the risperidone group vs. 70% in the haloperidol/amitriptyline group, a statistically significant difference. In the absence of a placebo group, one cannot be certain that the risperidone response rate was clinically meaningful, but in the context of the larger literature, a 51% response rate with antipsychotic alone may be clinically relevant. It is also notable that risperidone was particularly effective in the schizoaffective and schizophrenic groups, and that most of the difference in efficacy in this study was due to a lower response rate in the unipolar psychotic depressed group with risperidone monotherapy. A last point of perhaps some importance is that the mean risperidone dose in this study was 6.9 mg/day. However, the putative antidepressant effects of atypical antipsychotic agents is thought to be maximized at low doses, e.g., 1–3 mg/day of risperidone, where the serotonin-2 receptor blockade effect of these agents is maximal and the dopamine blockade effect of these agents is limited (45). In summary, this study is difficult to interpret but suggests some efficacy with risperidone monotherapy, more so in schizoaffective depression than in unipolar psychotic depression, and less than with polypharmacy of antidepressants plus typical neuroleptics.

In summary, the early literature with atypical antipsychotic agents suggests that these medications may well have more benefit in psychotic depression than do typical antipsychotic agents. However, they still tend to require polypharmacy with standard antidepressant medications for maximal benefit.

In psychotic depression, polypharmacy continues to be the rule. Thus, ade-
**Table 4**  Comparison of Switch and Combine Approaches

<table>
<thead>
<tr>
<th>Switch approach</th>
<th>Combine approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fewer side effects</td>
<td>More controlled studies</td>
</tr>
<tr>
<td>Better for initial complete nonresponse</td>
<td>Better for initial partial response</td>
</tr>
<tr>
<td>May identify single biochemical target</td>
<td>May benefit from multiple biochemical targets</td>
</tr>
<tr>
<td>Better compliance</td>
<td>Provides additive benefit with each drug</td>
</tr>
<tr>
<td></td>
<td>Unlikely to run out of treatment options</td>
</tr>
</tbody>
</table>

Sufficient treatment should involve use of both an antipsychotic and an antidepressant. Frequently, one or the other of these agents is ignored, as the patient’s psychosis or depression may be more recognized in isolation. For instance, in one study of patients judged to be “treatment-refractory” and referred for ECT, only 4% had received at least one adequate trial of a combination of antipsychotic + antidepressant for 4 weeks (49). Forty-seven percent had received no or minimal antipsychotic treatment. The flipside of this underuse of antipsychotics in this population is the underuse of antidepressants. In another study of psychotic versus nonpsychotic unipolar depression (43), only 51% of the psychotic group had ever been prescribed antidepressants, compared with 80% of the nonpsychotic group. Thus, perhaps due to a mistaken general opposition to polypharmacy, patients with psychotic unipolar depression are often undertreated.

**SPECIFIC ROLE OF POLYPHARMACY: ADVANTAGES AND DISADVANTAGES**

The basic question that arises in the treatment of depression is whether one should take the switch approach or the combine approach. The switch approach would be to take someone off an ineffective antidepressant, and then to try a completely new one. The combine approach would entail polypharmacy, keeping someone on an ineffective antidepressant and then adding another agent to augment its effect. There are advantages and disadvantages to each approach (Table 4).

From the perspective of empirical evidence, there have been more controlled studies of polypharmacy in depression than of switching from one antidepressant to another. This is partly the result of the influence of FDA regulations. As discussed in Chapter 1, since the FDA mandates parallel design studies of antidepressants but does not recognize a need for crossover studies, most con-
trolled studies use a parallel design. Crossover design studies would provide controlled data regarding the likelihood of responding to a specific antidepressant after a patient has not responded. While some of these studies exist, they are uncommon (50, 51).

Recently, the first study was conducted directly comparing the switching and augmenting approaches. In a naturalistic, open-label design, 74 unipolar non-psychotic depressed outpatients were treated with one or the other approach after nonresponse to at least one antidepressant at therapeutic doses for 4 weeks. Switch of antidepressant usually, though not always, involved moving from one antidepressant class to a biochemically different one. Augmentation generally involved the combination of two antidepressants or the addition of buspirone to SRIs. Lithium and thyroid hormone were not included in the augmenting strategies in this study. Overall, 56% (n = 20) responded to augmentation treatments, compared to 45% response in those who switched to a different antidepressant. This difference was not statistically significant but suggests perhaps some added benefit to the polypharmacy approach. Of those who did not respond to the first switch or augmentation (n = 18), 50% responded to a second treatment trial.

The polypharmacy approach has the advantage of additive benefits, that is, each added medication, provided it has at least some partial benefit, continues to add to the benefit of previous medications, as the patient inches closer and closer to maximal improvement. Thus, if the first antidepressant were to reduce depressive symptom burden by 50% (to use an arbitrary measure and figure), then the second might reduce it by another 20% of the original total, and a third augmenter by another 10%, leading to a total 80% reduction of original symptom burden. By taking the switch approach, one would be relying on a single antidepressant to reduce the entire symptom burden by itself, which frequently does not happen. As mentioned, randomized clinical trials of antidepressants define significant clinical response as a 50% reduction of symptom burden (using rating scales such as the HAM-D). Using that definition, such trials tend to report drug response rates of about 50–70% (51). Some patients undoubtedly have complete or near-complete remission of all depressive symptoms, but that group would be less than 50–70%. Thus, factoring in other aspects of real-world practice (like substance abuse) that limit treatment response compared to clinical trials, it is likely that only a minority of even standard unipolar depressed patients will respond sufficiently to a single antidepressant. This way of looking at things may explain why and when polypharmacy might be useful in the treatment of unipolar depression.

Another important issue is the question of achieving remission. It has been recognized that syndromal response in mood disorders often does not translate into functional response (52). In other words, patients frequently respond enough to an antidepressant (or a mood stabilizer for bipolar disorder) so that they are no longer diagnosable with a major depressive episode. This is often defined in
research studies as a 50% or more reduction in mood symptom rating scale scores. However, patients may still experience mild, but somewhat troublesome, depressive symptoms that do not completely resolve. In other words, the syndrome has “responded” to treatment, but full “remission” has not been achieved (53). The failure to achieve full remission is associated with continued functional impairment despite improvement in most depressive symptoms; patients frequently are unable to return to work or to enjoy their personal lives at premorbid levels. In these cases, an argument can be made for polypharmacy with medications, even after initial “response” to a single antidepressant, so as to remove even minor depressive symptoms (53). Of course, similar effects might be achieved by the combination of antidepressant and psychotherapy treatments (54).

It is noteworthy that some pharmaceutical companies are emphasizing the multiple biochemical effects of their antidepressants as being particularly useful. This is, in a way, “polypharmacy in one pill,” we might say. For instance, the makers of the drug venlafaxine have marketed it as being particularly beneficial since it inhibits norepinephrine as well as serotonin reuptake. They thereby imply that it will be more effective than SRIs, which “only” block serotonin reuptake. However, it is important to distinguish marketing points from potentially real scientific issues here. First, SRIs are not truly “selective” for serotonin (which is why we, along with some others, have taken to dropping the first “S” in the acronym) Fluoxetine demonstrates some norepinephrine reuptake blockade, which in some in vitro studies is similar in potency to venlafaxine (55). Sertraline shows evidence of significant dopamine reuptake blockade, perhaps even more in vitro than bupropion. And paroxetine is a moderate blocker of acetylcholine receptors. Thus, the SRIs do other things besides inhibiting serotonin reuptake. However, venlafaxine does not block norepinephrine reuptake until it is used in higher doses (>150 mg/day); below those doses, it functions essentially as an SRI (56). Thus, the presumed differentiation between these agents is not straightforward. More importantly, the real scientific question is whether multiple biochemical mechanisms, by polypharmacy or in a single drug, improves efficacy.

When the SRIs became available about a decade ago, it was hypothesized that by focusing on a single neurotransmitter mechanism of action (serotonin), they would possess certain advantages over the tricyclic antidepressants (which generally inhibited the reuptake of both serotonin and norepinephrine). One advantage was thought to lie in fewer side effects, not only because SRIs lacked the other receptor effects of TCAs (anticholinergic, antihistaminic, and antiadrenergic effects), but because the SRIs would lack side effects associated with norepinephrine reuptake (agitation, perhaps increased risk of mania, palpitations). If SRIs were as effective as TCAs—in other words, if norepinephrine reuptake was not necessary or additively beneficial—then the SRIs would be preferable. There have been many studies of SRIs compared to TCAs in unipolar depression.
(57), mostly done by pharmaceutical companies for regulatory approval, and thus mostly aimed at showing no difference between the two groups. In most cases, no difference was shown. The pharmaceutically sponsored studies were not designed, it should be noted, either in sample size or patient characteristics, to show more benefit with SRIs than TCAs, since that was not required by government regulators. Once the SRIs hit the market, their greatly reduced side effect profile led to their quickly overcoming TCAs in frequency of use. However, in a study in hospitalized patients with melancholic depression, investigators reported more benefit with TCAs than with SRIs (58), and in another study others described more benefit with venlafaxine than with SRIs (59). If one conceives of melancholia as a somewhat more severe form of depression, then these studies might suggest that drugs that inhibit both serotonin and norepinephrine reuptake might be more effective in severe depression than drugs that only inhibit serotonin reuptake. This conclusion would be consistent with the controlled evidence reviewed above indicating greater efficacy with the combination of SRI + TCA than with SRI alone.

Thus, these studies suggest that polypharmacy, or “polypharmacy in a single pill” (drugs with multiple biochemical effects), might be the most effective means of treating depression. However, the problem of side effects persists, and this literature is too nascent for us to be inclined to sweeping conclusions.

It would seem much more prudent for clinicians to continue to use antidepressants alone at times, and in combination at times, depending on the circumstances.

SUGGESTED GUIDELINES FOR CLINICIANS

It is common sense to begin with one antidepressant in the treatment of depression. Except in extreme cases, most patients can and want to be involved in the decision-making process. What we recommend is simply to describe the main antidepressants that are available, their basic mechanisms and side effects, and then to let patients choose which agent they wish to use. This approach has many advantages. First, there is no compelling scientific basis for using one agent, or even one class of agents, before another. If the doctor makes the decision, it will likely be on the basis of habit or, worse, marketing influences. Frequently patients, for one reason or another, prefer one agent or another; this may have to do with noting benefits in a relative, or with hearing negative reports about a drug on the news. Thus, a patient’s mindset may be negatively or positively disposed toward a specific agent before treatment. By letting the patient decide, one can maximize positive mindsets and hopefully potentiate the pharmacological effects of the drug with beneficial placebo effects as well as enhance compliance.

Figure 1 highlights the treatment options and our recommendations. Once
Fig. 1 Treatment strategies for unipolar depression: polypharmacy versus switching.

a single antidepressant is chosen, if there is no response at all, then switching to another antidepressant of a different class makes sense. If this agent also is ineffective, then it seems appropriate to engage in polypharmacy with two antidepressants or the addition of other augmenting agents like lithium or thyroid hormone. In the case of partial response to a first antidepressant, then we lean towards augmentation with relatively benign agents like thyroid hormone or buspirone, although, if the patient prefers, switch to another agent can be tried first.

For psychotic unipolar depression, one might consider monotherapy with an atypical antipsychotic agent initially, followed by the addition of an antidepressant in the case of nonresponse. However, using combined treatment from the start would also be appropriate. In all cases, extensive efforts should be made to assess refractory depressed patients for subtle delusional signs so as to make sure that all psychotic depressed patients get at least one fair trial of polypharmacy with antipsychotic plus antidepressant medications.

SUMMARY

Polypharmacy in the treatment of unipolar depression is relatively frequent, although it sometimes can be avoided by switching from one antidepressant class to another. Polypharmacy may be somewhat more effective than the switching strategy, however, especially in more severe depressive disorders. Polypharmacy is generally required for psychotic unipolar depression but appears to be woefully underemployed in that condition.

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INTRODUCTION AND HISTORY

Concerns about polypharmacy have grown with the rise of psychopharmacology. The risk of potential harm to the psychiatric patient seems most obvious in the use of neuroleptic drugs: short-term risks (orthostasis, poikilothermia, hyperprolactinemia, constipation, hesitancy, akathisia, early dystonia, arrhythmia, Parkinsonism, neuroleptic malignant syndrome) and long-term risks [tardive dyskinesia (TD), retinopathy, cognitive impairment, hepatopathy, light sensitivity/skin discoloration, parkinsonism] were soon noticed after the serendipitous discovery of the benefit of chlorpromazine in psychotic disorders (1). With the advent of other antipsychotic drugs, polypharmacy ensued based on clinicians wish to maximize benefits. Despite the fact that combining antipsychotic drugs was officially seen as increasing the risk of side effects, polypharmacy turned out to become more the rule than the exception (2).

At the outset, some caveats seem appropriate: as discussed below more in detail, both diagnostic and therapeutic issues are not clearly defined. “Psychotic disorders” are a heterogeneous group sharing some descriptive features, but without clearly identified etiological or pathogenetic commonalities. It is like describing a “red eye,” “swollen ankle syndrome” (or “fever”) as a patient’s diagnosis. Comparing treatments for these conditions has to be done with caution. For this reason, I will mainly speak of schizophrenia when discussing polypharmacy, as this is the paragon and most important group of psychotic disorders.
Treatment, on the other hand, is also not specific and highly context dependent. One is easily tempted to simplify what is complex and to assume diagnostic and therapeutic specificity where there is, in fact, very little known. Doing this, we end up treating a theoretical construct with an idealized therapeutic concept, instead of treating real subjects in their contexts with real and complex substances. Chemical therapy of psychotic disorders should be tailored to the patients’ individual needs and supplemented with environmental and psychological interventions to achieve maximal benefit.

Historically, the treatment of schizophrenia (dementia praecox) has fluctuated widely according to the underlying concepts of etiology and pathogenesis, with treatment modalities and outcome strongly dependent on the theoretical background of the time (3). Initially, “dementia praecox” had a very bleak prognosis, and Kraepelin found clinical improvement in no more than 17% of cases (4). Apart from diagnostic shortcomings 100 years ago [with inadvertent inclusion of cases with encephalitis, parkinsonism, and other organic states (5)], the narrowness of diagnostic criteria might have limited ““schizophrenia” to a group of most severely ill patients with inherently poor prognosis. A broader conceptualization of “the group of schizophrenias” by Eugen Bleuler (6) as well as new treatments such as insulin coma and electroconvulsive therapy (ECT) in the 1930s (see Ref. 3) led gradually to a more optimistic prognosis. After 1945, French scientists studied antihistaminic agents and took a closer look at the phenothiazines, which were already a well-known class of anthelmintic and antiseptic drugs. The first clinically usable drug was promethazine, still used today as a sedative and antihistamine. In 1951 chlorpromazine was introduced into anesthesia by Laborit to create “artificial hibernation” [hibernation artificielle (7)]. One year later the psychiatrists Delay and Deniker reported the improvement of psychotic (manic and schizophrenic) patients with the main agent of the “cocktail lytique,” chlorpromazine (8). Until 1956, the therapeutic principle was generally believed to be its antihistaminic, sleep-inducing, and temperature-lowering properties, and hopes soared for improved outcomes in acute phases of psychotic illnesses. Indeed, in the 1970s some studies reported clinical improvement in nearly 50% of schizophrenic patients after 10 years, but our international meta-analysis of 100 years of treatment in schizophrenia showed this to be most likely related to a broader symptom-oriented definition of schizophrenia, rather than treatment itself (3). In 1970, a transatlantic study highlighted the diagnostic discrepancies between New York and London psychiatrists (9) and started the return to narrower defined neo-Kraepelinian criteria for the diagnosis of schizophrenia. This was seen as the main explanation as to why outcome deteriorated again from the mid-1980s to the 1990s to 36.4% improvement—not different from the 35.4% improvement seen before the development of neuroleptic drugs from 1895 to 1955 (3).

In the light of such little success it is perhaps no surprise that clinicians
kept seeking better treatment results wherever they could find them, including combining different neuroleptic drugs. Despite early warnings to reduce the risk of neuroleptic-related side effects and avoid polypharmacy, studies of the phenomenon of polypharmacy have emphasized the gap between the theoretical, academic concept of monotherapy and the persisting clinical practice of polypharmacy. In 1975, Schroeder et al. complained that despite their own guidelines banning polypharmacy in the Veterans Hospital system, polypharmacy continued to be commonly practiced, and “14% of the surveyed hospitals reported having more than 25% of their patients receiving more than one antipsychotic drug” (10). Six years later, Carl Salzman noted that the average psychiatric patient received up to seven different drugs, uncritically given for dubious indications (11). However, polypharmacy did not go away, but even received support in some quarters (12). My own psychiatric training and practice in both Germany and the United States, spanning over 20 years, made me think about factors other than “pure science” responsible for differences in the rules of psychopharmacological treatment. This chapter—focusing on schizophrenia—will rely on both my personal experience and the scientific literature to shed some light on polypharmacy.

POLYPHARMACY IN A PERSONAL TRANS ATLANTIC EXPERIENCE

“Polypharmacy is bad”—that categorical statement was one of the first supervisory feedbacks I received when I began a second psychiatric residency in a Harvard-affiliated institution in the summer of 1989, after 10 years of clinical practice, research, and teaching in academic psychiatry in Germany. What had been state of the art in Germany was considered harmful in the United States—combining a high-potency with a low-potency neuroleptic (13), intentionally “mixing a cocktail” of drugs covering different profiles of affinities to different neurotransmitter receptors (to maximize benefits and minimize side effects). In Germany, the reigning concept of schizophrenia emphasized its heterogeneity and many subtypes, its syndromal rather than nosological character, as well as the nonspecificity of neuroleptic drugs (which affect a great variety of neurotransmitters). In the United States, things were clearly seen differently: schizophrenia, I was told, is now a neo-Kraepelinian, well-defined entity, biochemically known to be a problem of too much D2-dopaminergic activity (14), the sole target of specific “antipsychotic” treatment. Polypharmacy was seen as “clinical folklore,” without proof or merit; anxiety had to be targeted with a special anxiolytic, i.e., benzodiazepine, and extrapyramidal symptoms needed treatment with a special anticholinergic agent (15).

In Germany since the 1970s clinicians often combined a high-potency neu-
roleptic drug (e.g., haloperidol) with its predominant antidopaminergic action aimed at acute positive psychotic symptoms (hallucinations, delusional fears, thought disorder) with a low-potency neuroleptic drug (e.g., chlorpromazine or levomepromazine) for treatment of hyperactivity, anxiety, insomnia (antihistaminic effects), and extrapyramidal symptoms (anticholinergic effects) (16,17). Additional anticholinergic drugs and benzodiazepines then were not necessary. If this approach would fail, we would use clozapine (Leponex), a second choice due to its risk of agranulocytosis and the fact that it was a poorly understood ‘‘dirty drug’’ with multiple unusual receptor affinities (18).

Today, over 10 years later, we seem to have come full cycle in the United States and are now officially encouraged to add a conventional antipsychotic to an atypical one ‘‘if satisfactory outcomes—however defined—do not result from antipsychotic monotherapy’’ (19). As Stephen Stahl (18) put it: ‘‘Antipsychotic polypharmacy thus seems to be something everybody does and nobody admits,’’ admitted and documented in a fourth of outpatients (20) and more than half of schizophrenic inpatients (21). After years of an almost secret practice of polypharmacy in the United States, recently even official guidelines such as the Texas Medication Algorithm Project finally acknowledge its merits and recommend the combination of antipsychotics if monotherapy fails to achieve satisfactory results (22). Also, recently a prestigious review journal openly praised the virtue of combining haloperidol decanoate with an atypical neuroleptic in otherwise treatment-resistant schizophrenic patients (23). As Herbert Meltzer put it in a current CME article on polypharmacy (now more politically correctly called ‘‘combining antipsychotics’’): ‘‘The use of combinations of antipsychotic drugs to treat schizophrenia gained new currency after the development of the atypical drugs. Clinicians now can combine an atypical with a typical antipsychotic or combine two (or more) atypical antipsychotics. . . . Combining oral and depot neuroleptics may sometimes be a useful approach . . .’’, even ‘‘. . . combining low-potency and high-potency neuroleptic drugs to minimize sedation and EPS, while maintaining efficacy, has been a frequent practice . . . [in] some situations where funding is unavailable for atypical agent[s],’’ thus retrospectively validating the German practice of polypharmacy before the preferable new atypical drugs became available (24).

**CONCEPTUAL FALLACIES**

The well-intended recommendation of neuroleptic monotherapy and simultaneous ostracism of polypharmacy since the 1970s appears to be based on both empirical (observed increased physical and legal risks of polypharmacy such as tardive dyskinesia; for a good review and discussion see Ref. 25) and theoretical arguments (rather puristic nosological, pathogenetic, and therapeutic concepts).
However, the fact that the debate kept going on also testified indirectly to the obvious widespread practice of polypharmacy, which was hard to eradicate in the face of unsatisfactory treatment results.

While it is certainly important to act according to Hippocrates’ maxim ‘‘primum nil nocere,’’ it is also important to realize the rarity of serious side effects of neuroleptic drugs, the overlap of extrapyramidal side effects with dyskinesias of other etiology (‘‘spontaneous,’’ psychotic/catatonic, age-related, vascular), and the lack of prospective studies assessing polypharmacy. I think that fear of polypharmacy stemmed mostly from its legal implications, the influence of considerable litigation around neuroleptic-induced tardive dyskinesia (26).

With regard to theoretical concepts, it is important to clarify some common misconceptions based mainly on the nonspecificity of diagnostic and therapeutic factors. ‘‘Schizophrenia’’ is not a nosological entity but rather a group of heterogeneous psychotic conditions described at a syndromal level. These disorders can be classified and combined based on descriptive features (similar to Linnaeus’s description of plants), but little is known about their etiology and pathogenesis, and treatment response and prognosis are recently changing with the advent of new (‘‘atypical’’) drugs. Thus, in psychiatry the situation is different than in other areas of medicine, as we do not yet have clearly defined nosological entities but operate rather on a level of a ‘‘protoscience’’ (27). In addition, Leon Eisenberg’s statement applies especially to mental illness, i.e., that all concepts of disease are very much social constructions (28). DSM-IV’s concept of psychopathology assumes a relatively stable deficit within the individual (29) but neglects etiology and context in an attempt to improve over previous theory-laden diagnostic systems. In addition, the tendencies to biologize mental illness have increased the risk of medicalizing social ills, leading to secondary ‘‘reification’’ of DSM disorders.

This trend is further solidified by strong incentives from market forces (‘‘no reimbursement without DSM diagnosis’’) and research funding (grant-giving agencies tend to require the use of DSM diagnoses), shaping research and clinical aspects and impeding scientific progress [as originally suggested by Popper (30)]. These unidimensional within-individual descriptive approaches, even when coupled with the most elegant factor analyses and psychometric methods, not only fail to recognize rare syndromes (e.g., psychotic conditions like Asperger autism, Tourette’s, Couvade, and Capgras’ syndromes), but more importantly fail to take into account the multidimensional, transactional nature of persons within systems. DSM’s multiaxial assessments are rarely studied empirically and still fall far short of what is needed (31). DSM-based research has failed to address the etiological heterogeneity of schizophrenia, thus impairing understanding and progress (32).

The psychiatrist Hermann van Praag has demonstrated how today’s classification of psychiatric disorders is as confusing as 30 years ago, with the number of classifications paralleling the number of textbooks and blurred boundaries be-
 tween adjacent diagnoses, (e.g., schizophreniform psychosis, schizoaffective psychosis, brief reactive psychosis, and delusional disorder). In a series of psychopathological studies, van Praag showed that the unitary concept of schizophrenia is untenable, a blanket term for a series of different diseases (with Kay, his research differentiated six syndromes: besides the positive and negative syndrome dimension, he also found excited, depressive, paranoid, and cognitive clusters) (33). These empirically validated syndromes (rather than pseudonosological constructs) would be a better basis for an integrated approach to link descriptive (objective) and experiential (subjective) psychopathology with neurobiological and contextual variables, including drug profiles and effects. I have participated in research along these lines that has demonstrated the dimensional nature of psychotic phenomena (34), their neurobiological correlates [abnormal hemispheric asymmetry (35–37)] and corresponding effects of neuroleptic drugs on psychopathology and neuropsychology (38).

Too often, the descriptive and statistical “partial” diagnoses of the DSM are taken as nosological entities, which they are not (39), and then a simplified ephemeral scientific theory is used to define a puristic treatment approach (“ideally, antipsychotic drugs should be just D2-antagonists”). This phenomenon was particularly pronounced in the United States due to an attempt to make psychiatry more “scientific” and bring it into the realm of biological medicine. Ironically, I was involved in the preclinical testing of Raclopride, a designer antipsychotic with just that specific D2-antagonism. It raised high hopes, as it indeed blocked selectively D2 receptors in brain imaging and receptor-binding assays, but it did not bring the expected clinical benefits (40) and was then withdrawn from the market. It was theoretically ideal, but something was obviously wrong with this approach.

In reality, the effects of typical “antipsychotics” in the brain are by no means specific, either biochemically or clinically. Biochemically, they interact with a wide range of transmitters and receptors, well beyond dopamine (41). Even if we were to focus only on synaptic aminergic transmission, it has long been known that these neuronal systems are highly interconnected (e.g., serotonin and noradrenaline heteroceptors may modify the activity of dopaminergic neurons). Thus, if we imagine aminergic neurons to be connected like “fishes in a mobile,” it should become clear that by “pulling on one fish” all the others will start moving too, i.e., by blocking one type of aminergic receptor we can expect effects on other aminergic receptors as well. Apart from aminergic synapses, we now know that amino acids are neurotransmitters (42), and that peptides are co-localized with classic monoamine neurotransmitters (43). Neuronal signaling involves a large variety of substances, some of them synthesized in nonneuronal cells; even synaptic transmission is but one of several functional connections in the brain [others including glial cell signal transmission, axonal and dendritic transmission, and nonsynaptic diffusion neurotransmission (44,45)].
Clinically, antipsychotic effects are quite nonspecific, and the discovery of chlorpromazine was purely accidental (see historical remarks above): phenothiazines were already in use as anthelmintics and also used to produce artificial hibernation in anesthesia to safely allow for more time in surgical procedures. Their antipsychotic effects were found by serendipity. Even nowadays, “typical neuroleptics” continue to be prescribed not only as “antipsychotics” but also as “antibiotics” to treat malaria (46) and mycobacterial infections (47), uses of which many psychiatrists are unaware (some may now feel tempted to see a parallel to psychological and infectious aspects of ulcers and, given the recently discovered role of H. pylori, revive the concept of the “schizococcus”!).

Clozapine treatment—known in Europe since 1976, and practiced widely though cautiously—really became the most interesting antipsychotic drug after new and excellently designed studies in the United States (48) and subsequent skillful marketing, showing that clozapine was clinically superior to conventional antipsychotics, although it had only negligible antagonism to D2 receptors and affected many other neurotransmitters (especially serotonin). This stimulated a change in the biochemical paradigm of schizophrenia [back to factors other than dopamine (49)]. Similarly, we keep discovering new properties of new antipsychotic drugs: olanzapine and risperidone are not only excellent atypical antipsychotics, but also very effective medications for affective disorders, and reportedly benefit patients with obsessive-compulsive disorder (50). Apart from olanzapine’s aminergic actions, its recently discovered impact on GABAergic neurotransmission via increase of the brain-derived neurosteroid allopregnanolone may be an important factor in antipsychotic symptom relief (51).

Assessing the benefits, dilemmas, and pitfalls we now face, the psychiatric geneticist Kenneth Kendler has stated most recently in an interview that “there is a strong tendency in psychiatry to expect some white knight like genomics or neurochemical models to explain it all to us. I’m old enough to remember when we thought that depression was too little norepinephrine and schizophrenia was too much dopamine. We were strongly inclined towards simplistic solutions in our field, and a bit of scepticism is warranted. . . . Psychiatric disorders are among the most complex biomedical problems we face, yet everybody is hoping for a quick fix” (52).

IMPORTANCE OF SUBJECTIVE FACTORS

After nearly 50 years it is not at all clear what underlies the clinical benefit of typical antipsychotic drugs: in one analysis researchers found that the predetermined length of antipsychotic treatment studies correlated significantly with the rate at which patients were reported to improve. In other words, if a study was planned for 2 hours, patients improved after 2 hours; if planned for 24 hours,
improvement was observed after 24 hours; if planned for 3–4 weeks, positive results would start coming in after 3–4 weeks. The authors explained these results by referring to the expectations of both observer and patients about the course of response (53). This points to the importance of factors other than pharmacological or chemical: social, cultural, contextual, and subjective/expectational. I will focus here on subjective factors.

An obsession with objective assessment has led to the neglect of subjective dimensions in diagnosis and treatment [an “exorcism of the subject from the subjective syndromes” (54)]. Subjective features of psychosis, apart from being most important for individual suffering, clearly have defining power in the “objectifiable” response to treatment (55). Unfortunately, much in the celebrated recent (re-)discovery of “first-break psychosis” (regarding recognition of prodromal schizophrenia and potential for early intervention) is hampered by neglecting subjective dimensions and the ignorance of relevant international literature. German studies of psychopathology, for example, long ago described various subjective phenomena. The Basis Symptomes (“basic deficiencies”) are premonitory unstable neuropsychological deficiencies, including impaired attention, hyperacousis, perceptual distortions, malattribution of meaning, feeling of convictions, etc. (56,57). Coenesthetic phenomena have been extensively studied since the 1920s: difficult to describe fluctuating sensations in the body, often unpleasant or painful, and related to third ventricle enlargement (58). Trema is the term coined for an ominous increase in general affective responsivity by the (Gestalt psychology–oriented) German psychiatrist Conrad; his initial findings in a clinical case series have been empirically confirmed recently as part of the frequent first subjective stage of schizophrenia (59). Kurt Schneider’s term Wahnstimmung (a sub- or predelusional state) stands for a general affective state of suspiciousness before forming distinct delusional beliefs. These subjective states cannot be assessed by standardized interviews: they are vague, intensely distressing, and strange but difficult to verbalize, not readily observable, and only accessible with unrestricted attention to the subjective. A better classification of psychosis (and mental illness in general) would consider such subjective factors as well as the organisms attempts at coping with deficits [“defense mechanisms” (60)] in a developmental and evolutionary context; then we might discover valid nosological entities and etiologies that would then allow more appropriate multi-level treatment interventions (61,62). Unfortunately, we are a long way from that.

By paying better attention to individual subjective features [i.e., improving the recently decaying art of psychopathological assessment including the assessment of nonverbal communicatory features (63)], one can try to address the individual profile of target symptoms by rationally combining drugs covering these areas. It should be understood that this needs to be supplemented by psychosocial interventions shown to specifically improve relapse risk (64) and psychotherapy, which has generally been shown to significantly enhance treatment benefits (65).
Also, subjective response to treatment has been reported to be an important predictive variable of outcome in pharmacotherapy (66). By again paying enhanced attention to the schizophrenic patients’ subjective experience, we can reintroduce the subject into the subjective syndromes; seen this way, polypharmacy could be an attempt to indeed treat the patient and his or her needs—instead of treating a disease concept, we project onto him or her. In this sense, Rifkin recommended that “we must be sure to use our present treatments optimally, which means exerting extra effort to overcome continuing [subjective] symptoms, even if it means trying many different drugs and even combination of drugs” (67).

**DEFINITION OF POLYPHARMACY**

The recent trend toward accepting or even recommending polypharmacy under certain conditions may sound confusing and deserves clarification. First, we have to distinguish between irrational polypharmacy [sometimes seen as the result of intellectual laziness or economic considerations, and often decried as the cause of increased mortality and complications (68)], and rational polypharmacy (based on a theory of both the nature of the condition to be treated and the nature of the proposed treatment, as stated above). We will therefore need to clearly define and identify which type of polypharmacy is meant—something not addressed clearly in many discussions of polypharmacy.

**IRRATIONAL POLYPHARMACY**

Irrational polypharmacy can be seen in part as the result of intellectual laziness, professional incompetence, or just personal prescribing habits. These are doctor-related variables, and rather undesirable. However, there is also a second, patient-related factor to consider: sometimes patients request to receive two neuroleptics or to stay on two or more previously prescribed neuroleptics because of perceived subjective benefits. This cannot be summarily dismissed as just drug-seeking or fear of change: I myself have encountered individual patients in Germany as well as in the United States who got worse when I tried to simplify treatment and discontinue additional neuroleptic drugs and seemed then to improve again behaviorally, perceptually, and in general when put back on selectively combined antipsychotic regimens. Similarly, a study looking at the effect of reducing polypharmacy to monotherapy with neuroleptics found that less than half of the psychotic patients tolerated this change; the remainder had to continue on combined antipsychotic therapy, as neither dose increase nor change to a different drug was therapeutic (69). These observations are not just “clinical folklore,” but true
case-based data and deserve clinical and research attention, as they can lead to a better understanding of relevant pathogenetic factors.

An analogy might be helpful: similar to polypharmacy, the frequent abuse of anticholinergics, coffee, and nicotine in schizophrenic patients has mostly been seen as a nuisance and harmful behavior [smoking, apart from cancer and cardiovascular risks, may significantly lower blood levels of neuroleptics through induction of the CYP450-1A2 liver enzyme (70) which has also been implicated in TD risk (71)]. However, recent research has confirmed earlier observations on abnormalities of nicotinic receptors in schizophrenia (72) and may soon lead to therapeutic benefits for cognition and memory in schizophrenia and other neuropsychiatric disorders (73). Unfortunately, we are just beginning to study polypharmacy as a phenomenon and know little about its implications and potential. Prospective studies adding neuroleptic to neuroleptic are lacking (74), and the data used in this review are mostly retrospective in nature.

A third variant of irrational polypharmacy is related to cultural factors. First, we need to notice that we have different subcultures in our own culture: academic psychiatry is quite different from psychiatry in private practice, and again from psychiatric practice in state hospitals. Muijen and Silverstone reported that British hospitals with an associated academic psychopharmacology unit had the lowest prevalence of polypharmacy, while hospitals without such affiliation showed a much higher percentage of polypharmacology, ranging from 45% to 94% (with two or more antipsychotics as the most frequent type) (75). Similar trends have been reported in the United States, with a higher rate of polypharmacy in state hospitals (76). Community outpatient services also appear to have a higher rate of polypharmacy than academic centers, decreasing temporarily from 1970 to 1983 with the availability of depot injections, but since then increasing again (77).

CROSS-CULTURAL COMPARISONS

Similar differences of prescribing practices have been shown between different countries. For example, polypharmacy has been shown to be practiced widely in both Libya and Malta, but patients in Malta (resembling European patients more than Libyan patients) received higher doses of neuroleptics and often combinations with depot neuroleptics, while Libyan patients (with overall less pronounced and systematized positive symptoms) did not receive depot neuroleptics and were overall on lower doses (78). In Spain, nearly twice as many patients received at least two neuroleptics (73%) than in Estonia and Sweden (46%); interestingly, Spanish patients with their higher rate of neuroleptic combination therapy received (i.e., “needed”?) less anticholinergic drugs (42%) than Estonian patients (75%) on higher rates of neuroleptic monotherapy (79), supporting in part the
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German experience referred to previously. Polypharmacy was found to be frequent in Nigeria (80), England (81), Denmark (82), Germany (83), United States (84), and Israel (85). In Switzerland and the United States, identical patient material presented to psychiatrists in both countries showed that Americans tended to prescribe much higher doses than their Swiss colleagues, with low agreement about drug of choice between groups (agreement among Americans themselves was not above chance) (86).

There may be different reasons for the abundance of polypharmacy practice in Asian countries: in India, psychiatrists are sometimes under pressure to ‘‘sell’’ psychiatry as a legitimate kind of medicine in India’s pluralistic medical system, and also are pressured by clients to satisfy their expectations (87). In Japan, research has suggested that biological differences between Japanese and western patients may explain less chlorpromazine-induced sedation of schizophrenic patients, as well as more combination treatment and lower doses of neuroleptics, lithium, and tricyclic antidepressants (88). In Hong Kong, Lam noted that complex factors accounted for the not uncommon prescription of more than 10 different medications after a patient’s first outpatient consultation (89). In the western view, distinct disease entities exist and respond neatly to precise biochemical agents. Traditional Chinese medicine lacks the ontological epistemologies of western psychiatry. Instead, diseases are believed to arise from an imbalance of yin and yang forces, stagnation of qi (energy) and blood, and disequilibrium of internal organs. Chinese practitioners see treatment as dependent on restoring those balances with a combination of herbs, which may also counterbalance each other’s side effects. A typical Chinese prescription consists of 12–15 different types of herbal medicines. Chinese psychiatrists often prescribe antipsychotics along with herbal medicine. Given the strong contextual nature of polypharmacy, a dichotomous debate over “right or wrong” seems less fruitful than paying attention to conditions when polypharmacy can be indeed more helpful than monotherapy (90).

It is noteworthy how resistant polypharmacy has been in most cultures despite efforts to ban it, but how significantly it declined when better clinical treatments became available. The advent of clozapine in the United States has had the most impressive effect on polypharmacy, reducing it by 31% across cultural and subcultural barriers (91) and stimulating a rethinking of concepts in schizophrenia diagnosis and treatment research, which paved the way for a different, more rational view of polypharmacy.

RATIONAL POLYPHARMACY

‘‘Rational polypharmacy’’ may still sound like an oxymoron to some. But if one takes a closer look at the reasons for monotherapy, it may become clear why
polypharmacy can be at least as rational as monotherapy. Rational polypharmacy can be divided into two types: type I is defined using different classes and different therapeutic principles of drugs to treat one distinct nosological entity [e.g., L-dopa (dopaminergic) and biperiden (anticholinergic) for Parkinson’s disease]; type II involves treating one condition with two or more drugs from the same class (sharing the same therapeutic principle, e.g., two dopaminergic substances, L-dopa and bromocriptine, for parkinsonism). Problems have been seen with both, but type I polypharmacy has been disputed less critically than type II: for instance, the combination of a typical antipsychotic drug with an anticholinergic (to prevent extrapyramidal side effects), a beta-blocker (to treat akathisia), or a benzodiazepine (to promote sleep and reduce anxiety or relieve catatonic symptoms) has been commonly recommended as effective and beneficial. The second type of rational polypharmacy with antipsychotics—combining different neuroleptic drugs to optimize treatment results in schizophrenic patients—has no data from controlled studies and has generally been branded as unfounded and potentially harmful. However, the above-discussed conceptual changes as well as studies documenting the ongoing practice of polypharmacy have led to a recently renewed interest in and appreciation of this type of polypharmacy (92).

RULES FOR RATIONAL BEHAVIORAL POLYPYPHARMACY

First, it should be clear that an attempt should always be made to clearly define any type of symptomatic behavior or experience in schizophrenia or other psychotic disorders and then treat the target syndrome with a single atypical antipsychotic drug (appropriate in duration and dosage). The choice can be guided in part by the receptor-binding profile—much as in typical neuroleptics. The receptor affinities have been seen as predicting side effects (93), but are similarly predictive of therapeutic effects (94–96). The new atypical antipsychotics affect a large variety of different types of receptors and neuronal signaling systems in the brain, while at the same time presenting a significantly lower risk for many side effects of conventional ‘‘typical’’ antipsychotics. In contrast to typical neuroleptics, the atypicals also appear to better improve negative symptoms and cognitive features of psychosis. For instance, the partial serotonergic agonism (5HT1a) shared by clozapine, quetiapine, and ziprasodone is seen as relevant to their beneficial effect on cognition, anxiety, and depression, as well as their low incidence of EPS (97). However, there are circumstances when an adequate trial with a single atypical drug does not seem to work appropriately, or where atypicals are unavailable (forensic settings, or uninsured patients). These conditions may then call for creative adaptation of known drug and receptor profiles to the patient’s individual array of symptoms. Other situations of rational polypharmacy may
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involve cross-tapering, combining a depot with an oral antipsychotic drug, combining clozapine with other atypical drugs, combining atypical drugs different from clozapine, adding a typical to an atypical neuroleptic and adding an atypical to a typical antipsychotic (see [98] for details).

**TYPE I POLYPHARMACY: COMBINING DIFFERENT CLASSES OF DRUGS**

Wolkowitz recently defined this type of polypharmacy as ‘‘augmenting neuroleptics with additional medication,’’ such as lithium, carbamazepine, reserpine, benzodiazepines, ECT, antidepressants, propranolol, clonidine, valproic acid, and L-dopa (99) (Table 1). Its goals are ‘‘(1) to allow the use of lower neuroleptic doses, thereby lessening the incidence or severity of neuroleptic side-effects; (2) hasten therapeutic response; (3) target a broader range of schizophrenic symptoms; (4) target neuroleptic nonresponders.’’ Given the heterogeneous nature of both schizophrenia and the effective principles of psychopharmacological agents, it seems rational to formulate specific treatment plans with regard to patients’ symptom profiles, and psychobiological and cultural factors.

In cases of nonresponse, complicating factors such as noncompliance, inadequate dose, or plasma level [carbamazepine may lower neuroleptic levels by 50% (100)], coexisting use of alcohol or stimulants (amphetamines, cocaine, LSD), and misleading side effects (akathisia or akinesia taken for manifestations of psychosis) have to be carefully addressed or ruled out.

**Benzodiazepines**

Benzodiazepines added to neuroleptics are frequently used to facilitate sleep, reduce anxiety and aggressive tension, and reduce the intensity of psychotic symptoms. Wolkowitz reviewed 16 double-blind studies, of which 7 found bene-

**Table 1** Adjunctive Treatments in Schizophrenia

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<th>Benzodiazepines</th>
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<td>Carbamazepine</td>
<td>Antidepressants</td>
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<tr>
<td>d-Cycloserine</td>
<td>Propranolol</td>
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<tr>
<td>Polyunsaturated fatty acids</td>
<td>Lithium</td>
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<td>ECT</td>
<td>Clonidine</td>
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<td>L-Dopa</td>
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*Source*: Modified from Ref. 99.
fit and showed mixed or transitory results only (99). Certain subgroups may respond to or need benzodiazepines (101–104). In general, target symptoms for benzodiazepines in schizophrenia include acute psychotic agitation, high-intensity psychotic symptoms (delusional fear, hallucinations, negative symptoms), psychomotor excitation (catatonic or drug-induced restlessness or stupor), anxiety, panic symptoms, or early signs of relapse. Catatonic stupor can resolve temporarily with lorazepam, but in general a neuroleptic drug needs to be coadministered for lasting benefit.

Carbamazepine

Carbamazepine is most helpful for psychomotor excitement, impulsivity, verbal and motor aggressiveness, or accompanying temporal lobe signs and symptoms (partial seizures, EEG abnormalities, deja vu, olfactory hallucinations, macro- and micropsia, hypergraphia). Benefits take 4–6 weeks to appear, and blood levels as well as liver function tests need to be monitored in regular intervals (105–107). It is important to remember that carbamazepine may reduce active neuroleptic blood levels, thus often requiring an increase in neuroleptic dosage. Oxcarbazepine, a carbamazepine metabolite newly available in the United States, produces fewer drug interaction and does not require laboratory testing for blood levels.

D-Cycloserine

D-Cycloserine is a partial agonist with approximately 60% activity at the glycine site of the N-methyl-d-aspartate (NMDA) receptor. It is thought to facilitate learning in animals and has been reported to reduce negative symptoms and cognitive impairment in schizophrenic patients. At a dose of 50 mg/day, but not at 25 or 250 mg, D-cycloserine produced a significant 21% reduction in negative symptoms (SANS) and significant improvement in reaction time as measured by Sternberg’s Item Recognition paradigm (a test requiring prefrontal cortex activity) (108). Interestingly, this worked only with adding D-cycloserine to conventional neuroleptics, not when adding it to clozapine (109,110), possibly because of clozapine’s atypical receptor affinities not matching D-cycloserines selective enhancing effect on D₁ and D₂ receptor blockers (111).

Polyunsaturated Fatty Acids

Based on evidence of altered neuronal membrane structure and metabolism in schizophrenia, essential fatty acids (fish oil) have been used in the treatment of schizophrenia (112). When polyunsaturated fatty acids were added to neuroleptics, eicosapentaenoic acid (EPA) (from fish oil but not primrose oil) was more
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Effective than placebo for scale-derived mental state outcomes. Even single administration of EPA delayed the need for neuroleptics for 12 weeks in one third of patients hospitalized for relapse (113,114).

ECT

First applied to treat schizophrenic patients by Cerletti and Bini in the 1930s, it has become clear that ECT is less effective than neuroleptics for most forms of schizophrenia. However, acute catatonic or mixed affective-psychotic states respond well, while chronically ill patients respond more poorly (115). Its use as a first-line augmentation has been advocated in acute patients, and usually more treatments are required than in depression (116,117). Symptoms especially responsive include catatonic features (psychomotor agitation or stupor, grimacing, mannerisms), delusions, hallucinations, hostility, depression, and suicidal features. Apart from the direct ECT effect, it may also increase neuroleptic blood levels (118).

Valproic Acid

Valproic acid appears less helpful as an add-on than carbamazepine. A review found only three out of eight studies with clearly positive results, four showed negligible or even negative effects, and one study mixed results (119). In a recent double-blind, randomized study, 249 patients with schizophrenia experiencing an acute exacerbation of psychosis were randomized to receive either risperidone or olanzapine monotherapy (n = 125) or to receive divalproex added to either risperidone or olanzapine (n = 124). The divalproex/antipsychotic combination group experienced statistically significantly more improvement in psychotic symptom scores (PANSS scale) and had a lower drop-out rate from treatment. There was no evidence of significantly worse side effects in the combination group, even with weight. This fascinating study suggests that mood stabilizer polypharmacy may be appropriate in patients with schizophrenia (in addition to bipolar disorder) and did not appear to impose a major side effect burden. This study is the largest controlled polypharmacy study in schizophrenia utilizing a mood stabilizer in recent years.

Antidepressants

Depressive symptoms may be part of schizophrenia in about 60% of patients, especially in the prodromal phase and after remission of acute psychotic symptoms. They need to be addressed in both psychopharmacological and psychosocial treatment and not be confounded with negative symptoms: in the negative syndrome of schizophrenia, affect is rather blunt than depressed, and dorsolateral
Frontal deficiencies with amotivation, perseveration, difficulties changing the mental set, low concentration, and aspontaneity are typical and tend to respond to neuroleptic treatment, especially with clozapine and newer atypicals. If depressive symptoms are correctly identified, the clinical benefit from antidepressants (which otherwise can exacerbate hallucinations and delusions) is reported to go beyond depressive features and may include improvement of overlapping negative psychotic symptoms such as aspontaneity and lack of interest and energy (120). As a guideline, additional antidepressant treatment is most likely beneficial in schizophrenic patients with no acute positive symptoms, and after remission of psychosis (postpsychotic depression), after adequate neuroleptic and antiparkinsonian medication. All classes of antidepressants have been successfully tried, including tricyclics, SRIs, monoamine-oxidase inhibitors (MAOIs), and lithium. It is important to monitor possible interactions and plasma levels, as plasma levels of antidepressants or neuroleptics may each be elevated by 50–70% (121,122). Sertraline and citalopram have the lowest likelihood of P450 liver enzyme inhibition or drug-drug interaction.

Propranolol

The positive expectations raised by past trials with propranolol in doses up to 4000 mg/day (123) could not be maintained in later studies; observed benefit was now seen as most likely due to β-adrenergic improvement of neuroleptic-induced akathisia (124,125). However, patients with neurological brain disorders, impulsivity, and aggressive features often respond favorably to additional treatment with beta-blockers (126). Elevation of plasma levels of neuroleptics may occur and requires clinical attention (127).

Lithium

Lithium has both been praised for increasing benefit in previously nonresponding schizophrenic patients (128,129) and accused of causing possible brain damage when added to neuroleptics (130). While neurotoxicity is rare, reversible side effects such as confusion or delirious states may be seen more frequently, in addition to the usual side effects of lithium such as hypothyroidism, polyuria, tremor, diarrhea, and skin reactions (acne). Predictive factors of a positive response to lithium add-on treatment in schizophrenia include affective factors such as the presence of predominant affective symptoms, personal or family history of affective illness, schizoaffective disorder, acute onset and good interepisode functioning, manic excitement, irritability, hostility, and uncooperativeness (131). Wolkowitz concludes in his review that lithium augmentation in schizophrenia lacks good predictors and should be considered empiric at best (132).
Clonidine

Similar to blocking β-adrenergic effects, the blocking of α-adrenergic processes with clonidine, an α2-adrenergic receptor agonist that decreases norepinephrine release, has been tried to improve unsatisfactory treatment response in schizophrenia. Results of studies are mixed, with two studies reporting positive results and four studies showing either no benefit or even increased aggressive symptoms (133). With such unclear benefit and considerable side effects ranging from hypotension and sedation to rebound hypertension and increased psychotic symptoms, clonidine augmentation cannot be recommended. If at all, one would want to increase norepinephrine (as done by the atypical clozapine) to enhance frontal cognitive processes known to be impaired in schizophrenia; indeed, a small double-blind study with a α2-antagonist has shown encouraging clinical benefit (134).

L-Dopa, Famotidine, and Negative Symptoms

L-Dopa is known to occasionally produce psychotic symptoms in parkinsonian patients, such as manic-like excitation and hypermotility, delusional thinking, paranoia, and hallucinations—all positive symptoms of schizophrenia. However, when given to schizophrenic patients with predominantly negative symptoms believed to be the result of hypofrontality and dopaminergic deficit, about 10–30% of patients are reported to improve in motivation, social interest, and alertness (135). Similarly, famotidine has been reported to improve mainly negative symptoms of schizophrenia. Paranoid features and absence of substance abuse were positive predictors of a favorable response to famotidine 20 mg b.i.d. (136). Marked improvement in motivation, program participation, social interaction and verbal as well as physical interactions were observed after 2 weeks of treatment with this selective H2-receptor antagonist. This raises again the point of different biochemical factors involved in the group of schizophrenias and suggests a role of histaminic receptors at least in the negative syndrome type of schizophrenia: central H2-receptor stimulation leads to a decrease of spontaneous activity and exploratory behavior in animals (137), suggesting a possible overactivity of these receptors in negative schizophrenic symptoms. Blocking these receptors with famotidine might therefore improve aspontaneous, disinterested schizophrenic patients. Further studies are needed to assess this hypothesis.

TYPE II POLYPHARMACY: COMBINING DIFFERENT ANTIPSYCHOTIC DRUGS

This type of polypharmacy can be seen in analogy to treatment in other areas of medicine, where one attempts to maximize benefits and minimize side effects by
combination therapy within the same class of agents. In parkinsonism, L-dopa and direct dopamine agonists given together often allow for clinical improvement without dose increase, thus reducing side effects such as end-of-dose phenomena and dyskinesias (138). In epilepsy, “polytherapy” often helps to increase or maintain benefits while reducing drug side effects, although this has to be applied judiciously (139). Oncological treatment has probably the longest tradition of this therapy concept to use polypharmacy for maximum benefit and minimum damage (140). In the treatment of affective disorders, polypharmacy has become the way of choice to overcome treatment resistance and the emergence of tolerance (141).

Similarly, in the treatment of schizophrenia and psychotic disorders, a thoughtful combination of different neuroleptics may lead to therapeutic benefit where antipsychotic monotherapy has failed. As Stephen Stahl has put it: “Clever combinations of pharmacologic mechanisms may enhance the efficacy of antipsychotic drugs and alter the course of schizophrenia. A new therapeutic goal of the emerging atypical antipsychotics is to mix a pharmacological nectar of multiple neurotransmitter receptor actions that can reliably trigger ‘awakenings’ from schizophrenia and arrest the downhill course of illness” (142). Unfortunately, the lack of controlled studies evaluating the effectivity of combining different neuroleptics and the neglect by leading researchers to develop a pharmacological rationale for combining antipsychotic drugs of the same or different class make general recommendations rather difficult. An excellent recent overview is given by Meltzer (143).

Official treatment algorithms—except for the Texas Medication Algorithm Project (144)—so far have not considered combining neuroleptic drugs, in part because of the widely held belief in the equivalency of neuroleptics analogue to their D2-receptor blockade activities and the attempt to avoid any unnecessary risk of TD (see Refs. 145 and 146). However, not even the “selective serotonin reuptake inhibitors” are the same: their pharmacological selectivity has found to be relative rather than absolute, and the secondary properties distinguishing these drugs from each other are therapeutically relevant (147). Similarly, research has shown that different antipsychotic drugs induce distinct behavioral effects as well as differential changes in the biosynthesis of synaptic proteins and their encoding mRNAs (148). Similarly, neuroleptic induced changes of the ultrastructure and proportion of synaptic subpopulations in the caudate nucleus suggest distinct differences of antipsychotic drugs (149), with so far not well-understood clinical significance. Today we are beginning to accept the relevance of other than just D2-receptor activity changes for “antipsychotic” effectivity [serotonergic modulation (150), glutamatergic effects (151)] and might learn to combine a dimensional (instead of categorical) view of psychopathological core syndromes in psychotic disorders with related changes of receptor activity, which
may be matched most beneficially with receptor profiles of different neuroleptics. Figure 1 compares different typical and atypical antipsychotics, Figure 2 atypical antipsychotics receptor profiles.

Van Praag’s functional approach, attempting to correlate biological with psychological dysfunction on a dimensional scale (rather than trying to treat uncertain nosological entities in a categorical approach), suggested that altered serotonine, dopamine, and noradrenaline metabolism are not disorder-specific but related to psychopathological dimensions such as anhedonia, aggression/anxiety, hypoactivity/inertia, etc. (154). The recently acknowledged benefit of combining

![Fig. 1](image)
neuroleptic drugs in treatment-resistant schizophrenic patients (155) warrants further studies—both clinical controlled studies and basic research—to develop a clear rationale and better fine-tune our attempts to help psychotic patients.

COMBINING TYPICAL NEUROLEPTICS

Combining typical neuroleptics is often seen when cross-tapering is done from one to another neuroleptic drug, with intermittent overlap. However, this is unnecessary, as neuroleptics show considerable residual effects after discontinuation. One drug can be started right after discontinuation of the previous drug, without fear of relapse in most patients. An exception is a change from a high to a low anticholinergic agent, such as from chlorpromazine to haloperidol, as cholinergic rebound symptoms (diarrhea, hypersalivation) can lead to complications. Often, depot neuroleptics can be complemented by oral neuroleptics in unstable or difficult to dose patients (156). The addition of low-potency neuroleptics such as chlorpromazine or thioridazine can help to secure better sleep, prevent
EPS, and exert mild antidepressant effects (157), thus avoiding extra anticholinergics and sedatives with their own additional side effects (delirium, impaired memory, craving, addiction) while synergistically increasing the antipsychotic benefit. However, today we prefer to use new atypical antipsychotics, which achieve the same objective with less risk or side effects (unless one considers drug costs a side effect). Loxapine can be seen as an exception, as it shares some features with clozapine and may have some atypical properties, which may add benefit when combined to a typical neuroleptic (158). However, there are no controlled studies so far on this combination.

**COMBINING ATYPICAL WITH TYPICAL NEUROLEPTIC DRUGS**

Despite the general superiority of atypical drugs in improving negative symptoms and cognitive impairment in schizophrenia, patients may still show significant impairment in many areas of psychopathology. The practice to use typical neuroleptics to augment risperidone and olanzapine was more pronounced than with clozapine and quetiapine, based on prescription surveys (159). This may also have to do with the high price of atypical neuroleptics. According to Meltzer, 4% of clozapine-treated patients, 12% of olanzapine-treated patients, and 20% of risperidone-treated patients were also receiving a typical neuroleptic—numbers Meltzer considers grossly underestimated (160). The addition of thioridazine to risperidone is reported to decrease anxiety and agitation not responsive to risperidone alone (161). If patients develop an “excitation syndrome” (“mania”) in the initial treatment phase with risperidone (162) or olanzapine (163), the addition of a typical neuroleptic may help to reduce agitation and decrease “manic-like” symptoms.

The opposite—adding an atypical drug to a typical neuroleptic in treatment-resistant schizophrenic patients—also has been advocated. In one study, anxiety and hallucinations reportedly improved after adding low-dose risperidone to typical neuroleptics (164). This strategy was reported to be especially useful in drug-abusing dual-diagnosis patients. Also, low-dose typical neuroleptics combined with atypical antipsychotics appears to turn nonresponders into responders: Two thirds of 31 treatment-resistant patients with schizoaffective disorder improved when low-dose typical neuroleptics (haloperidol, trifluperazine, fluphenazine) were combined with atypicals (risperidone, olanzapine, quetiapine) (165). Remarkably, no serious increase in side effects was observed, contradicting the general assumption of the danger of polypharmacy. However, if combining pimozide with olanzapine [another successful combination (166)], clozapine (167) or other atypicals, an ECG should be obtained because of the risk of possible QT prolongations and arrhythmias. This warning was recently extended to thioridazine and ziprasidone.
COMBINING ATYPICALS WITH ATYPICALS

In patients in extended care units with persistent psychotic symptoms on atypical antipsychotics, more than half are reported to receive one or even two more neuroleptics. Often, clozapine is combined with risperidone or haloperidol, providing additional D₂-receptor antagonism and antipsychotic benefit, but also risk of EPS, prolactin elevation, and cognitive dysfunction (168). In Europe, rather low doses of clozapine (50–150 mg/day) are used and often combined with a typical neuroleptic to improve response while keeping clozapine-related sedation, weight gain, and hypersalivation low (169). In contrast, in the United States Meltzer recommends treating at least for 6 months with doses up to 900 mg/day of clozapine before deciding to add another neuroleptic or switch to another agent (170). The best documented augmentation of clozapine is with sulpiride, an atypical D₂-blocking agent not available in the United States. Treatment-resistant schizophrenic patients who only partially responded to clozapine over 12 weeks received either sulpiride 600 mg/day or placebo in a double-blind design (171). Sulpiride augmentation resulted in significant improvement of both positive and negative symptoms, without additional side effects noted. In the combination of clozapine with risperidone, Tyson et al. reported an increase of clozapine blood level possibly explaining the additional benefit (172), although this is not undisputed (173).

Other studies confirm the benefit of adding risperidone to clozapine by demonstrating amelioration of symptoms previously resistant to clozapine, but without evidence for pharmacokinetic interactions such as blood level changes (174,175). Therapy failures of this combination are published as well (176). What might predict success or failure of this combination is unclear and needs further study.

Olanzapine has been tried successfully to turn clozapine nonresponders into responders (177). This combination is especially interesting as both clozapine and olanzapine are reported to improve verbal learning, memory, and fluency, while risperidone appears rather to improve working memory (178). Such promising distinctive effects on cognitive dysfunction deserve further study to use neuroleptic drug combinations more selectively and differentiated in the treatment of identified psychopathological abnormalities of schizophrenic patients.

CONCLUSION

Monotherapy of schizophrenia and other psychotic disorders with an atypical neuroleptic for at least 6 weeks at appropriate dosage is the preferable first-line treatment. If a patient with schizophrenia cannot obtain atypicals, typical neuroleptics alone or in combination are a good choice, and selective attention to psy-
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chopathological syndromes and receptor profiles can enhance the chances of beneficial response. If a patient does not respond to an atypical drug, augmentation with a typical or another atypical is a promising option. Paying attention to the patient’s subjective state and response will help maximize benefits and minimize side effects, in addition to other treatment modalities, such as psychosocial interventions, psycho-education, and supportive psychotherapy as indicated.

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DEFINITION

Generically and in context, the term “polypharmacy” refers to the use of multiple medications for the treatment of anxiety disorders. Some definitions include a specifier, such as “greater than or equal to two medications” (1). Despite the technical neutrality of its meaning, “polypharmacy” carries an implicit pejorative undertone as well, so much so that the meaning of the word has been historically imbued with this accusation of misconduct. In this chapter, I will undertake an examination of the term as it applies to anxiety disorders in large part, extending on general principles to illustrate the more direct impact on the treatment of anxiety disorders.

NEUROBIOLOGICAL BASIS OF THE POLYPHARMACY OF ANXIETY DISORDERS

As Table 1 indicates, anxiety disorders cover a broad range of syndrome clusters (2). Although the neurobiology of each of these disorders is complex—the details of which exceed the length of a chapter such as this—the following summaries provide some understanding of the neurobiology as we currently understand it for some of the major disorders:

1. Panic disorder: the locus coeruleus, amygdala, and frontal cortex are some of the major neuroanatomical targets for polypharmacy in this disorder. From a neurochemical standpoint, the serotonin system,
Table 1  Classification of Anxiety Disorders

Classification of Anxiety Disorders

Panic disorder without agoraphobia
Panic disorder with agoraphobia
Agoraphobia without history of panic disorder
Specific phobia
Social phobia
Obsessive-compulsive disorder
Posttraumatic stress disorder
Acute stress disorder
Generalized anxiety disorder
Anxiety disorder due to general medical condition
Substance-induced anxiety disorder
Anxiety disorder NOS

GABA system, and norepinephrine system have all been implicated in panic disorder (3–5).

2. Posttraumatic stress disorder: the hippocampus and frontal cortex are the main neuroanatomical targets of this disorder. From a neurochemical standpoint, the GABA system, norepinephrine system, and serotonergic system have all been implicated (6,7).

3. Obsessive-compulsive disorder: here, the basal ganglia, frontal cortex, thalamus, and cingulate gyrus are the important neuroanatomical targets. The serotonin system as well as the noradenergic system are the predominant neurotransmitter systems (8).

On the basis of these diverse neuroanatomical targets, it may be deduced that polypharmacy would be a natural correlate.

MEDICATION CLASSES AND COMMON POLYPHARMACY COMBINATIONS USED IN ANXIETY DISORDERS

Although the anxiety disorders are each quite different (Table 1), the first-line medication for all anxiety disorders is a selective serotonin-reuptake inhibitor (SSRI) unless there is some contraindication to the use of these medications. Perhaps the next most popular medication class is the benzodiazepines (9). While it is uncommon to prescribe two different SSRIs, it is less uncommon for practitioners to prescribe two different benzodiazepines. For example, clinicians may
give consideration to prescribing alprazolam for panic attacks with temazepam or oxazepam for insomnia. In addition, it is even more common for an SSRI to be prescribed with a benzodiazepine, usually clonazepam.

The use of two or more benzodiazepines may be complicated by the differing half-lives and absorption rates of medications, so that trying to distinguish withdrawal effects due to a short-acting benzodiazepine, such as alprazolam, from an impending panic attack, may be difficult. In addition, the specific side effects of sedation, dependence, and respiratory suppression may all be additive (10). Thus, polypharmacy with two or more benzodiazepines is probably best avoided.

Combining an SSRI with a benzodiazepine also poses certain considerations. Medications such as fluoxetine may cause initial jitteriness, so that the benzodiazepine may need to medicate more than the anxiety disorder. Using low doses of the SSRI may be helpful to combat this problem. However, in populations such as the elderly or head-injured, the disinhibition of benzodiazepines may again be confused for unrelenting anxiety, and using this in combination with a jitteriness-inducing SSRI may add to the complexity of the picture. In addition, paroxetine may be one of the more sedating SSRIs, and this effect may add to the sedation of benzodiazepines (10).

Other combinations with benzodiazepines such as nefazodone or buspirone may also occur, and the risks associated with these combinations of medications are similar to SSRIs. One lethal combination that should always be avoided is the combination of a monoamine oxidase inhibitor (MAOI) with an SSRI, which may lead to hypertensive crisis (11), or serotonin syndrome. Serotonin syndrome can also occur with other combinations such as buspirone with an SSRI (12).

Other combinations in the polypharmacy of anxiety disorders include situations of comorbidity where patients with a comorbid bipolar disorder may also be on a benzodiazepine or SSRI. The additive side effects with benzodiazepines applies here, and the combination with an antidepressant or antianxiety SSRI places patients at an increased risk of rapid cycling. The use of antidepressant/antianxiety agents should therefore probably be avoided in the treatment of anxiety in bipolar disorder (13). Usually, a medication such as valproic acid (14) or gabapentin (15) may be helpful for panic attacks, but one is faced with a problem in bipolar depression with anxiety, for the current trend is to use combination therapy rather than monotherapy, and so polypharmacy still finds a home in the treatment of patients with comorbid mood and anxiety symptoms. In this regard, atypical antipsychotic agents may be preferable for the treatment of anxiety in bipolar disorder (16); olanzapine is currently being studied for the treatment of GAD, and quetiapine in low doses may help alleviate anxious symptoms. But again, one is faced with the problems of additive side effects, particularly weight gain, when used in combination with standard mood stabilizers.

A useful approach to situations that seem impossible to treat with mono-therapy is to consider the following questions:
1. Is another drug really needed? In many cases, treatment resistance may best be approached by replacing the current agent with another anxiolytic agent rather than adding another medication. Clinicians often hesitate to do this since patients feel insecure tapering off one medication onto another. Patients with anxiety disorders are often extremely sensitive to the withdrawal effects of tapering medications. However, initial care in cross-tapering or very gradual replacement of one medication by another may prove to be the better choice in the end as the problems of polypharmacy may be avoided.

2. Why can psychotherapy not address residual or refractory symptoms? Since treatment of anxiety disorders is largely symptom based, it is important to be sensitive to the side effect:benefit ratio as one increases the current medication dose or adds another medication. At a certain clinical level, the side effect:benefit ratio reaches a plateau such that any addition of further medications leads to a decrement in response. At this point, it may be useful to add on psychotherapy as an alternative treatment given that there are no overt physiological side effects that would be additive (17).

3. Does the patient meet criteria for another diagnostic indication for the proposed drug? Treatment resistance may be thought to be due to a newly detected diagnosis, the alternative treatment of which may be psychotherapy, a new agent, or an agent that covers more than one diagnosis. If a patient with panic attacks is taking clonazepam, for example, a new diagnosis of bipolar disorder may be handled by adding valproic acid and by removing the clonazepam, since valproic acid may help both the panic attacks and bipolar disorder. Also, the new diagnosis needs to be appreciated in context. For example, the new diagnosis in a patient with panic disorder may be “depression.” However, elucidating the nature of the depression may be important, as adding an antidepressant to a benzodiazepine may make sense in recurrent unipolar depression but is less of a first-line choice in bipolar depression. Here again, adding a mood-stabilizing agent such as valproic acid may cover all symptoms.

4. Is there another way to conceptualize the anxiety or another way to understand the mood symptoms in comorbid situations? The occurrence of anxiety in general is easy to conceptualize as a diagnostic syndrome or as symptoms related to the primary disorder. Here, clinical expertise may be more valuable than blanket use of the DSM-IV. For example, a depressed person with “decreased interest in day-to-day activities” or “psychomotor retardation” with “guilt” and “decreased energy” may avoid social situations. The latter may present as a phobia and be inaccurately treated as such. In addition, pa-
tients with a history of a manic episode may have panic attacks that are related to the fear of having another manic episode or repressed conflicts that are avoided unconsciously due to the threat of mania. This may be more appropriately addressed within the context of one of the complications of mania rather than a separate syndrome. It is precisely this kind of challenge that is difficult to meet in time-limited appointments, as the solution to addressing these concerns is not obvious. At this point, choosing an obvious solution such as polypharmacy may not necessarily be the best solution.

5. Is the patient at special risk for the problems of polypharmacy? A history of structural or functional brain deficits such as in the case of head injury or mental retardation may predispose to an increased sensitivity to side effects of multiple medications. In addition, many elderly patients may be sensitive to the effects of polypharmacy. Also, specific intellectual deficits may compromise the positive effects of polypharmacy if they affect compliance and accuracy of taking medications.

6. Is there a contraindication to the use of multiple medications? Examples here include cardiac conditions such as congestive heart failure that may contraindicate propranolol used in the treatment of social phobia (18) or a history of alcohol dependence that makes a benzodiazepine less of a first choice. In these cases, adding medications may exacerbate the medical illness and worsen the overall condition of the patient.

7. Can the patient afford to take medications? An important practical issue relates to whether the patient can afford to take multiple medications. Ignoring this factor may affect treatment compliance and results of multiple medications. In some cases, financially compromised patients may in fact buy all their medications but may compromise other aspects of their lives that worsen their conditions. Eating, sleeping, and maintaining the general standard of a patient’s life are important to consider when proposing measures with increased cost.

8. How will adding more medications affect overall compliance? The use of multiple daily doses of medications reduces compliance and may affect outcome (19). As mentioned above, multiple factors such as side effects and cost related to polypharmacy may affect compliance.

9. Does the patient stand to gain more from adding a medication than removing one or lowering the dose of one? Here, a clinical appreciation of a risk:benefit analysis may be useful. Conscious contemplations of such questions may aid decisions when used in combination with clinical intuition.
10. What drug interactions should be avoided? This is an obvious question that, often ignored in the past, probably poses the single greatest general risk of polypharmacy. In psychiatry we have still to understand how the drugs that we use work. For instance, it is clear that although we understand that SSRIs involve serotonin receptors, it is not clear what is happening at and beyond the second messenger level. Add to that another unknown mechanism of action, and we have two unknown mechanisms of action, with unknown mechanisms of side effects. Thus, known drug interactions are one problem, but unknown mechanisms may lead to drug interactions that were not anticipated.

REASONS FOR POLYPHARMACY OF ANXIETY DISORDERS

Reasons Related to Diagnosis

The classification of anxiety disorders into its subtypes is complex (Table 1). In the diagnostic nomenclature, categories such as panic disorder (PD) and generalized anxiety disorder (GAD) reside side by side with obsessive-compulsive disorder (OCD) and posttraumatic stress disorder (PTSD). This heterogeneous grouping of fairly straightforward anxiety symptoms related to sympathetic overdrive and phobias with symptoms of disorders as specific as OCD, or as diverse as PTSD, where dissociative symptoms, quasi-psychotic symptoms, and neurovegetative symptoms of depression all combine to define a particular syndrome, is a metaphor for the loose boundaries that plague the diagnostic nomenclature of anxiety disorders (Table 2). In addition, extensive comorbidity often complicates the clinical presentation of anxiety disorders in general (20).

This concept of loose boundaries in psychiatric diagnoses relates directly to polypharmacy, as the use of multiple medications may rest on the nature of the diagnoses and the symptom cluster contained in each diagnostic category. This subject is discussed in greater detail in Chapter 1.

For example, more than two thirds of the clinical population with panic disorder present with major depressive disorder (MDD) as well, a diagnosis that originates in an entirely different subset of disorders (the mood disorders) (21). As a result, it is common to combine the use of a benzodiazepine with an SSRI in new-onset panic disorder, despite the possibility of using a benzodiazepine as the sole agent in the treatment of panic disorder. In this case, however, numerous other factors may contribute to the choice of an SSRI, one of which is that it allows the tapering off of the dependency-producing benzodiazepines which act more immediately, while the SSRIs take longer to work. The combination of depression and anxiety is a diagnostic factor that is pervasively intrusive in many other situations related to anxiety disorders.
Table 2  Reasons for Polypharmacy in the Treatment of Anxiety Disorders

Related to diagnosis:
1. Heterogeneous grouping of anxiety syndromes
2. Comorbidity
3. Loosely defined anxiety syndromes, e.g., GAD

Related to medications and biology:
1. Nonspecific action of medications
2. Multiple neuronal systems involved in the pathophysiology of anxiety
3. Incomplete treatment/response to medications

Related to clinicians:
1. Clinician impatience
2. Clinician beliefs
3. Clinician ignorance
4. Clinician insecurity
5. Managed care pressures

Related to patients:
1. Increased anxiety about diminished initial response
2. Comorbid substance abuse
3. Comorbid antisocial personality disorder

Other situations in which depression and anxiety seem to co-exist include GAD, where the distinction from MDD is rather obscure, as well as PTSD, where the target symptoms often combine into categories of depression, anxiety, and psychosis. Furthermore, the temporal and causal relationships between depression and anxiety are also usually unclear at the time of clinical presentation. In surrendering to this ignorance, the clinical treatment option is often to combine various medications rather than to invoke a temporal patience in prescribing, the latter of which might involve an empirical decision to treat a patient sequentially. In this case, the clinician may rely on the overall clinical picture to inform himself or herself as to whether the mood disorder appears to be primary or secondary. Here, the clinician may initially withhold the antidepressant until such time that it appears that the mood disorder is unrelated to the anxiety disorder or that it is of sufficient severity and intensity that it requires treatment with an antidepressant.

This obscurity of temporal and causal relationships is by no means specific to anxiety disorders, but has been recognized to the extent that the concept of “anxiety spectrum” disorders has been reported in the literature (22). In my opinion, the spectrum idea appears to be a first step to declaring that the appar-
ently rigid diagnostic system in psychiatry is probably less well defined in reality. Nevertheless, it also highlights how this absence of definition in anxiety disorders may contribute to the use of polypharmacy in that target symptom–directed treatment may span many syndromic clusters.

In relation to loose diagnostic boundaries that contribute to polypharmacy, personality disorders present yet another hodgepodge of mixed target symptoms that may lead to polypharmacy. It is not uncommon for patients to present with a combination of borderline personality disorder and panic attacks, or PTSD and borderline personality disorder. In this diagnostic group, the relationship between anxiety and transient paranoid ideation, as well as anxiety and irritability, may be apparent. Furthermore, the anxious symptoms related to fear of abandonment as well as recurrent suicidal ideation and impulsive gestures may often meet technical criteria for an anxiety disorder and therefore lead to treatment with anxiolytic medications as well.

Furthermore, the issue of comorbidity in anxiety disorders has been insufficiently addressed in the literature. Comorbidity suggests that another illness exists at the same time as an anxiety disorder. But it supposes that we are dealing with discrete entities rather than symptoms grouped by the eye of the observer. Merely proving a checklist of symptoms may lead to grave errors of misdiagnosis. Many examples of this exist in anxiety disorders and may lead to unnecessary polypharmacy. The following are examples of such situations:

1. Panic attacks may be confused with hypomania if the patient presents as distractible, anxious, and unable to sleep. The reverse can also occur, with mania sometimes being misdiagnosed as panic attacks partly due to the fact that patients are acutely aware that they are anxious and seek help for anxiety but are often unaware of experiencing mania (lack of insight).
2. Obsessive ruminations may be part of the clinical picture of depression rather than OCD.
3. Social phobia may be part of the prodrome of schizophrenia.
4. OCD with poor insight may be misdiagnosed as a primary psychotic disorder; conversely, what is sometimes referred to as schizo-obsessive disorder may be misdiagnosed as OCD.
5. GAD may be misdiagnosed as major depressive disorder with reported symptoms of worry, decreased concentration, fatigue, and insomnia.
6. The anxiety of borderline personality disorder may be construed as being panic disorder.
7. Simple or social phobia or severe panic disorder may be misdiagnosed as paranoia.

Careful consideration of these factors would allow more intelligent decisions regarding polypharmacy.
Reasons Related to Available Medications

The predominant medications used in the treatment of anxiety disorders include benzodiazepines and SSRIs. In addition, TCAs, nefazodone, and MAOIs are also used. It seems that these agents act fairly nonspecifically, as most of them are indicated for the treatment of anxiety and depression. This clinical nonspecificity is combined with a supposed neurochemical specificity, as benzodiazepines are thought to effect their actions through GABA receptors predominantly, SSRIs through serotonin receptors predominantly, tricyclic antidepressants through norepinephrine receptors predominantly, and MAOIs through dopamine and norepinephrine pathways predominantly. When one compares this with pathways currently implicated in anxiety, one may see that it appears that multiple chemical pathways are thought to be implicated in anxiety disorders (23,24).

In panic disorder, studies have emphasized the relative importance of norepinephrine in the locus coeruleus, as well as the possible roles of the other anatomical areas that contain a diversity of chemical receptors, such as the amygdala and the frontal cortex. Furthermore, PTSD has been shown to affect areas such as the hippocampus, and OCD has been shown to involve the fronto-thalamo-basal-ganglia circuit, which is extremely diverse in its receptor populations. Thus, it may be that each of the medications addresses only a specific component of anxiety and that multiple medications combined may address the entire pathway implicated in anxiety. The biochemical details are also more complicated than at first glance. For instance, SSRIs are not purely serotonergic and generally have secondary effects on norepinephrine pathways via interneuronal connections in the medial forebrain bundle (25). Furthermore, from a functional standpoint, the mood-elevating effects of the SSRIs and the anxiolytic effects of the benzodiazepines may all contribute to a reduction of anxiety.

Another issue relating to the use of multiple medications relates to the combined use of benzodiazepines with SSRIs as initial treatment of panic disorder. Although the American Psychiatric Association has issued a position statement encouraging the use of benzodiazepines in the treatment of panic disorder, the long-term use of benzodiazepines is often an issue of contention in the face of dependency (26). This issue seems relatively unexamined in relation to the treatment of anxiety disorders. Implicit in the aversion to dependency symptoms is not only a clinical awareness of the dangers of physiological dependency (including the need for higher and higher doses of medications and the difficulty of withdrawal symptoms in the case of discontinuation), but an ethical dilemma of weighing this against the unknown long-term effects of SSRIs. The psychodynamic considerations of this dilemma are discussed in Chapter 12. Notwithstanding these dilemmas, the combined use of a benzodiazepine with an SSRI is therefore a common choice among clinicians who may hope to discontinue the benzodiazepine later, but who find that this is very difficult to do in a subpopulation of patients, thereby finding themselves on the way to polypharmacy.
Another medication-related reason for polypharmacy is that incomplete responses to medications may necessitate augmentation with other medications. For example, a patient with GAD on fluoxetine and diazepam may benefit from the addition of buspirone if the depression is incompletely treated in order to augment the effect of fluoxetine.

**Reasons Related to Clinicians**

Various factors related to clinicians may predispose to polypharmacy. These include the following:

1. Clinician impatience: some clinicians may be unwilling or unable to tolerate gradual improvement in symptoms and, in an attempt to alleviate anxiety more quickly, may add more medications sooner.
2. Clinician beliefs: some clinicians may allow their beliefs regarding ‘‘the more the better’’ to override their concerns about additive side effects of medications.
3. Clinician ignorance: clinicians may be ignorant about the treatment of refractory or residual symptoms of anxiety. For example, the conversion of panic disorder to limited symptom panic attacks with medication may be further (if not exclusively) helped by psychotherapies such as cognitive behavioral therapy (CBT) or short-term psychodynamic psychotherapy. Adjunctive use of therapies rather than medications relies on the psychopharmacologist’s openness to these modalities of treatment, as well as the willingness of the psychopharmacologist to work with CBT therapists. In addition, recent studies have shown that CBT may be as effective as medication in alleviating panic attacks, and clinicians would need to know this to feel comfortable using this option instead of more medication. Furthermore, treatment refractoriness does not necessarily mean that medication doses should be increased or that more medications should be added. For example, the use of neuroleptics in the PTSD population is often accompanied by ‘‘anxiety,’’ which can be more adequately treated by lowering the dose slightly (based on the possibility that the anxiety is really a form of akathisia) rather than adding a benzodiazepine.
4. Clinician insecurity: clinicians who feel insecure about their prescribing skills may use multiple medications as an act of bravado to demonstrate their willingness to be aggressive with medications. In addition, they may become overwhelmed by demanding patients or patients with personality disorders and may submit to their request for more medications in order to ‘‘quiet them down.’’
5. Managed care pressures: the average outpatient visit may be only 15
Polypharmacy of Anxiety Disorders

Due to inadequate time, clinicians may overly prescribe medications as the time for diagnostic formulation and reassessment is so short.

Reasons Related to Patients

Anxious patients are prone to becoming more anxious if their medications do not work immediately. As a result, patients may escalate, thereby feeling that they need more medication instead of less of it. Other diagnostic issues such as comorbid antisocial personality disorder may lead patients to want to abuse medications, and patients may find a way to encourage treaters to prescribe more medications. This issue often arises in patients with a diagnosis of alcohol dependence who are treatment refractory to all medications except benzodiazepines for anxiety. Here clinicians may add medications in the hope of ameliorating all symptoms.

PROBLEMS ASSOCIATED WITH THE POLYPHARMACY OF ANXIETY DISORDERS

Most anxiety disorders are chronic and/or recurrent such that the pharmacological treatment of these disorders is usually long term. In this regard, polypharmacy poses a problem, as patients are exposed to the problems of polypharmacy over a long period of time.

Broadly speaking, the problems of polypharmacy in anxiety may be summarized as follows (Table 3):

1. Multiple medications may lead to multiple side effects. Besides this being a problem in of itself, patients with anxiety disorders may have a particular sensitivity to physiological alterations that may exacerbate their anxiety. In fact, the leading psychological theory explaining the vulnerability to panic disorder is that patients with panic disorder have a “fear of fear” (27). Thus, producing perceptible physiological alterations could conceivably worsen symptoms for patients.

2. Polypharmacy may increase the likelihood of dangerous drug interactions. Patients with anxiety disorders may have medical comorbidity as well and may be on medication for these disorders, too. For example, many patients with panic disorder have comorbid cardiac conditions (28) or hyperthyroidism (29). In addition, patients with anxiety as part of a personality disorder may have chronic pain conditions such as fibromyalgia or other conditions such as endometriosis. In these conditions, combining the bradycardia of propranolol with the respiratory
Table 3  Problems Associated with Polypharmacy in Patients with Anxiety Disorders

1. Anxious patients have an increased sensitivity to multiple side effects.
2. Medical comorbidity is an important variable in patients with anxiety disorders.
3. Medication can be expensive.
4. Medications may cause anxiety.

Depression of benzodiazepines may be problematic for patients with a history of a myocardial infarction or chronic obstructive pulmonary disease. In addition, three-way drug interactions may arise in patients with psychiatric comorbidity such as bipolar disorder and panic disorder if they have an additional diagnosis of hypertension—all quite ubiquitous conditions. That is to say that clinician vigilance would need to increase and interdisciplinary communication would need to increase to avoid these problems. Given that this structure of treatment communication is in fact declining, polypharmacy poses an additional problem.

3. Multiple medications are more expensive. Thus, using multiple medications may place a strain and psychosocial burden on patients who are already psychologically compromised.

4. Using multiple medications may further complicate the diagnostic picture. The diagnosis of anxiety disorders is already quite murky in the clinical world. Add potential additive side effects of medications, such as the disinhibition of benzodiazepines combined with the anxiolytic effects of SSRIs and the stimulating effects of amphetamines in a patient with treatment refractory depression and anxiety, and we have an even more complicated clinical picture. This makes diagnosis and, therefore, treatment even more problematic.

PSYCHOLOGICAL AND ETHICAL CONSIDERATIONS RELATED TO POLYPHARMACY OF ANXIETY DISORDERS

The prescription of medication occurs from a clinician to a patient. Inherent in the prescription of medication in polypharmacy are the following factors:

1. The clinician makes a decision about polypharmacy.
2. The patient makes a request for more help.
3. The clinician and patient both have needs in the relationship: the clinician needs to feel helpful; the patient needs to feel better.
4. The clinician and patient both have a past and future, each of which has a bearing on the present.
When a clinician decides to treat a patient’s anxiety disorder with polypharmacy, several psychological factors may determine how this decision is made (these are discussed in more detail in Chapter 12). Questions that may be relevant for anxiety disorders include the following:

1. What is the clinician’s countertransference? In other words, what unconscious factors in the clinician’s life are at play when the clinician decides to add more medications? Is it possible that the clinician has felt hopeless in handling the anxiety of a loved one in the past? Does the clinician feel he needs to make up for a past mistake? Is the clinician compensating for being otherwise unavailable? Is the clinician trying to augment a sense of personal power by “preening” in the form of showing off more prescriptions?

2. What is the patient’s transference? Does the patient feel empty? Does the patient want the clinician to prove that he is more powerful? Does the patient feel that the anxiety may be quelled by receiving “more” of anything?

3. What kind of grieving process is going on in the acceptance of the “illness”? In coming to terms with the diagnosis of an anxiety disorder, is the polypharmacy part of the “bargaining” stage of grief?

4. What defense mechanisms are operating? Is there an unrecognized projective identification such that the clinician feels the anxiety of the patient without recognizing that it is the patient’s anxiety that is being felt through an unconscious identification process? Is the decision to give more medication based on this unmetabolized anxiety that the clinician feels?

The question as to whether there are ethical considerations in the decision to use polypharmacy is complex. At a fundamental level, the clinician is obligated to provide the best possible service to the patient without doing any harm to the patient. Presumably, the decision about the best possible treatment is informed by research studies and clinical experience. Most medication trials in anxiety disorders do not reflect the clinical population treated since most trials exclude comorbidity. Thus, whereas depression and substance abuse are common, studies often do not include those diagnoses. Furthermore, there are few studies to date focusing on the polypharmacy of anxiety disorders. Thus, whereas guidelines for monotherapy exist, most conclusions about polypharmacy have not been studied in a standardized manner. Add to this the consideration that information gathered in a standardized manner on a statistical sample usually does not pertain exactly to a given individual, and the picture becomes even less clear.

Given that the placebo response may be relatively lower in OCD than panic disorder trials, for example, it is possible that the effects of polypharmacy are very different for each diagnosis in the “anxiety disorders” category. As pointed
out earlier, it is also unclear as to whether the side effects are additive in the long term, and in considering “do no harm” in psychiatry, there is relatively little evidence of the effects of long-term treatment of anxiety disorders. Still more complex a consideration would be the question as to how the “self” is altered in using medication treatment and whether this is exacerbated with polypharmacy.

The provision of relief of suffering is also a complex religious issue, as most religious orders would speak to a certain function of anxiety and suffering in inspiring a closeness with God. Furthermore, from a spiritual standpoint, psychiatry tends to aim for the elimination of all anxiety that is distressing to the patient, and although this appears to be borne out of kindness and consideration, it leaves questions related to the spiritual and protective functions of anxiety unaddressed. Even more contemporary nontheistic approaches to such questions as how to deal with anxiety might advocate a certain awareness and observation of this state, rather than the eradication of anxiety.

From a pharmacological perspective, it has always been unclear whether the medications involved in polypharmacy actually reduce anxiety or some related faculty that is not usually measured in clinical trials. For example, to what extent do the benzodiazepines (even more so in combination with other medications) reduce awareness of anxiety rather than anxiety, and how generalized is this reduction of awareness? In the pharmacological literature, this is sometimes referred to as “transient sedation.” Does the transience of this effect relate to the passing of this reduction of clarity of awareness or to a certain adaptation to this new level of consciousness? Reports that panic attacks occur “out of the blue” or that OCD is one of the most “biological” illnesses is curiously associated with little awareness of the origins of these symptoms in the patients themselves. It is interesting to consider whether this reduction of awareness of symptom onset or the apparent suddenness of these symptoms suggests an already compromised state of awareness and that the drugs we use may “solve” the problem by entirely eradicating awareness factors, rather than enhancing awareness. Polypharmacy of anxiety disorders may potentially worsen this dilemma.

**Rational Versus Creative Polypharmacy**

Opponents to this line of thinking might advocate for “rational” polypharmacy. It is unclear whether this would be more beneficial than creative polypharmacy, which has received little consideration in the literature since it is perceived to be associated with more risks (Table 4). An example of rational polypharmacy would be adding a medication that acts at GABA receptors to a medication that acts at serotonin receptors to provide additional nonredundant benefit. Another example at a clinical level would involve the consideration that a medication targeting localized social anxiety (performance anxiety) such as propranolol
Table 4  Some Differences Between Rational and Creative Polypharmacy

<table>
<thead>
<tr>
<th>Rational polypharmacy</th>
<th>Creative polypharmacy</th>
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</thead>
<tbody>
<tr>
<td>1. Linear, data-based</td>
<td>1. Nonlinear, clinically based</td>
</tr>
<tr>
<td>2. Does not account for ignorance regarding actual knowledge of receptor interactions</td>
<td>2. Integrates knowledge of receptor interactions with clinical experience</td>
</tr>
<tr>
<td>3. Based on group effects and extrapolated to individuals</td>
<td>3. Based on integrating knowledge of group effects and clinical experience and anecdotes</td>
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could be added to a medication targeting generalized social anxiety such as an SSRI.

However, the delineation of a definitive logical stream may be deceptive in that, in the case of the former example, we have little idea how different receptor systems truly interact at the level of neuronal pathways or systems, and in the latter example we are not giving consideration to the additive side effects of both medications.

Contrasting with this rational approach would be a creative approach, which works from different treatment perspectives. This approach assumes that a certain knowledge of the overall clinical picture coupled with a knowledge of clinical psychopharmacology and receptor physiology leads to a complexly processed decision (sometimes referred to as a “hunch”) to add a medication to the current regimen. For example, clinical anecdote might suggest that “adding a touch of quetiapine at bedtime” may reduce the anxiety and restlessness of a particular individual or that a combination of “prn alprazolam” with “standing clonazepam” may be helpful. In general, pharmacological consultation often relies on this kind of intervention, usually by experienced clinicians. The disadvantage of this approach is that it seems unexamined or not provable, yet if viewed from the point of view that medicine is, at least in part, an art, it may be justifiable.

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Polypharmacy of Posttraumatic Stress Disorder

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INTRODUCTION

History and Prevalence

Posttraumatic stress disorder (PTSD) is among the most prevalent Axis I diagnoses, with a lifetime occurrence of 7.8–12.3% in a number of studies (1–3), which would make it more common than both schizophrenia and bipolar disorder. Little has been known about the biology and pharmacology of PTSD until the last 10 years. Over the past 20 years there have been few controlled studies and even fewer double-blind studies of medication effectiveness in PTSD. Surprisingly, there have been no articles published on polypharmacy in PTSD. This is troubling because many clinicians who treat clients with chronic PTSD find that monotherapy is the exception, polypharmacy the rule. As the pathophysiology of PTSD is revealed in more depth and treatment strategies are designed to deal more directly with the chemical deficits in PTSD, one can hope that this situation will change. A closer look at the complicated clinical and chemical picture of PTSD will highlight the difficulty in treating PTSD with a single psychotropic agent.

Posttraumatic stress disorder has been recognized within the mental health field for the past 100 years. Until recently it was termed “combat neurosis” or “shell shock” and thought of as a condition related to combat traumas. Over the past 15 years it has become clear that PTSD can be the outcome of many different types of traumas, ranging from natural disasters to automobile accidents, to assault, childhood abuse, or terrorist attack. Witnessing serious injury or death due to any of the above may also cause PTSD. The diagnosis of PTSD first appeared in DSM-III (4) and is currently part of DSM-IV (5).
The idea that PTSD is a normal response to a major traumatic event may have held up research into the pathophysiology of PTSD (6). PTSD is not the usual response to severe trauma. Lifetime exposure to a severe trauma is estimated to be 33% of a given population (7,8). Of those exposed to a major trauma, only 10–20% will develop PTSD (3). The research on the biology and treatment of PTSD is still relatively new within psychiatry, so it is not surprising that it remains difficult to predict who will develop PTSD, and it remains a condition that is often misdiagnosed or not diagnosed at all and therefore mismanaged or not treated.

Diagnosis

The diagnosis of PTSD is based on four criteria (5) (Fig. 1). The first is the exposure to a traumatic event. A traumatic event has been characterized as a situation in which a person experienced, witnessed, or was confronted with an event that involved actual or threatened death or serious injury or a threat to the physical integrity of others. When evaluating PTSD in adults who were abused as children, the clinician must consider the perception of the trauma through the

Fig. 1  Diagnosis of PTSD.
eyes and body of a child, not an adult. A well-meaning clinician may minimize the impact of traumatic events reported by an adult as having occurred in early childhood. Particularly in cases of incest or intrafamilial physical violence, a child’s dependency on his or her adult abusers can mimic the trappings of political torture.

After exposure to the event, a client must experience symptoms in three different clusters to qualify for the diagnosis of PTSD. Reexperiencing symptoms include intrusive recollections of the trauma, nightmares, or flashbacks where clients feel as though they are reliving the trauma or abuse. Avoidance symptoms may include an inability to recall the trauma, a decrease in motivation, detachment from others, a constriction of affect, a foreshortened sense of the future, and disinterest in life. Finally, PTSD clients often have an increased physiologic arousal with irritability, insomnia, anger anxiety, or panic symptoms. The symptom profile of PTSD is variable and complex, with symptoms that overlap with anxiety and affective disorders. It is easy to see how a clinician not considering PTSD or without the knowledge of a past trauma could end up with another diagnosis. It is therefore essential that all clinicians incorporate a trauma assessment and PTSD questions in their evaluation interviews.

Clients at risk for developing PTSD after a life-threatening event include individuals with preexisting anxiety or depression, an early history of adversity or abuse (i.e., childhood separation from parents, childhood abuse, both physical and sexual, early parental divorce, sexual assault), and high neuroticism scores (9).

Treatment—Overview

When diagnosed appropriately, treatment options for PTSD include a range of psychotherapeutic interventions along with psychotropic medication. For milder symptoms of PTSD, the American Psychiatric Association (APA) guidelines (which polled leading researchers and clinicians in the field of PTSD) (10) suggest starting with psychotherapy (focusing on anxiety management, cognitive therapy, exposure therapy, play therapy for children, or psychoeducation) and, if these do not produce sufficient relief, the addition of psychotropic medications. Psychopharmacologists polled felt that for moderate to severe symptoms of PTSD it was best to start with psychotherapy combined with medication treatment. Though there are no studies looking at polypharmacy in PTSD, both anecdotal reports and APA guidelines suggest that polypharmacy is often needed. The APA guidelines point out that if a client does not have a sufficient response to an SSRI, nefazodone, or venlafaxine during a clinical trial, it is often necessary to add other psychotropic medications. A look at the complicated neurobiological picture of PTSD may highlight the need for multiple medications to treat the PTSD spectrum.
THE NEUROBIOLOGY OF PTSD

The symptom profile of PTSD is complicated and individually variable, with three main symptom clusters: reexperiencing the trauma, hyperarousal, and avoidance symptoms. Recent studies of the biology of PTSD indicate that different neurotransmitter systems may be responsible for the different symptom clusters seen in PTSD. If proven true, it would support the practice of polypharmacy, as medications that work on different transmitter systems would be needed to attack different symptom complexes.

The Stress Response System

Although PTSD is an abnormal response to extreme, traumatic stress, it is helpful to understand the normal stress response system as background knowledge to help understand where the system breaks down in individuals who develop PTSD (11). Yehuda poses the central question in PTSD as "why there has been a failure of the body to return to the pretraumatic state."

An individual’s response to a traumatic stress begins in the amygdala. The amygdala is the interface between the sensory system and the motor, behavioral system that will help the individual deal with the stress (12). The amygdala determines whether a stress response will be initiated. If the threat warrants a stress response, then the amygdala sends messages through its multiple connections. Projections to the reticularis pontis caudalis potentiate the startle response (13). Projections travel from the amygdala to the lateral hypothalamus and to the rostral ventral medulla initiating the sympathetic nervous system, the catecholamine response (14). There are also projections from the amygdala to the stria terminalis, which initiates the hypothalamic-pituitary-adrenal (HPA) axis response (15). Based on these pathways, one would expect to see elevations in both catecholamines and cortisol when an individual is under acute stress. Catecholamines are the facilitators of the “flight, fight, or freeze response” seen in organisms under acute threat. Catecholamine release results in an increase in blood flow and glucose availability to skeletal muscles to prepare for fighting or fleeing (16). Cortisol is an “antistress hormone.” It shuts down the stress response system, and as the stress response diminishes and the need for cortisol is less, the cortisol feeds back through the HPA axis turning off the secretion of CRF and, through the axis, cortisol itself.

Stress Response, PTSD, and the HPA Axis

Individuals with PTSD exhibit a number of interesting variations to this acute stress system. First, there does seem to be an exaggerated sympathetic response to any ongoing stress or reminders of the trauma. This is most clearly seen in
studies of PTSD clients given an α₂-antagonist, yohimbine. This drug increases PTSD symptoms as well as increasing MHPG levels (a metabolite of the catecholamines) in trauma survivors (17).

Yehuda (11) has studied the HPA axis in PTSD extensively and has discovered a number of unusual patterns (Fig. 2). She found a number of unique changes in PTSD that differentiate it from depressive disorders. Individuals with chronic PTSD have a decreased level of cortisol, an enhanced negative feedback of cortisol on the glucocorticoid receptors of the pituitary gland, and supersuppression of dexamethasone. The glucocorticoid receptors seem to be upregulated in both sensitivity and number. Therefore, under further stress, norepinephrine released is only mildly opposed in those with chronic PTSD. Van der Kolk (18) has postulated that the high levels of norepinephrine in PTSD may be directly related to hyperarousal symptoms including agitation, sleep impairments, nightmares, and flashbacks.

Fig. 2  Hypothalamus-pituitary-adrenal axis—enhanced negative feedback in PTSD.
It was once believed that the low levels of cortisol in individuals with PTSD were the result of adrenal exhaustion (19). However, this argument has been countered by two studies that show low cortisol levels at the time of the original stress. Yehuda et al. (20) measured cortisol levels immediately following an automobile accident with follow-up measures 6 months later. In individuals who eventually developed PTSD, the cortisol levels immediately following the accident were significantly lower than in those individuals who did not develop PTSD. In a second study looking at cortisol levels postrape (21), women who had a prior history of rape had lower cortisol levels postrape than did women who did not have a history of rape. This suggests that events occurring prior to a traumatic event may have an impact on the future development of PTSD.

One of the hallmarks and crucial symptom complexes of PTSD is the reexperiencing of traumatic material in the form of intrusive memories, nightmares, and flashbacks. Pitman (22) has theorized that the high levels of neuropeptides and catecholamines at the time of the acute stress result in memories of the traumatic event being “overconsolidated” or remembered in an exaggerated state because of the high level of distress that accompanies them. Yehuda (11) takes this one step further, arguing that “the increased distress that accompanies the traumatic reminders might activate stress response systems and primarily CRF.” The CRF is then hyperreleased. This travels to the pituitary to stimulate adrenocorticotropic hormone (ACTH) release and ultimately to the adrenals to secrete cortisol. However, because of the enhanced negative feedback of cortisol to the pituitary glucocorticoids, the cortisol ends up “turning down the volume” on its own production of cortisol. So as the HPA axis is continually exposed to CRF, it also is being continually sensitized to the cortisol and stress (11).

Ideal Drugs—CRF Antagonists and Neuropeptide Y Agonists

Based on the information regarding the role of CRF in the development and pathophysiology of PTSD, it would seem that a CRF antagonist, given at the time of an acute trauma to prevent the dysregulation of the stress response system, would be the treatment of choice (23) for PTSD prevention. Though trials of drugs are underway, there is no CRF antagonist on the market for clinical pharmacologists who are now treating clients with severe PTSD symptoms. Another option that would treat PTSD closer to its “core” problem would be a neuropeptide Y enhancer. Friedman (23) describes neuropeptide Y as being heavily concentrated in the brain stem, amygdala, hypothalamus, and cortex. Its action is as an endogenous anxiolytic. Neuropeptide Y attenuates the action of CRF and other stress-released peptides. A study of military personnel undergoing basic training found that those with high levels of neuropeptide Y tolerated the stress signifi-
Polypharmacy of Posttraumatic Stress Disorder

Significantly better than those with lower levels (24). However, like a CRF antagonist, we do not yet have access to a commercially available neuropeptide Y enhancer, therefore we are left to fall back on other drugs that will intervene in the adrenergic system.

Inescapable Shock

The clinical picture of PTSD is variable both in cross section and over time. A review of the research data provides evidence for both consistent findings (i.e., changes in the HPA axis) and also some seemingly contradictory findings (i.e., one person feels better when administered an opioid antagonist, another person feels more symptomatic, one person can have intrusive symptoms when stimulated with the serotonin agonist MCPP, while another feels intrusive symptoms only when an adrenergic agonist, yohimbine, is administered.) This complex clinical pattern is difficult to treat and difficult to explain. Another model that may provide some clues to the neurophysiology of PTSD is the animal model of inescapable shock. When an animal is exposed to a chronic stress with no hope for escape, it is affected on many different levels. It has deficits in learning to escape novel adverse situations, it has decreased motivation for learning new contingencies, there is evidence of chronic subjective distress (25), and there is evidence of an increase in tumor genesis and immunosuppression (26).

When a rat is exposed to shock from which it cannot escape, it responds initially with an outpouring of neurotransmitters including serotonin, epinephrine, dopamine, and endogenous opioids (27). In response to the massive outpouring of neurotransmitters over time, the rat brain will downregulate the postsynaptic receptors in an effort to decrease the overwhelming stimuli (Fig. 3). With continued shock, the neurotransmitters may become temporarily depleted as utilization exceeds synthesis. Despite the fact that the overwhelming stimuli may be occurring, the rat brain perceives a period of neurotransmitter depletion and the postsynaptic receptors upregulate (Fig. 4). With ongoing shock the postsynaptic receptors increase in number and sensitivity. When a normal or large volume of transmitters is released into the upregulated receptor state, the response is exaggerated and the signal is amplified (28,29) (Fig. 5). Under further stress, the transmitters cycle through periods of depletion and amplification. Van der Kolk has postulated that this may be behind the “all-or-nothing” responses seen in clients with PTSD (30).

If we use this model of inescapable shock to look at the psychopharmacology of PTSD, it is not difficult to imagine the need for polypharmacy. Given that many neurotransmitters are involved and the symptoms are so varied in quality and quantity, trials of many medications may be needed to adequately decrease the symptom profile, allowing a person to feel functional.
A look at the multiple transmitter systems known to be involved in PTSD may help a practitioner further understand the mechanisms behind symptoms complexes and make the task of polypharmacy less of a hit or miss proposition.

Serotonin

Since SSRIs are the first line of treatment for chronic PTSD, it may be wise to look at the role of the serotonin system in the stress response system and in PTSD. It is clear from animal research that serotonin affects many of the pathways that are altered in PTSD including sleep regulation, aggression, cardiovascular activity, motor function, anxiety, mood, and neuroendocrine secretion (23). Southwick and associates (31) have argued that serotonin affects both adrenergic and HPA pathways. In a study of Vietnam veterans with PTSD given MCPP and yohimbine, some veterans exhibited panic attacks and flashbacks to combat when given MCPP, a serotonin agonist that affects serotonin-2 and serotonin-1C receptors.
A different group of veterans responded with nightmares and flashbacks when given the norepinephrine agonist yohimbine. These variable responses to adrenergic and serotonin agonists suggest the idea of various subtypes of PTSD (23) and also may highlight the trouble in trying to treat PTSD chemically. A client with intrusive symptoms may have a primary dysregulation in the norepinephrine or serotonin systems or in both.

**Opioids**

The endogenous opioids play an important role in the stress response system. Animal models have revealed that under acute stress such as electric shock, restraint, or forced swimming, a diminished response to pain is observed, called stress-induced analgesia (32). Research has also shown that patients with PTSD have lower pain thresholds, lower beta-endorphin levels, and decreased produc-
Signal amplification. (From L. Langhammer.)

tion and release of methionine-enkaphalon and perhaps less stress induced analgesia (33,34). Clinical research into the psychopharmacology of opioid dysregulation in PTSD suggests that the opioids play a role in the emotional numbing seen in PTSD; however, like with norepinephrine and serotonin, it is difficult to interpret who has elevated levels of opioids and who has lower baseline levels of opioids. Some veterans given an opioid antagonist will respond by feeling more alive and less constricted emotionally, while others respond by feeling more overwhelmed and anxious with panic attacks and flashbacks. It is theorized that if a trauma survivor had elevated levels of the opioids that were causing him to "numb out," blocking them with an opioid antagonist may, in fact, decrease the avoidance symptoms of PTSD. If, on the other hand, a survivor had low levels of the endogenous opioids, lowering the levels further with an antagonist may worsen untreatable intrusive, hyperarousal symptoms (34).
Glutamate

The excitatory neurotransmitter glutamate has recently been explored in connection with dissociation. Though dissociation is not necessary for a diagnosis of PTSD, it is a symptom that can be quite disabling to clients and difficult for clinicians to treat. There has been scant research into the psychotropic treatment of dissociation in large part because until recently it has been poorly understood. Glutamate plays an important role in the stress response system.

Chambers (35) has described dissociation as a distortion in the processing of information related to self and the environment. Research has shown that dissociation at the time of the original trauma is the best predictor of long-term PTSD and dissociation (36,37). There is a growing body of literature that suggests that high levels of glutamate at the time of the trauma is the cause of ongoing dissociative states. High glutamate levels may also contribute to long-term structural damage in the brain that leads to PTSD (35,38).

The balance of inhibitory input and excitatory input in critical brain pathways maintains organized perception (Fig. 6). Glutamate is the main excitatory transmitter, while the inhibitory transmitters include the monoamines, L-dopamine, norepinephrine, and serotonin, as well as GABA. During times of acute stress the brain responds by releasing both excitatory neurotransmitters and inhibitory neurotransmitters. How glutamate signals are modulated in key areas of the brain determines the way the individual perceives a stressful stimuli and in what form it reaches consciousness (35).

The balance of these inhibitory and excitatory neurotransmitters in the cortex, thalamus, amygdala, hippocampus, and “motivation response systems” determines the extent of dissociation (Fig. 6). The cortex serves as the cognition and association area of the brain, the thalamus serves as the sensory relay station between the cortex and the limbic system, the amygdala is the danger signaling component of the limbic system, and the hippocampus is implicated in learning and memory. The hippocampus is important in differentiating signals, since some clues represent danger only in certain settings. Dissociation is thought to represent a relative hypersecretion of glutamate within these pathways (35).

Receptor chemistry for glutamate is also complicated. Glutamate binds to many receptors. When considering dissociation and the response to trauma, the NMDA receptor and the non-NMDA receptor, AMPA are most important. The NMDA receptor is in high concentrations in the cortex, hippocampus, and amygdala. When glutamate binds to the NMDA receptor, the complex modulates the influx of calcium into the nerve cell, eventually producing long-term changes in function and structure of the excitatory neurons and neuronal networks in which they live (39).

Glutamate binding to the AMPA receptor initiates a more rapid response,
Fig. 6  The stress response system. (From Ref. 35.)
mediating the rate of firing of neurons. It is felt that the immediate disruption in perception associated with dissociation is due to an overstimulation of the AMPA receptor subtype. Studies have shown that when an individual is given a glutamate antagonist such as ketamine or PCP, the glutamate NMDA receptors are blocked preferentially. When blocked, the body responds by excreting more glutamate, which is then left to bind to the other receptors, including the rapidly acting AMPA receptors (40). In these experiments, individuals with an increase in stimulation of the AMPA receptors present with symptoms that look similar to dissociation, with disrupted perception, impaired attention and judgment, and altered coding of memories (41,42).

Currently, a psychotropic treatment strategy for dissociation based on this model would consist of trying to restore the balance of excitatory and inhibitory neurotransmitters. One could restore deficient inhibition via the GABA or opiate systems with either benzodiazepines or opiate analogs. Another option would be to decrease excessive glutamate stimulation. Lamotrigine, for example, decreases the presynaptic release of glutamate (43). This is an area that needs much more clinical research.

POLYPHARMACY IN PTSD

Lack of Research Data

There have been no clinical studies of polypharmacy in PTSD. A review of the literature shows that in many controlled studies of antidepressants or other medications for PTSD, the use of another agent is often acceptable within the guidelines of the study (44,45). When the symptoms of PTSD are defined as moderate to severe, APA guidelines direct clinicians to combine psychotherapy with psychotropic medications, even polypharmacy when needed (10). Why are multiple medications used so frequently in treating PTSD?

Multiple Symptoms, Multiple Neurotransmitters

As has been reviewed above, each symptom complex within the diagnosis of PTSD (intrusive reliving, hyperarousal, and avoidance) may be caused by deficiencies or excesses in the action of a different neurotransmitter. Therefore, psychotropic treatment may mean treating with more than one drug, particularly if each drug treats a different symptom complex. Additionally, similar symptoms in two different people may be caused by different neurotransmitters. For example, nightmares or flashbacks can be associated with low levels of serotonin, high levels of norepinephrine, or both (17). The APA guidelines recommend starting with an SSRI, nefazodone, or venlafaxine for initial treatment of PTSD regardless of the symptom complex most prevalent at initial diagnosis. However, if there
is only partial response or if there is clearly other symptoms left after treating with an SSRI, the guidelines are clear that adding another medication to an SSRI to maximize functionality is warranted (10).

Comorbidity

Another explanation for polypharmacy in clients with PTSD is the unusually high comorbidity rates. PTSD is usually a comorbid diagnosis. The National Comorbidity Study (2) found that in 59% of men and 44% of women with PTSD, diagnosis met three other psychiatric disorders. In this study the most common comorbid diagnoses were affective disorders, other anxiety disorders, and substance abuse. The Vietnam Experience Study (46) found that among veterans with PTSD, 66% also met criteria for an affective or anxiety disorder and 39% had current substance abuse. Another look at Vietnam veterans (47) found that 98.9% of those diagnosed with PTSD met criteria for at least one other psychiatric disorder (substance abuse 73%, antisocial personality disorder 31%, and major depression 28%). Cashman and colleagues (48) looked at 277 female victims of assault and found 60% with comorbid major depression and 25% with substance abuse disorders. There were also higher than normal rates of personality disorders, namely borderline, avoidant and paranoid personality disorders. There are also documented connections between bulimia nervosa and PTSD in women. A recent study (49) identified childhood sexual abuse to be a nonspecific risk factor for the development of bulimia but not anorexia. In 294 women sampled with eating disorders, 52% reported symptoms of PTSD (50). There has been work showing a connection between somatoform disorders and PTSD (51). Though there is little research on psychosis in PTSD, there is evidence that clients hospitalized with major psychotic illnesses have an alarming and often undetected rate of trauma and PTSD. Mueser and associates (52), in a study of 275 severely chronically mentally ill individuals, found that 43% met the criteria for PTSD, though only 2 currently carried the diagnosis, and that almost all of them reported exposure to at least one traumatic experience.

Though it is not clear whether the comorbid diagnosis sets the stage for development of PTSD or whether PTSD precedes the development of a comorbid disorder, what is clear is that the comorbidity seen with PTSD complicates the diagnosis and treatment of both conditions. Zlotnick et al. (53), assessing PTSD with comorbid anxiety disorders, found that a history of alcohol abuse (and a history of childhood sexual abuse) both seemed to prolong the time to symptom remission in PTSD. Breslau and colleagues (3), examining young urban adults, found that those with chronic PTSD were more likely to have a comorbid anxiety or affective disorder than those without chronic PTSD. Alcohol use and depression have also been shown to prolong the course of illness in PTSD (54).

Given that up to 80% of clients with PTSD have some other Axis I diagno-
sis, it is clear that treatment strategies cannot focus on simply treating the pathophysiology of PTSD. A correct diagnosis is important for initiating psychopharmacology and other treatments. This diagnosis must be made by a skilled clinician who has experience differentiating some of the overlapping symptom complexes in comorbid diagnoses. For example, to a clinician not experienced with some of the extreme mood lability seen in PTSD, the mood fluctuations may be identified as bipolar disorder rather than PTSD and therapy with a mood stabilizer added prematurely. Given that the symptoms of chronic PTSD are more tenacious when there is a comorbid diagnosis, it is reasonable to assume that in many instances multiple medication trials and augmentation strategies may be used to get an acceptable response rate.

**Low Response Rates for Drugs and PTSD**

There is no a single medication that treats PTSD in its entirety. As was described earlier, a CRF antagonist or a neuropeptide Y agonist given at the time of the trauma or even later in the course of PTSD may correct the underlying HPA axis dysregulation, but these are not yet available (23). Even the most optimistic treatment tends to show a 30–50% reduction in PTSD symptoms. Given the severity of an individual’s PTSD symptoms, this reduction may be enough to put them back into the functional world. However, for many individuals with moderate to severe symptoms of PTSD, even a 50% reduction in symptoms leaves them with a significant disability. In those individuals, medications are often combined in order to combine overall efficacy.

One strategy for treating PTSD is to begin medicating with an SSRI, nefazodone, or venlafaxine. An adequate trial of an antidepressant for PTSD is 8 weeks. If there is no response, the clinician and client should choose another agent from the list of serotonin-enhancing medications. If there is partial response but the client still has functional impairment, the clinician should begin cautiously adding medication. The decision of what to add will be based on the remaining symptom type and severity (10). With partial responses to an SSRI, the APA guidelines recommend adding a mood stabilizer such as valproic acid. If after 8 weeks of SSRI treatment there is a partial response but with significant anxiety remaining, a short-term use of a benzodiazepine or buspirone is indicated. If the symptom remaining is sleep impairment, consider adding trazodone, and finally, if the client continues to have irritability and intrusive symptoms, an antiadrenergic agent such as clonidine should be added.

**Lack of Knowledge of the Clinician**

Many psychiatrists have not been trained intensively in the diagnosis and treatment of posttraumatic stress disorder. They may misdiagnosis PTSD as major
depression or another anxiety disorder. They may not be aware of the literature that documents the SSRIs to be effective for the treatment of PTSD but often at higher doses and with longer onset to action than for depression (55). A well-meaning psychiatrist may switch or augment an SSRI too early in the course of treatment. If an augmenting agent is added at 4–6 weeks rather than at 8 weeks, a response seen at 8–10 weeks may be assumed to be the result of the additional drug. In fact, the response may have been to the SSRI alone, needing longer to work for PTSD. In this scenario, the client with PTSD may be exposed to unnecessary polypharmacy.

Given the acuity of PTSD patients, particularly in extreme cases of abuse, it is not difficult to understand the clinician’s desire to minimize intense suffering as quickly as possible. However, I have often treated clients where multiple medications are added to combat the vast array of symptoms. Rather than systematically adding medication and assessing what is working and what is not and then taking away a drug that does not have clear efficacy, the psychiatrist keeps adding one medication after another. Clients can literally end up with a drug from every class and still have severe symptoms. The amount of distress in clients with severe PTSD and a lack of knowledge about what is a reasonable expectation for any drug used to treat this disorder can result in clients being prescribed dangerous amounts of medications without a substantial decrease in symptoms or increase in daily functioning.

ADVANTAGES AND DISADVANTAGES OF POLYPHARMACY

Advantages

The advantages of polypharmacy are clear. This is a disorder for which we currently do not have medications to treat the most central underlying physiological dysregulation. Therefore, in most cases, monotherapy for PTSD is going to provide a partial response at best. For moderate or severe PTSD or for clients who do not have a robust response to monotherapy, combining agents is the best option. Though complicated by drug interactions and dynamic issues around taking medications, for some, polypharmacy is the only hope of producing an acceptable level of life functioning.

Drug Interactions

Given that polypharmacy is not unusual in PTSD, the first question to ask would be what are the drug interactions. An SSRI, venlafaxine, or nefazodone is the first-line treatment of choice for all categories of PTSD except in individuals
who have a clear comorbid diagnosis of bipolar disorder (10). In general the SSRIs are relatively safe drugs to use, but the clinician needs to be cautious about the cytochrome p450 liver enzyme system. With the relatively low response rate to any medication for PTSD, it is likely that a medication change or augmentation strategy will be used particularly early in the treatment. Combining two drugs that compete for enzymes is not an absolute contradiction, but the client must be informed of and monitored for any signs of serotonin toxicity or other sudden side effects.

Additionally, individuals with chronic PTSD and trauma histories are at increased risk of other health and immune function problems (56–59). It is essential that a thorough medical and medication history be done so that medications are not prescribed that would interfere with other medications or exacerbate physical symptoms from a chronic illness. For example, trauma survivors may have complaints of gastrointestinal problems, such as irritable bowel. The SSRIs may cause a worsening of these symptoms, or if the psychiatrist has not taken a thorough history and discovered irritable bowel syndrome on routine questioning, follow-up monitoring of gastrointestinal side effects from the SSRIs may become confused. At each follow-up psychiatric visit, the clinician should inquire about changes in health and medications status.

**Suicide and Self-Destruction**

Clients with PTSD and trauma-related personality disorders (i.e., borderline personality disorder) have an extremely high rate of helplessness, suicidal ideation, suicide attempts, completions, and self-destructive behaviors. The risk of giving a potentially lethal or self-destructive client multiple medications which need to be taken with care and which, when taken self-destructively, could become fatal must be weighed against the risk of not treating some of the more severe symptoms of PTSD, which may leave a client more acutely suicidal and self-destructive. It is imperative that the psychopharmacologist become very sophisticated in discussing suicidality and self-destructive behavior. Since most clients with PTSD will remain chronically self-destructive throughout the early stages of trauma treatment (they often need to keep the SI as the last resort, something they have control over), it is essential that the clinician communicate compassionately and in depth with them and their other treaters about any shifts in suicidality or self-destructive behaviors. Having a suicide plan, particularly if it involves overdosing on medication, as is often the case, needs to be carefully factored into any decision regarding multiple medication dosing.

Acute suicidality alone should not rule out the possibility of more aggressive treatment, but it does mean working with the client to create a safe way to prescribe and dose multiple medications. I have a number of clients who have
their therapist hold medications, who get only a few days or a week at a time. Restricting medications in these people who so desperately need them to continue the healing work may be more harmful in the long run.

**Stigma**

Trauma and abuse of individuals often leaves a deep legacy of shame for individuals. Unfortunately, in our society, treatment by any mental health professional can also cause a significant amount of stigma and shame. Many individuals who have been traumatized can feel damaged and unworthy—the idea of taking medications seems like a weakness, a crutch that they should not have to turn to. Many have been coping with overwhelming symptoms on their own for years before seeking out therapy. Letting go of control and taking medications can be retraumatizing. If a client does not understand the pathophysiology of PTSD and does not understand that there is not yet the perfect drug to treat PTSD, then giving more than one medication can increase the stigma—it may be seen by the client as evidence that he or she is more sick or deficient. It is the job of the psychiatrist to thoroughly describe PTSD, its relationship to violence and abuse, and the limitations current psychiatric medications have in treating this disorder. This shared knowledge may allow a client to feel empowered to choose pharmacy and polypharmacy as a way out of the isolating symptoms, rather than experiencing the need for medications as a trigger of further symptoms.

**SUMMARY/GUIDELINES FOR CLINICIANS**

PTSD is a frequent and disabling condition. The symptom profile is complex, including symptoms of intrusion, avoidance, and hyperarousal. The clinical picture is usually further complicated by comorbid diagnoses, often affective disorders or other anxiety disorders, or substance abuse. Research into the neurobiology of PTSD is relatively new and ongoing. Deficits seem to be unique to PTSD and involve the stress response system, namely the HPA axis. There is dysregulation in multiple neurotransmitter systems, including norepinephrine, serotonin, glutamate, and the endogenous opioids. Though the profile is similar overall in individuals with PTSD, each client must be assessed based on his or her own history and symptom complex. Different neurotransmitter systems may cause similar symptoms in different people.

Treatment options have not been extensively studied, though at this point the treatment of choice for PTSD seems to be the SSRIs nefazodone or venlafaxine. Even the most effective treatment strategies usually improve symptoms by only 30–50%, leaving much remaining disability when monotherapy is used. Polypharmacy is the rule rather than the exception in PTSD. There are no studies
Polypharmacy of Posttraumatic Stress Disorder

looking at the use of polypharmacy in PTSD, but the following guidelines may be helpful when combining medications for the treatment of PTSD.

1. If monotherapy is not working, first reevaluate diagnosis. Have you missed a comorbid axis I or II diagnosis?
2. If you are adding to an SSRI, have you given the client a high enough dose of the medication and for a proper length of time for PTSD? Remember, PTSD responds more slowly, less robustly, and at higher doses of antidepressants than does depression.
3. Is your client capable of managing multiple medications; does he or she fully understand the potential drug interactions?
4. If adding a potentially lethal drug such as a TCA or a mood stabilizer, has the client’s safety been assessed thoroughly? If suicidal, is there a plan to limit the number of pills given at any one time?
5. Have you chosen a drug that minimizes drug interaction, particularly within the cytochrome P450 enzyme metabolism system?
6. Have you done a medical assessment regarding other drug use, either recreationally or medically, and factored this into the recommendation?
7. When adding a benzodiazepine to an SSRI at the start of treatment for anxiety management and hypnosis, taper off the benzodiazepine within 6–8 weeks to see if the anxiety or insomnia is improved with an SSRI alone.

If these questions are answered in the course of assessment and treatment, then a careful, reasoned form of polypharmacy can effectively be used to alleviate the suffering of this painful condition.

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INTRODUCTION

In addition to the psychiatrist’s usual concerns about poly(psychoph)armacy, treating the medically ill psychiatric patient introduces many additional considerations related to the effects of organ dysfunction and the side effects of nonpsychiatric medications. Both medical illnesses and nonpsychiatric medications have the potential to affect neuro-psychiatric symptoms as well as to interact adversely with many psychotrophic medications. Likewise, psychotropic medications themselves have many neuropsychiatric and somatic side effects. The newer antidepressants and atypical antipsychotics offer many advantages over the older generation of psychiatric drugs, but even they require caution in order to minimize iatrogenic morbidity in the medically ill patient.

Polypharmacy is the rule in the patient with psychiatric and general medical illness. This chapter focuses primarily on the way medical illness and nonpsychiatric medication complicate the use of psychotropic medications. Drug-drug interactions between psychiatric and nonpsychiatric medications are reviewed only briefly in chart form at various points, and the reader should refer to a recent psychiatry textbook for detailed information in this area (1). The goals of this chapter are to identify the possible complications raised by medical illness and nonpsychiatric medications and to derive guidelines with which to approach patients with medical comorbidities. After a brief discussion of the importance of collaborating with nonpsychiatric physicians and the aging process, the bulk of the chapter focuses on polypharmacy in settings of medical and psychiatric illness. The chapter is organized by organ systems, which illustrate the commonly
encountered pharmacokinetic (gastrointestinal and renal section) and pharmacodynamic (respiratory, cardiac, and neurological section) issues. A separate section on delirium highlights and reviews the major role of polypharmacy in both the etiology and the treatment of this common disorder.

**THE MEDICAL ARENA**

Optimal management of the medically ill psychiatric patient places additional burdens upon the psychiatrist. To begin with, caring for these patients requires an awareness of basic physiology. Their care also introduces the need for communication and collaboration among various medical providers. Multiple providers are necessary with the medically ill when the patient’s condition is too complicated for any one provider. However, iatrogenic illness can occur if the care is not coordinated, and this places a particular onus upon the psychiatric provider, who is often out of the normal loop of communication among medical providers. Historically, several “cultural” factors have contributed to the separation of psychiatry from the rest of biomedicine. Foremost among them is the nature of psychiatric matters and the heightened need for confidentiality. In addition, psychiatrists traditionally work in geographically separate offices from other medical providers. This plus adherence to the 50-minute, uninterruptible hour and the minimal use of office staff have led many medical providers to experience psychiatric providers as being inaccessible and unavailable for consultation. The evolution of psychiatry as a profession that deals with both the biological and psychological nature of psychic distress, and our involvement in the care of medical patients, requires increasingly creative and flexible measures to overcome these barriers and effect better communication with medical colleagues.

The medically ill psychiatric patient may have one or more nonpsychiatric providers. When present, a primary care physician usually provides oversight for the care of these patients. Regular collaboration between the psychiatrist, the primary care clinician, and relevant specialist physicians is imperative for effective management of complicated medication regimens. Collaboration, however, means more than simple communication. The psychiatrist may be the most knowledgeable person with regard to certain aspects of the patients’ care and must take an active role in the overall care of these patients. Faced with important studies demonstrating, for example, that 35% of primary care patients have psychiatric illness (2) or that their diagnostic sensitivity to depressive disorders is 35.7% (2), primary care physicians are under pressure to improve their psychiatric acumen. Attempts at improved sensitivity, however, may be leading to low specificity and consequent inappropriate psychopharmacy and polypharmacy in an already medically compromised population. In this vein, Margolis found preliminary diagnoses posited by nonpsychiatrist house staff to be confirmed by psychi-
Polypharmacy in the Medically Ill Psychiatric Patient

A thorough review of the polypharmacy in the elderly can be found in Chapter 8. However, aspects of aging (not necessarily restricted to the geriatric population) must be discussed in any chapter on medical illness. Both illness and medication use are much more prevalent as we age. Although most psychiatric conditions present in early adulthood, most are also chronic or intermittent illnesses, and therefore comorbid medical illness becomes common over time. A practicing psychiatrist will inevitably treat older patients with medical illnesses. Medical illnesses and aging have significant effects upon the way the body handles medications; their combined effects may have profound implications for polypharmacy.

General Considerations of Aging

An individual ages according to his or her unique biology and experience. Contributing factors include genetic predisposition, the degree of health care maintenance, exposure to diseases, and trauma and health-related behavior. In general, many organ systems lose functioning at the rate of about 1% per year after age 30. Among the organ systems, the kidney, lung, and skin age more rapidly than the heart and liver in both sexes (5). That said, aging results in substantial variability in individuals such that older people tend to become less like each other rather than more like each other (6). One cannot assume that organ systems age consistently within any one individual. Therefore, just because a patient has renal failure, one cannot conclude that he will have cardiac or respiratory problems.

Risks of Polypharmacy

Aging raises risks for polypharmacy in three distinct ways. The most obvious way is related to developing new illnesses with the addition of new medications.
Medical illnesses can change the body’s tolerance of psychotropic medications, sometimes in dramatic ways. This type of complication is illustrated in the following two examples: (1) a depressed patient has a myocardial infarction with consequent congestive heart failure and can no longer tolerate his usual dose of tricyclic antidepressants because of decreased cardiac output and consequent hypotension; (2) a patient stable for years on a selective serotonin-reuptake inhibitor (SSRI) develops explosive diarrhea and is then diagnosed with new inflammatory bowel disease and can no longer tolerate the SSRI because of its gastrointestinal irritation.

A second and less obvious complication from aging is the insidious effect it has upon the pharmacokinetic and pharmacodynamic properties of drugs. Because such changes tend to be gradual, these effects are often underappreciated and lead to pharmacotherapeutic complications down the road. The adage of ‘‘start low, go slow’’ is common wisdom in the treatment of the elderly. Therefore, initial doses of medication are usually lower in the elderly than in a younger patient. However, lowering the dose of medications in our patients as they age, especially if they have been stable on a dose of medication for years, is rarely considered. Yet patients may do just as well on a lower dose of medication, and lowering the dose could avoid some of the complications caused by inevitable changes in our physiology and metabolism as we age. For example, due to permeability changes in the blood-brain barrier, lower blood levels of lithium are needed to get adequate cerebral spinal fluid (CSF) levels. These levels in the elderly are 0.4–0.6 rather than the 0.6–1.2 commonly recommended for most adult patients.

A third way polypharmacy may potentially complicate management has to do with the general principles of ‘‘compliance’’ or ‘‘adherence’’ and the nature of the doctor-patient relationship. Compliance with long-term medication regimens across various age groups has been found to be approximately 50% (7). In addition, when there are more illnesses present, more doctors are involved and more medications, frequently resulting in more room for medication errors with associated morbidity and mortality. Several studies have documented the growing problem of adverse drug reactions, misuse of medications, and cost implications of drug-related morbidity and mortality (8–13). A recent study examining the discrepancies between what medications patients were taking and what their internist thought they were taking illustrates this point, especially in the elderly. Bedell et al. (14) reviewed 312 patient charts and compared the medications listed in the charts to the medications the patients were actually taking. Discrepancies were found in 76% of the cases. Older age and polypharmacy were the factors most significantly correlated with the discrepancy. Several other studies have confirmed that the larger the number of medications, the lower the compliance in the elderly (15–18). One can only imagine how this may be compounded with
patients who are seeing several different doctors, of different specialties, who rarely communicate with each other.

Pharmacokinetic and Pharmacodynamic Considerations of Aging

There are four components to pharmacokinetics: absorption, distribution, metabolism, and excretion. Absorption does not seem to be significantly affected by aging despite the changes in gastric motility and perfusion of the gut that are known to occur. Some aspects of drug distribution are affected by aging and others are not. In general, outside of chronic illnesses, the binding of drugs to carrier proteins is not affected by normal aging, as meaningful decreases in serum albumin do not normally occur. On the other hand, the volume of distribution of many drugs does change as we age. Lean muscle mass decreases, while fat deposits as a percentage of body weight increase with aging. Consequently, the volume of distribution for lipophilic drugs increases and the volume of distribution for hydrophilic drugs decreases with age. Thus, considering pharmacokinetics alone, tolerance for lipid-soluble drugs like benzodiazepines would increase and tolerance for lipid-insoluble drugs like lithium would decrease with age.

Aspects of metabolism and excretion are also affected by aging, but here, too, differences between individual patients will often be more impressive than the changes attributed to the aging process itself. There is a progressive decrease in liver mass after the age of 50, and blood flow is reduced 40–45% in a 65-year-old compared to a 25-year-old. Using animal models, normal aging is accompanied by reduced activity of liver microsomal drug-metabolizing enzymes as well as diminished microsomal enzyme induction. In humans the evidence is indirect and inconsistent, but the present consensus is that phase I oxidative metabolism may be impaired with advancing age but that aging has little impact on phase II metabolic pathways (12). Despite these changes, genetic, environmental disease, and other patient-specific factors seem to have a greater effect on hepatic drug metabolism than the aging process itself.

In general, the drug elimination half-life of a drug varies in direct proportion to the volume of distribution and inversely to the clearance of the drug. Therefore, the half-life will increase as the volume of distribution increases or if the clearance decreases. This is an important consideration because epidemiological data consistently supports the increased occurrence in the elderly of side effects from drugs with longer half-lives (19–21).

Beyond the implication of aging for drug pharmacokinetics, aging also produces changes in the pharmacodynamics of drug response. Older patients may require lower doses of medications because the elimination of the drug is slowed with aging (pharmacokinetics) or because the aging brain may simply be more...
sensitive to any one level of the drug (pharmacodynamics). This is due, in part, to increased permeability in the blood-brain barrier. Changes in pharmacodynamics are also due to factors in the microenvironment of the cell, cell membrane, or receptors, but the exact changes are still poorly understood. While we generally assume that aging leads to increased sensitivity to a drug, this is not always true. For instance, the response to beta-blockers seems to decrease with age. At the same time the pharmacokinetic and pharmacodynamic properties of some drugs may vary divergently in an aging patient. Benzodiazepines are a good example of this. The larger volume of distribution of the benzodiazepines in the aging patient should increase tolerance to the drug, but this effect is more than compensated by the pharmacodynamic changes that occur leading to increased sensitivity (and potential toxicity) to these drugs in the aging patient.

POLYPHARMACY AND DISEASES OF THE GASTROINTESTINAL TRACT AND KIDNEY

Diseases of the gastrointestinal (GI) tract and kidney have critical importance to pharmacotherapy and the practice of polypharmacy. The gastrointestinal tract and kidney are intimately involved in the absorption, metabolism, and excretion of drugs. In addition, diseases of the gastrointestinal tract are common, as illustrated by the fact that the antiulcerant drugs are among the most commonly prescribed groups of drugs, and everyday illnesses that are self-treated, such as nausea, constipation, and diarrhea, can affect the absorption of drugs.

Absorption and Distribution

The bioavailability of orally administered drugs is dependent upon several functions of the GI tract. Bioavailability is determined by both the rate and extent of absorption as well as the extent of its metabolism in the gut wall and the extent of ‘‘first-pass’’ metabolism in the liver. Absorption is governed by properties of the drug and characteristics of the GI tract, which include the integrity and function of its surface area, ambient pH, and local blood flow. In general, rapid GI motility and decreased perfusion lead to decreased absorption, and slower motility leads to increased absorption. Most psychotropic drugs are absorbed in the proximal ileum when given orally, so surgery or diseases affecting the ileum can drastically affect absorption. Severe gastroparetic conditions caused by diseases or drugs, short bowel syndromes, and surgical resection can all slow absorption. Common diseases like diabetes mellitus and common psychiatric drugs with anticholinergic properties such as the antiparkinsonian agents, tricyclics, and narcotics can affect absorption by decreasing GI motility. Disease or resection of the
large intestine is less likely to affect the bioavailability of psychoactive drugs because the large intestine is minimally involved in their absorption.

Speed of absorption through the GI tract is also related to drug formulation. The formulation with the fastest absorption is, in decreasing order: solution, followed by suspension, capsule, tablet, and enteric-coated tablet. The absorption rate is clinically relevant when the rate of onset of action is important, such as the need for rapid sedation. With chronic administration of a drug, the extent of drug absorption tends to be more important than the rate. Food in the GI tract affects the rate of absorption more than the extent of absorption and therefore tends to be minimally important with chronic administration of a drug. Prior to reaching systemic circulation, orally administered drugs may be extensively altered by the liver in first-pass metabolism. Inhaled drugs and those administered parentally or sublingually avoid first-pass metabolism totally, while first-pass effects are reduced by about 50% for rectally administered drugs (23). Doses of drugs administered in these ways should be reduced accordingly.

Hepatic and kidney function also influence the volume of distribution of medication. As the volume of distribution of a drug is a function of plasma and tissue-binding properties in addition to lipid solubility, hepatic function can influence the volume of distribution by its production of plasma protein, primarily albumin and 1α-glycoprotein. Many psychotropic drugs are highly (80–95%) bound to plasma proteins. Decreased hepatic function or nephrotic syndrome can therefore lead to lower plasma proteins and increased unbound:bound drug ratios. In general, decreased protein binding usually means that the drug is more available to metabolic and excretion processes as well as to pharmacodynamically active sites. Therefore, if metabolic and excretory processes are uncompromised, altered plasma protein levels usually have negligible effects upon steady-state serum concentrations of the free drug. Thus, protein binding tends to be clinically relevant only for drugs with a low therapeutic index such as warfarin or carbemazepine. When given in conjunction with psychotropic drugs that also are highly protein bound like paroxetine, even in the absence of hepatic dysfunction, it is prudent to decrease doses of paroxetine and closely follow clotting indices or blood levels.

**Metabolism**

There are two main mechanisms of metabolism in the liver. One is called oxidative biotransformation (Phase I metabolism), marked mainly by dealkylation, deamination, and sulfoxide formation. The second mechanism involves acetylation, methylation, and conjugation with glycine and sulfate, generally called Phase II metabolism. Many drugs undergo Phase I followed by Phase II metabolism. Phase I is closely associated with the cytochrome system and thus is involved in drug-drug interactions via the inhibition or induction of the various cytochrome
systems (Table 1). Phase II can also occur in other organs and therefore is not as dependent on hepatic function as Phase I. It is noteworthy to remember that some drugs can have multiple effects upon hepatic metabolism. For instance, alcohol will inhibit hepatic metabolism acutely, induce metabolism when used chronically, and finally permanently reduce liver function if it causes cirrhosis.

Because most medications and almost all psychotropics undergo metabolism in the liver, diseases of the liver must be considered in polypharmacy and all psychotropics must be used judiciously. Even lithium, which undergoes no metabolism in the liver, is affected by liver disease if it results in cirrhosis, ascites, increases volume of distribution, and thus lower blood levels. Carbamazepine and valproate, among commonly used psychotropics, require particular caution with intrinsic hepatic disease as they have both been known to lead to hepatic failure (in fewer than 1/10,000 patients) and should not be used together in this setting. The risk of anticonvulsant-related hepatic failure is highest in children below age 2 and in persons receiving polypharmacy with two or more anticonvulsant agents simultaneously. In most persons, medical complications of hepatic dysfunction with anticonvulsants are uncommon, and mildly abnormal liver function tests normalize after discontinuation of the anticonvulsant. Nefazodone also requires caution given the three recent reports of fulmanant liver disease (24), and chlorpromazine should be avoided with primary biliary cirrhosis. In addition, among the benzodiazepines it is prudent to use oxazepam, lorazepam, or temazepam, as they are less dependent upon hepatic function for their metabolism.

Excretion

Renal disease is also important for several psychotropic medications that rely upon the kidney for a significant portion of their elimination. Lithium is the most critical of these medications, largely because of its low therapeutic index. Lithium excretion is primarily affected by glomerular filtration rate (GFR) and proximal reabsorption. It is filtered at the glomerulus. Approximately 55% is reabsorbed in the proximal tubule (25) and 15% in the descending loop, roughly parallel with sodium. Reabsorption is increased by dehydration, volume depletion, and sodium depletion, all common among the medically ill and a particular worry with patients on diuretics. Chronic exposure to lithium impedes renal function in many persons. This effect is usually reflected in a mild to moderate decline over time in GFR and a very slow increase in creatine levels. In relatively few cases, lithium can be associated, usually after decades of use, with more severe chronic renal insufficiency that is irreversible. Acute lithium toxicity can produce acute renal failure, requiring dialysis at a level of $\approx 3.0$. Significant drug interactions also occur with some commonly used over-the-counter and prescribed medications. For instance, an otherwise healthy and stable patient on lithium can become toxic simply from using a nonsteroidal anti-inflammatory drug (NSAID).
Table 1  Selected Gastrointestinal-Psychiatric Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interactive effect</th>
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<tbody>
<tr>
<td>Cimetidine</td>
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<td>↑ Carbamazepine</td>
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<td></td>
<td>↑ Valproic acid</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>↑ Citalopram (+/-)</td>
</tr>
<tr>
<td>Gel-type antacids</td>
<td>↓ Neuroleptic absorption (+/-)</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>↑ Astemizole (+/-)</td>
</tr>
</tbody>
</table>

Source: Adapted from Ref. 93.

for a minor muscle strain. More commonly, NSAIDs can lead to mild elevation of lithium levels. Finally, carbamazepine alone has an antidiuretic action and is associated with both mild and significant levels of hyponatremia (26–32).

POLYPHARMACY AND RESPIRATORY ILLNESS

Respiratory illness is associated with a variety of neuropsychiatric symptoms. Respiratory distress itself is almost synonymous with the sense of anxiety. Recurrent bouts of respiratory distress may elicit remarkable amounts of anticipatory anxiety and agoraphobia. Dyspnea is a subjective feeling and, like pain, is clearly influenced by emotional factors and is not necessarily related to measurements of actual pulmonary function (33). Patients with severe end-stage COPD often have chronic anxiety, and this may be difficult to distinguish from their dyspnea. In addition, when present, anxiety will likely lead to a heightened sense of dyspnea. There also is an association between depression and pulmonary disease (34), and where severe airway narrowing occurs, depression may be associated with increased morbidity or mortality (35). As is the case with many medical illnesses, respiratory disease can lead to behavioral disturbances (such as sexual inhibitions) with resultant psychic distress. With chronic or severe respiratory disease, including COPD or sleep apnea, there can also be direct central nervous system damage and resultant cognitive impairment.

There are remarkably few concerns involving polypharmacy and diseases of the respiratory system. Psychiatric drugs, with some major exceptions, have few significant respiratory side effects. On the other hand, neuropsychiatric side
effects of drugs used for inherent respiratory diseases range from mild to severe, incapacitating, and life threatening. The methylxanthines, antihistaminic and anticholinergic drugs, and the various sympathomimetic bronchodilators commonly cause some anxiety, insomnia, and irritability and more rarely can lead to hallucinations, psychosis, and delirium. Of all the pulmonary drugs, the corticosteroids seem to be the most frequent cause of significant neuropsychiatric side effects. There is little in the literature, however, documenting the incidence of side effects secondary to steroids. Mood symptoms are the most common, but insomnia, anxiety, personality changes, hallucinations, psychosis, and delirium can also occur. Among the mood effects, emotional lability, depression, hypomania, and overt mania with psychosis can be seen. Depression seems to be more common than mania, but there are several reports of recurrent mania due to the use of corticosteroids (36). The occurrence of both depression and mania secondary to corticosteroids have led some authors to emphasize the similarities of the side effect profile to bipolar disorder (37). Many of the side effects seem to be dose dependent. The incidence of psychosis is less than 1% in patients receiving 40 mg or less of prednisone per day but rises to about 28% in patients receiving 80 mg or more (38). The onset of psychosis seems to be abrupt, more often than not within the first 6 days of treatment (39). Psychotic symptoms usually abate if the steroid is stopped, do not seem to presage a psychiatric condition, and while suggesting a diathesis, do not reliably predict future episodes if the patient is rechallenged with steroids (40). The mood disorders secondary to corticosteroid use do respond to the use of lithium, neuroleptics, antidepressants, and other mood stabilizers in those cases where ongoing corticosteroid use is necessary. However, there is some evidence that the tricyclic antidepressants lead to a worsening of symptoms (39,40).

The majority of psychiatric drugs are tolerated well in patients with respiratory diseases, and there are few drug interactions of consequence (Table 2). The major concern is respiratory depression with some psychiatric drugs. Several of the antipsychotics, most of the sedative-hypnotics, and most anxiolytic medications can suppress respiratory drive, and the effect can be additive when multiple drugs are used. Clinically this is most relevant in the medical patient with already compromised respiration. Benzodiazepines are a particular concern in the chronic obstructive pulmonary disease (COPD) patient who is adapted to chronic states of hypercapnea. Normally respiration is stimulated by either hypoxia or hypercapnea. Patients with longstanding COPD, however, lose the normal respiratory drive in response to hypercapnea. As benzodiazepines decrease respiratory drive to hypoxia, they can cause loss of the remaining stimulus for respiration and dangerous respiratory depression. In these cases baseline blood gases should be obtained prior to the use of benzodiazepines, and they should be avoided if pCO₂ is elevated (41). Benzodiazepines can also be dangerous in patients with sleep apnea and therefore should be avoided (42). Buspirone may have a particular
Table 2  Selected Respiratory-Psychiatric Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interactive effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvoxamine</td>
<td>↑ Theophylline</td>
</tr>
<tr>
<td>Clozapine</td>
<td>↑ Theophylline</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>↓ Theophylline</td>
</tr>
<tr>
<td>Rifampine</td>
<td>↓ Valproic acid</td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>↓ BNZ</td>
</tr>
<tr>
<td></td>
<td>↓ Lithium</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>↑ BP (severe) with MAOI Co-administration</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>↑ BP (severe) with MAOI Co-administration</td>
</tr>
<tr>
<td>Phenylpropanolamine</td>
<td>↑ BP (severe) with MAOI Co-administration</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>↑ Anticholinergic activity of atropine</td>
</tr>
<tr>
<td></td>
<td>↑ BP when co-administered with ephedrine</td>
</tr>
</tbody>
</table>

Source: Adapted from Refs. 33, 93.

role in the anxious patient with COPD because it does not suppress respiratory drive and may have a respiratory stimulant effect (43).

POLYPHARMACY AND CARDIOVASCULAR ILLNESS

Cardiovascular illnesses are pervasive and highly influenced by the presence of psychopathology. Mood disorders, particularly major depression, represent significant risk factors for developing coronary artery disease (CAD) (44), and CAD is likewise a risk factor for the development of major depression (45). The latter scenario, in turn, is a potent predictor of post–myocardial infarction (MI) mortality (46). Other psychiatric predictors of cardiovascular-related deaths include schizophrenia (47) and presence of anxiety symptoms (48). Thus, few psychiatrists are strangers to this high-need, high-risk population in whom even psychopharmacologic monotherapy with first-line agents can be complex. Important pharmacokinetic interactions are listed in Table 3 (49). The major pharmacodynamic consideration when employing psychiatric polypharmacy in patients with cardiovascular disease is that of cumulative drug-induced effects on cardiac conduction.

The tricyclic antidepressants (TCAs) are the best-studied psychotropics with regard to cardiac conduction. Their prolongation of the His-ventricle interval with sparing of the atria-His interval at therapeutic and supratherapeutic levels is consistent with class I antiarrhythmic action and manifests on the electrocardio-
<table>
<thead>
<tr>
<th>Drug</th>
<th>Interactive effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-blockers</strong></td>
<td>↑ neuroleptic levels</td>
</tr>
<tr>
<td>Propranolol</td>
<td>↑ propranolol levels with fluvoxamine, paroxetine coadmin.</td>
</tr>
<tr>
<td></td>
<td>↓ propranolol levels with carbamazepine coadmin.</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>↑ metoprolol levels with paroxetine, (+/-) citalopram coadmin.</td>
</tr>
<tr>
<td><strong>Ca(^{2+}) channel blockers</strong></td>
<td>↑ or ↓ Lithium levels (+/-)</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>↑ Carbamazepine levels</td>
</tr>
<tr>
<td>Verapamil</td>
<td>↑ Carbamazepine levels</td>
</tr>
<tr>
<td>Enalapril</td>
<td>↑ Lithium levels</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>↑ Lithium levels</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>↑ Lithium levels</td>
</tr>
<tr>
<td>Triamterene</td>
<td>↑ Lithium levels</td>
</tr>
<tr>
<td>Digoxin</td>
<td>↑ Free digoxin with fluoxetine coadmin. (+/-)</td>
</tr>
<tr>
<td>Encaainide</td>
<td>↑ Encainide levels with paroxetine coadmin.</td>
</tr>
<tr>
<td>Flecaainide</td>
<td>↑ Flecaainide levels with paroxetine coadmin.</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>↑ Mexiletine levels with paroxetine coadmin.</td>
</tr>
<tr>
<td>Propafenone</td>
<td>↑ Propafenone levels with paroxetine coadmin.</td>
</tr>
<tr>
<td></td>
<td>↑ TCA levels</td>
</tr>
<tr>
<td>Quinidine</td>
<td>↓ Quinidine levels with carbamazepine coadmin.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>↑ Prothrombin time with fluvoxamine, sertraline coadmin.</td>
</tr>
<tr>
<td></td>
<td>↑ Prothrombin time with valproate coadmin.</td>
</tr>
<tr>
<td></td>
<td>↓ Prothrombin time with carbamazepine coadmin.</td>
</tr>
</tbody>
</table>

*Source:* Adapted from Ref. 93.
Such an analysis should, especially in patients with ischemic heart disease, also take into consideration the risk of TCA-induced inhibition of parasympathetic input to the heart, with consequent tachycardia and diminished heart rate variability (58–60). Even the relatively mildly anticholinergic TCA nortriptyline has exhibited significant (10–11%) increases in heart rate in head-to-head comparisons with fluoxetine (61) and paroxetine (62).

The selective serotonin-reuptake inhibitors appear to have no effect on cardiac conduction intervals. This benign aspect of their side-effect profile has been borne out in samples of patients with congestive heart failure (CHF) or conduction disease given fluoxetine (61), patients with ischemic heart disease given paroxetine (62), and patients status post–acute MI given sertraline (63). While the sertraline study also found no significant effect on heart rate, fluoxetine was noted to produce a 6% decrease in heart rate and paroxetine a 4% decrease that resolved after several weeks. Prior to these studies, several case reports implicated fluoxetine in episodes of bradycardia and syncope, alone (64–66) and in the context of cardiac disease (67). Another potential reason for concern about the use of SSRIs in cardiac patients is a risk for inducing or facilitating coronary vasoapasm. Not fully studied, this effect has been noted in an animal model of atherosclerosis (68) and suspected in human mortalities (69).

Of the remaining antidepressants, no overt arrhythmogenic effects are known, and minimal data exist on their use in patients with cardiac disease. Buropion has been studied in 36 patients with CHF, conduction disease, and/or ventricular arrhythmias. No effects were found on ECG intervals, heart rate, or ejection fraction. Nor was there any effect on preexisting arrhythmias or heart blocks (70). Two of 16 patients with baseline premature ventricular contractions (PVCs) experienced increased frequency of these on trazodone, but no effects on the cardiac conduction were noted (71).

Typical antipsychotics produce several ECG changes, including T-wave flattening or notching, manifestation of U waves, and prolongation of the QTc and QRS intervals (72,73). T-wave changes are the most frequent, appear at lower relative doses than other ECG changes, and have been noted by multiple investigators to be found in approximately 50% of patients taking low-potency phenothiazines (74,75). Clinically significant QTc prolongation with typical antipsychotics is thought to be less frequent. Reports of up to 23% incidence are likely influenced by the sometimes high dosages (e.g., >2000 mg chlorpromazine equivalents) and lenient definitions of significance (e.g., >420 ms) used (76). Studies specifically examining the use of typical antipsychotics in patients with cardiac disease are lacking. In a sample of 495 patients, Reilly et al. (77) found antipsychotic dosage, use of TCAs, thioridazine or droperidol (haloperidol approached significance, and has been associated with QTc prolongation and, rarely, torsade de pointes with high-dose intravenous use), and age, but not presence of cardiovascular disease, to be robust predictors of QTc prolongation to
The authors note, however, that selection bias may have been towards inclusion of only more mildly ill cardiac patients.

Clozapine may produce nonspecific T-wave changes and dose-dependent prolongation of QTc, but the latter is felt to rarely be significant (78). Likewise, the atypical antipsychotics quetiapine, risperidone, and olanzapine all appear to produce QTc prolongation, but not of clinically significant magnitude. Ziprasidone, recently FDA-indicated for the treatment of schizophrenia, appears to produce mild to moderate prolongation of the QTc, though prolongations to over 500 ms are rare (79). Clinical experience, particularly with medically ill populations, is needed to better delineate the definitive cardiac risks of these agents. Given that atypical antipsychotics are metabolized by the hepatic cytochrome P450 system, there is at least a theoretical potential that SSRIs may increase atypical antipsychotic levels and, in susceptible persons, may possibly increase the risk of cardiac arrhythmias. As with the TCAs, anticholinergic side effects of both atypical and typical antipsychotics may result in heart rate elevation that is of concern in patients with ischemic heart disease.

Among the established mood stabilizers, lithium frequently produces T-wave changes, likely reflecting its displacement of intracellular potassium (80). Clinically significant conduction abnormalities are rare at therapeutic levels. Sinus node dysfunction or AV block may occur, though usually as a result of toxicity. It has been suggested, albeit based on a very small sample, that lithium may exacerbate ventricular arrhythmias but not impair cardiac function (81). Carbamazepine is structurally similar to the TCAs and seems to exhibit both class IA and IB antiarrhythmic properties (82). In addition, sinus node dysfunction has been noted anecdotally (83). Valproate has not been reported as possessing significant effects on cardiac conduction.

Benzodiazepines are generally considered to be safe and well tolerated in patients with cardiovascular disease, including those in the acute post-MI period (84). The uncomplicated use of diazepam during electric cardioversion, coronary angiography, and cardiac catheterization suggests lack of significant effects on cardiac conduction (72).

While the advent of SSRIs, other novel antidepressants, and atypical antipsychotics may soothe psychiatrists’ nerves over iatrogenic morbidity and mortality in patients with cardiovascular illnesses, the treatment-refractory patient in whom polypharmacy is considered has often exhausted these options. Even when such polypharmacy is confined to novel agents, vigilance remains necessary. For example, the combination of a serotonin-reuptake inhibitor and risperidone has been linked with cardiac arrests and a death in elderly patients (85), possibly due to inhibition of risperidone metabolism by cytochrome 2D6 and/or 3A isoenzymes (86). The inhibition of clozapine metabolism by fluvoxamine (87) could conceivably create an analogous risk of similar complications in vulnerable populations.
Polypharmacy in the Medically Ill Psychiatric Patient

Given the mortality and sudden death risks engendered by class I antiarrhythmic activity and QTc prolongation, respectively, in patients with cardiac disease, psychiatric polypharmacy in this population must take the prospect of cumulative effects in these areas into strong consideration. This is especially important given data suggesting that some degree of QTc prolongation may accompany even unmedicated psychiatric illness (88,89). Based on the available data, it is clear that combining TCAs with typical antipsychotics should be avoided here. The combination of TCAs with thioridazine seems to be particularly prone to producing ventricular tachycardia and fibrillation (90–92). The QTc-prolonging potentials of other antipsychotics and carbamazepine, though less notorious, may be of additional significance when combined with other psychotropics possessing this property. Cumulative anticholinergic effects and consequent tachycardia must also be considered when combining psychotropics in patients with ischemic heart disease.

POLYPHARMACY AND NEUROLOGICAL ILLNESS

Psychiatric polypharmacy in the setting of neurological illness occurs both by intent and by coincidence. The former is due to the complicated and often treatment refractory nature of “organic” psychiatric syndromes, while the latter is due to the overlap of medications used in psychiatry and neurology. The principles underlying the pharmacokinetic interactions in this area are no different than in any other. Particular attention, however, needs to be paid to the cytochrome P450–inducing effects of many anticonvulsants, which may lead to decreased serum levels of psychotropics. Important pharmacokinetic interactions between neurological and psychiatric medications are listed in Table 4. Pharmacodynamically, the psychiatrist employing polypharmacy in this challenging population will most frequently confront concerns over cumulative drug-induced effects on seizure threshold, parkinsonian symptoms, and mental status.

Polypharmacy and Seizure Threshold

While the cumulative effect of psychiatric polypharmacy on seizure threshold has not been specifically studied, it has been implicated as a risk factor for the occurrence of convulsions in psychiatric patients with and without preexisting neurological disease (94,95). Other risk factors include presence of “organic” brain disease, personal and/or family history of epilepsy, an abnormal electroencephalogram (EEG), high doses or rapid dose changes of psychotropics, history of electroconvulsive therapy (ECT), and benzodiazepine or alcohol abuse or withdrawal (94–96).

Iatrogenic seizures are obviously events to be avoided. However, the pro-
Table 4  Selected Neurological-Psychiatric Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interactive effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>↓ Neuroleptic levels</td>
</tr>
<tr>
<td></td>
<td>↓ Tricyclic antidepressant (TCA) levels, and potential additive cardiotoxicity</td>
</tr>
<tr>
<td></td>
<td>↓ Nefazodone levels</td>
</tr>
<tr>
<td></td>
<td>↓ Paroxetine levels (+/-)</td>
</tr>
<tr>
<td></td>
<td>↓ Valproic acid levels</td>
</tr>
<tr>
<td></td>
<td>↓ Phenytoin levels</td>
</tr>
<tr>
<td></td>
<td>↓ Carbamazepine levels (auto-induction)</td>
</tr>
<tr>
<td></td>
<td>↑ Carbamazepine with fluvoxamine coadministration (+/-)</td>
</tr>
<tr>
<td></td>
<td>↑ Carbamazepine and 10,11-epoxide metabolite levels with fluoxetine coadmin.</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>↑ Neuroleptic levels (+/-)</td>
</tr>
<tr>
<td></td>
<td>↑ TCA levels (+/-)</td>
</tr>
<tr>
<td></td>
<td>↑ Benzodiazepine levels (except lorazepam) (+/-)</td>
</tr>
<tr>
<td></td>
<td>↑ Barbirurate levels</td>
</tr>
<tr>
<td></td>
<td>↑ Phenytoin levels (+/-)</td>
</tr>
<tr>
<td></td>
<td>↑ Lamotrigine levels</td>
</tr>
<tr>
<td></td>
<td>↑ Carbamazepine 10,11-epoxide metabolite</td>
</tr>
<tr>
<td></td>
<td>↑ Valproic acid levels with fluoxetine coadministration (+/-)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>see Carbamazepine interactions, above</td>
</tr>
<tr>
<td></td>
<td>↑ Phenytoin levels with fluoxetine coadministration (+/-)</td>
</tr>
<tr>
<td></td>
<td>↑ Phenytoin levels with psychostimulant coadministration</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>↓ Neuroleptic levels</td>
</tr>
<tr>
<td></td>
<td>↓ TCA levels (+/-)</td>
</tr>
<tr>
<td></td>
<td>↓ Paroxetine levels</td>
</tr>
<tr>
<td></td>
<td>↓ Valproic acid levels</td>
</tr>
<tr>
<td></td>
<td>↑ Phenobarbital levels with psychostimulant coadministration</td>
</tr>
<tr>
<td>Primidone</td>
<td>↑ Primidone levels with psychostimulant coadministration</td>
</tr>
<tr>
<td>1-Dopa</td>
<td>↑ Blood pressure with monoamine oxidase inhibitor (MAOI) coadmin.</td>
</tr>
<tr>
<td>Selegilene</td>
<td>Reports of serotonin syndrome with serotonin reuptake inhibitor (SRI) coadministration</td>
</tr>
<tr>
<td></td>
<td>Possibility of serotonin syndrome with TCA coadministration</td>
</tr>
<tr>
<td>Sumatriptan/Zolmitriptan</td>
<td>Serotonin syndrome with MAOI coadministration</td>
</tr>
<tr>
<td>Warfarin</td>
<td>See Table 3</td>
</tr>
</tbody>
</table>

Source: Adapted from Ref. 93.
convulsant properties of some psychotropic drugs and ECT have been hypothe-
sized to be instrumental to their efficacy in the treatment of interictal psychoses
and affective disorders of epilepsy (as well as in primary affective disorders).
“Forced normalization” refers to the (rare) occurrence of emergent psychosis
when an epileptic patient’s seizures are suppressed and the EEG normalizes (97).
It has been proposed (98) that underlying this phenomenon is increased inhibitory
activity occurring as a compensation for the abnormal excitatory activity of
chronic epilepsy. Such inhibitory activity, when unopposed by epileptic excita-
tion, may underly interictal psychoses (98) and affective disorders (99). Such an
explanation might account for the superiority of neuroleptics and antidepressants
over anticonvulsants in the treatment of these syndromes. Blumer and associates
have reported largely beneficial effects in both symptomatic settings with TCAs
at half of the conventional dose ranges in combination with SSRIs in small patient
samples. Changes in seizure frequency with this treatment were not specifically
noted (99,100).

With regard to specific classes of psychotropics, the observed association
of antipsychotics with seizures is a relatively longstanding one. A 1967 sample
of 859 patients on phenothiazines found a 2% incidence of seizures in those
patients with preexisting organic brain pathology compared with 0.9% in those
without, despite lower doses being used in the former group (101). Overall, how-
ever, iatrogenic seizures were found to be a dose-dependent occurrence, with an
incidence of 9% at doses corresponding to ≥1000 mg/day of chlorpromazine
compared with 0.3% at doses of ≤200 mg/day and 0.7% at doses lying between
these extremes. Systematic data is otherwise lacking in this area, though molin-
done has been suggested by some to be less likely to effect the seizure threshold
than other typical antipsychotics (102,103).

Among the atypical antipsychotics, clozapine is the most notoriously sei-
zure-inducing, with incidences of 1.3% (104) and 2.8% with a calculated 10% risk
over 3.8 years of treatment (105) in large samples. As with the typical anti-
psychotics, risk for seizures is dose-dependent and increased by rapid upward
titration. Devinsky et al. found seizure rates of 4.4% at doses over 600 mg/day,
2.7% at 300–600 mg/day, and 1% at <300 mg/day (105). Generalized tonic
clonic seizures are the rule, but myoclonic (105,106) and complex partial (106)
seizures have been noted as well. EEG changes are noted in 53–74% of patients
on clozapine (107,106), and it is advisable to obtain an EEG on every patient
with preexisting brain pathology before starting this medication. Even if seizures
occur, dose reduction with more gradual upwards titration, if necessary, and/or
addition of an anticonvulsant other than carbamazepine usually permits continued
treatment. Premarketing trials of olanzapine, quetiapine, and risperidone found
incidences of seizures to be 0.9, 0.8, and 0.3%, respectively (108). There are two
reports in the literature of seizures associated with olanzapine therapy (109,110),
one with quetiapine, and one with risperidone (111). In one of these reports
the patient had a preexisting diagnosis of epilepsy, and in none of them was the patient receiving monotherapy with the implicated agent.

Looking to the antidepressants, much is made of the proconvulsant effects of the tricyclics and related compounds. Initial studies suggesting high incidences of seizures on these drugs, however, were likely confounded by the high (up to 450 mg imipramine/day) doses used (112). More recent large-scale retrospective studies yielded incidences of 0.05% (113) and 0.4% (114), with the authors of the latter also pointing out a lack of any reviewed evidence for seizures at therapeutic TCA levels. Within this group of antidepressants, maprotiline seems to confer an exceptionally high risk for seizures (95,115), and there is limited evidence to suggest that doxepin may have an anticonvulsant effect in some depressed epileptic patients while maintaining a much smaller risk of exacerbating seizures in others (116).

Evidence in the literature for proconvulsant effects of SSRIs is currently at the case report level (117–119). In fact, in a rare prospective study, fluoxetine was found to lead to reduced frequency of complex partial seizures in all 17 epileptic subjects in whom it was added on to their anticonvulsant regimens. Six subjects had complete resolution of seizures and no changes in serum anticonvulsant levels were noted (120). Data on venlafaxine, nefazodone, and mirtazepine is lacking at this point. An incidence of seizures of 0.36–0.48% has been noted with bupropion at ≥450 mg/day administered without regard to risk factors (121,122). A lower risk of seizures (0.15%) with ≥300 mg/day of the sustained-release preparation of bupropion is called into question by the dosing restriction, as well as exclusion of patients with eating disorders, epilepsy, or family histories of epilepsy from study (123). Nonetheless, these figures compare favorably with clinical trial data, suggesting a 0.1% seizure rate with SSRIs, and concerns over the proconvulsant effect of bupropion, particularly the sustained release preparation, may be overblown (124).

While marked lithium toxicity (usually ≥2.5 mEq/L) carries a high seizure risk, the effects of therapeutic levels of lithium on the EEG and seizure threshold are less clear. Lithium has been found to produce EEG abnormalities (background slowing, focal slow waves, spikes) and seizures (125), but also to normalize the EEG and reduce seizure frequency in a small series of psychiatric patients with epilepsy (126). Dopamine agonists also have mixed data regarding their effects on the seizure threshold. Among these, psychostimulants are used widely, safely, and effectively for patients experiencing apathetic syndromes associated with neurological disease. Direct studies of seizure incidence in this context are rare but seem to bear out this clinical observation with the caveat that at least in epileptic traumatic brain-injured patients, methylphenidate may rarely increase seizure frequency, particularly when used in conjunction with other threshold-lowering psychotropics, such as TCAs (127).

Overall, thoughtfully applied psychiatric monopharmacy can be used safely
in a sizable majority of patients prone to seizures, with retrospective studies finding decreased or unchanged seizure frequencies in 77–91% (128,129). All that is currently known about utilizing polypharmacy in this population is that it is an unquantified risk factor for seizure onset or exacerbation. Nonetheless, this is hardly reason to avoid the practice entirely in patients with refractory symptoms. With the exceptions of maprotiline, amoxapine, and (at least standard-release) bupropion, which should be avoided, and clozapine, which should be held in final reserve, most psychotropics can be considered for use. In terms of broad principles, one ought to use the lowest possible doses and gradual dose increases, particularly with typical antipsychotics and TCAs. The dose-dependent nature of seizure threshold reduction with psychotropics should be kept in mind, as should evidence to suggest that half of usual doses of these medications may be all that is necessary in epileptic patients. Combining a typical antipsychotic and TCA is not advised as first-line polypharmacy in seizure-prone patients due to potentially additive reduction of seizure threshold, but it is not contraindicated. For now, risperidone, quetiapine, olanzapine, and molindone may be favored over other antipsychotics, though literature supporting this recommendation is sparse. Likewise, SSRIs, venlafaxine, nefazodone, and mirtazepine appear safer at this point than TCAs and monoamine oxidase inhibitors. Hypotheses regarding forced normalization and utility of cautious employment of threshold-reducing agents also warrant consideration.

**Polypharmacy and Parkinsonian Symptoms**

The use of psychiatric polypharmacy in Parkinson’s disease and other syndromes involving parkinsonian symptoms (e.g., progressive supranuclear palsy, multiple system atrophy, diffuse Lewy body disease, basal ganglia stroke) is an essentially unstudied area. Even monotherapy is fraught with difficulties involving parkinsonian symptom exacerbation in this population well known for its high prevalences of psychotic, affective, anxious, and behavioral symptoms/syndromes. Psychotic symptoms occur in over 20% of patients receiving chronic levodopa treatment (130) and are frequently seen with other dopaminergic antiparkinsonian agents. With dosage reduction often impossible due to worsening of movement symptoms, and typical antipsychotics poorly tolerated, clozapine has emerged as the treatment of choice in this situation. Friedman and Factor’s recent review (131) notes an overall 85% rate of improvement of psychotic symptoms in the literature on clozapine in Parkinson’s disease. They further point out the consistent findings that very low doses (6.25–50 mg/day) are necessary, antiparkinsonian medications can usually be continued/increased, parkinsonism is not significantly exacerbated, and, in fact, tremor is often reduced. Unfortunately, not all patients improve, and up to 23% may not tolerate this treatment (132) due to sedation, orthostatic hypotension, confusion, and, rarely, agranulocytosis.
ETER has been useful in relieving psychosis in some patients with Parkinson’s disease. Reserved for patients whose psychosis is accompanied by a clear sensorium, ECT may lead to rapid, though transient, improvement, which can be maintained with low-dose clozapine maintenance (133).

While the safety and efficacy of low-dose clozapine for psychotic symptoms in Parkinson’s disease is supported by a randomized, double-blind, placebo-controlled study (134), data on other atypical antipsychotics are limited. Risperidone and olanzapine both appear to bear risks of worsening parkinsonian symptoms in this population (131). While encouraging evidence is accumulating to suggest the utility of low-dose (usually <100 mg) quetiapine in relieving psychotic symptoms without worsening parkinsonian symptoms, there is mixed enthusiasm about its efficacy when replacing clozapine (135,136). Given the side effects and “high-maintenance” nature of clozapine treatment, quetiapine is a viable alternative as first-line treatment for psychosis in the context of iatrogenic psychosis in Parkinson’s disease. There are no data to support or refute the simultaneous use of low doses of two atypical antipsychotics in Parkinson’s disease, and this practice is not recommended.

Even more prevalent than psychosis in Parkinson’s disease are clinically significant depressive symptoms, which may affect up to 40% of these patients (137). TCAs are generally considered to be no more or less safe here than in other populations, but solid data to support this are lacking. The SSRIs have received attention in recent years for their ability to produce movement symptoms. The available literature does not allow for an estimated risk of exacerbation of these symptoms when SSRIs are administered to patients with preexisting parkinsonian syndromes. A prospective study of 13 patients with tardive dyskinesia, of which 11 also had neuroleptic-induced parkinsonism, found neither worsening nor improvement of their movement symptoms when citalopram was added (138). A retrospective review of 23 patients with Parkinson’s disease on fluoxetine along with carbidopa/levodopa found worsening of symptoms in three patients, none of whom self-discontinued the former due to this effect (139). Among extrapyramidal symptoms, SSRIs are most clearly associated with akathisia, and this effect may need to be closely assessed in persons with Parkinson’s disease. It appears that patients with parkinsonian syndromes are at risk, albeit low, for symptom exacerbation on SSRIs. Sertraline may theoretically be safer in this regard due to relatively greater dopamine reuptake inhibition than the other SSRIs (140).

As a dopamine reuptake inhibitor, bupropion might be considered unlikely to exacerbate parkinsonian symptoms. At this time, however, there is only one small study to support this idea (141). Other newer antidepressants, including nefazodone, venlafaxine, and mirtazapine, currently lack any significant data in this area. Monoamine oxidase inhibitors (MAOIs) are usually contraindicated in Parkinson’s disease patients, not due to side effects, but rather due to risk of hypertensive crisis when co-administered with carbidopa/levodopa. Gabapentin
was found to improve parkinsonian rigidity, bradykinesia, and tremor in a small placebo-controlled study (142) and thus warrants consideration as it is increasingly investigated for its potential utility for affective and anxiety symptoms.

Generally, the benefits of treating depression in patients with parkinsonian syndromes outweigh the small risk of movement symptom exacerbation. As with other medically ill patients, low doses and slow upwards titration of antidepressant medication (usually a SSRI here, perhaps preferentially sertraline) is the rule. When polypharmacy for depression is deemed necessary for this population, there is no literature to guide decision making. Combination of a SSRI or TCA with liothyronine, a SSRI with a predominantly adrenergic TCA (e.g., desipramine), or a SSRI with bupropion may all represent choices that minimize cumulative adverse effects on movement symptoms. Lithium augmentation also represents a viable choice, with lithium having been reported as useful in reduction of parkinsonian akinesia (143), though at times at the expense of emergent dyskinesias (144).

**Polypharmacy and Mental Status**

All patients with cortical or subcortical neurological disease should be considered to be at elevated risk for mental status changes when psychotropic medications of any type and number are employed. With careful drug selection, low doses, and gradual titration, however, even psychiatric polypharmacy can be successfully negotiated in these patients. A discussion of polypharmacy and the etiology and treatment of mental status changes is found in the following section on delirium.

**POLYPHARMACY AND DELIRIUM**

With an approximately 20% prevalence in hospital populations (145) and an associated mortality rate of up to 33% (146), the diagnosis and treatment of delirium most often falls within the purview of the consultation-liaison psychiatrist. Nevertheless, delirium may make its appearance during the course of any psychiatric treatment of the medically ill patient, or, for that matter, during the pharmacological treatment of the ‘‘purely’’ psychiatric patient, as in the settings of aging and polypharmacy. After briefly discussing the clinical presentation of delirium, this section will concentrate on the contributions of polypharmacy to its etiology and of psychiatric polypharmacy to its treatment.

**Basic Concepts and Clinical Description**

Delirium goes by many names, including ‘‘encephalopathy,’’ ‘‘acute confusional state,’’ ‘‘acute brain failure,’’ and several others. As defined by DSM IV, it is characterized by disturbances of consciousness and cognition, which arise
acutely, tend to fluctuate through the day, and have a direct physiological cause
(147). The clinical presentation of delirium is considerably more variable than
these reductionistic criteria suggest. In their classic paper describing this syn-
drome of diffuse “cerebral insufficiency,” Engel and Romano note that “delir-
ium may simulate any type of mental disorder, neurotic or psychotic” (148).
This point is of particular importance to the psychiatrist working in medical-
surgical wards or nursing homes, where delirious patients are often packaged with
consultation requests to “rule out” depression, anxiety, psychosis, or dementia.
Armstrong et al. found 46% of delirious patients to be misdiagnosed by nonpsy-
chiatric consultees (149), while Farrell and Ganzini found 41.8% of inpatient
referrals for depressive disorders to be delirious (150). When pharmacotherapy
targeted at these misdiagnoses is maintained or initiated, iatrogenic worsening
of mental status can follow. Psychiatrists working in other arenas also need to
be alert to the possibility of delirium whenever confronted by an acute change
in a known patient’s presentation.
Subtle cases of delirium will often declare themselves to the observant
diagnostician through the waxing and waning of symptoms (particularly of alert-
ness and attention), though this is also characteristic of diffuse Lewy body dis-
 ease, a point of considerable importance given these patients’ adverse reactions
to neuroleptics. An electroencephalogram can usually settle a diagnostic dilemma
through its demonstration of generalized slowing in delirium.

**Polypharmacy and the Etiology of Delirium**

The neurochemical mechanisms through which medications can cause delirium
are not always clear. Recent reviews of the pathophysiology of delirium implicate
several neurotransmitter aberrations but point most prominently to elevated dopa-
mine activity and lowered cholinergic activity (151,152). Support for the for-
mer is indirect and based largely upon analogy to psychotic disorders and respons-
sivity to neuroleptics. Some evidence for a cholinergic basis of delirium comes
from the finding of higher serum levels of anticholinergic drugs in delirious com-
pared with nondelirious postoperative patients (153).
The importance of this partially anticholinergic theory of delirium cannot
be overestimated. To the psychopharmacologist it is reason for caution in the use
of one or more psychotropics with known anticholinergic activity, particularly
in the elderly and/or medically ill patient. Tricyclic antidepressants may cause
delirium in 10% of patients prescribed them, with a 15% incidence in patients
over 40 years of age (154). While amitriptyline appears to carry the greatest risk
(and the greatest anticholinergic potency), all TCAs should be looked at with
caution in patients vulnerable to delirium. While the newer antidepressants are
generally safe in this regard (their ability to cause delirium through other mecha-
nisms, such as the serotonin syndrome, SIADH-related hyponatremia, or idio-
polypharmacy in the medically ill psychiatric patient, it should be noted that paroxetine does have low-level anticholinergic activity. Antipsychotics, particularly those of low to medium dopamine-blocking potency (thioridazine and, to a lesser degree, chlorpromazine, mesoridazine, loxitane, and molindone) are likewise concerning in their anticholinergic activity, as are the antiparkinsonian drugs (benztropine, diphenhydramine, biperiden, trihexphenidyl) that often accompany them. Grohmann et al. found a 0.91% incidence of apparently psychotropic drug-induced delirium among 11,308 medicated psychiatric inpatients, with the worst offenders being imipramine, amitriptyline, maprotiline, thioridazine, clomipramine, tranylcypromine, biperiden, and lithium (155). The patients who developed delirium were usually on multiple psychotropic medications. Higher-risk combinations included co-administration of neuroleptics with biperiden or anticholinergic TCAs, thus illustrating the effect of accumulated anticholinergic load. A more recent but much smaller study revealed a 14.6% incidence but found only antiparkinsonian drugs and their dosages to correlate with delirium (156). This latter finding, however, is likely confounded by the decreased use of TCAs and conventional antipsychotics over the past several years. Nonetheless, SSRIs, including fluoxetine and sertraline, have been reported to contribute to delirium through inhibition of metabolism of the anticholinergic antiparkinsonian agent benztropine (157,158).

To the consultation-liaison psychiatrist evaluating the medication regimen of a medically ill delirious patient, this partially anticholinergic theory of delirium is equally important. In their important radioreceptor assay study, Tune et al. found varying anticholinergic levels in several commonly prescribed drugs not ordinarily thought to possess this property (159). Among those found to have levels associated with cognitive changes in the elderly were (in descending order) cimetidine, prednisolone, theophylline, hydrochlorothiazide, ranitidine, digoxin, furosemide, and warfarin. While each of these in isolation is unlikely to cause delirium at therapeutic doses/levels (steroid-induced psychiatric symptoms are not true deliria), the authors stress that polypharmacy involving these drugs could lead to mental status changes. The place of cimetidine as a far-ahead number one on this list and the appearance of ranitidine are interesting given the delirium-inducing potential of histamine-2 receptor–blocking drugs and case reports of treatment of delirium associated with these agents with physostigmine (160,161).

Of course, it would be overly simplistic to approach the pharmacological etiologies of delirium from an exclusively anticholinergic angle. Dopaminergic agents, local anesthetics, narcotics (particularly meperidine and its metabolite n-meperidine, which has anticholinergic properties), benzodiazepines, and barbiturates are all well known to be capable of causing or contributing to delirium. Antibiotics, nonsteroidal antiinflammatory drugs, calcium channel blockers, and even tacrine (a pro-cholinergic agent) have all been implicated (162). Indeed, it would be nearly impossible to memorize all of the medications and interactions
that can induce delirium. Pragmatically, the literal or mental construction of a clinical timeline as advocated by Cassem and Murray (163) is the most sensible method of discerning possible correlations between deteriorated mental status and changes in medications or in the physiological environment in which they are working. Using this mode of investigation, one is less likely to overlook "innocent"-looking drugs and combinations, as well as prone to be a bit lenient towards "the usual suspects" if the evidence against them does not add up.

Polypharmacy and the Treatment of Delirium

Despite the high prevalence of delirium in hospitalized medically ill populations, there are no FDA-approved pharmacological treatments specific to it. This may be largely because the cornerstone of the management of delirium is addressing the underlying cause(s).

An interesting convergence of managing a cause of delirium with treating the associated cerebral pathophysiology is the use of physostigmine (an acetylcholinesterase inhibitor that crosses the blood-brain barrier) in the treatment of anticholinergic drug toxicity that cannot be managed by supportive care alone. Early dosing recommendations of 2 mg intravenously (IV) at intervals of every 15–120 minutes as needed for control of central and peripheral anticholinergic symptoms (164) remain appropriate today. Usually only a few doses are required, but the safe use of up to 77 mg over a 52-hour period as an IV drip has been reported in a patient with benztropine and amitriptyline toxicity secondary to overdose (165). There have been no significant examinations of the use of this treatment in combination with other pharmacological interventions directed towards the pathophysiology of delirium. Though benzodiazepines have been used in combination with physostigmine (166), the only study to specifically examine the use of both drugs did so separately and found physostigmine to be superior to benzodiazepines for cure as well as for relief of agitation in patients presenting with central and/or peripheral evidence of anticholinergic toxicity (167). Cardiac monitoring, close following of vital signs and of peripheral signs of cholinergic toxicity are recommended during this treatment. Arrhythmia, ulcerative colitis, gangrene, gastrointestinal or genitourinary obstruction, and asthma are considered relative contraindications (166), though the latter is disputed (167). It is interesting to speculate on utilizing physostigmine, perhaps in combination with other psychopharmacology (see below), in the treatment of cases of delirium with less overtly or directly anticholinergic etiologies, but this remains fertile ground for study.

In other situations involving delirium with agitation, central dopamine blockade with haloperidol is the treatment of choice while the underlying cause is being addressed. Haloperidol’s minimal anticholinergic effect and low levels of α₁-adrenergic antagonism and sedation is a very desirable combination for the
Polypharmacy in the Medically Ill Psychiatric Patient

A delirious patient. The low sedative potency of haloperidol is a point often lost on psychiatrists and nonpsychiatrists alike, though empirical experience reveals a truly “tranquil”-izing rather than hypnotic effect when it is used in delirium. The lowered incidence of extrapyramidal side effects of haloperidol when given via the IV route further increases its attractiveness in this context (168). An ECG and magnesium and potassium levels should be obtained before instituting IV haloperidol treatment in order to minimize the low-likelihood, but potentially disastrous, complication of torsades de pointes. The incidence of this iatrogenic arrhythmia is unknown, but it may be less than 0.4% (169), and Hunt and Stern point out that with appropriate screening and monitoring, “the continued judicious use of IV haloperidol is warranted, even in the patient with a rhythm disturbance” (170).

Lorazepam is used frequently in the treatment of agitation associated with delirium but may “treat” this solely through sedation, which in and of itself may worsen the existing situation. Indeed, in a comparison of monotherapy of delirium with low-dose haloperidol, chlorpromazine, or lorazepam in AIDS patients, the latter had to be discontinued in all six patients receiving it due to ataxia or further exacerbation of mental status changes (171).

On the other hand, the combination of haloperidol and lorazepam has proven quite useful in the treatment of delirium and often may be preferred over the use of haloperidol alone (e.g., when there are dose-limiting side effects of haloperidol or control of agitation is inadequate). Lorazepam appears to further reduce the incidence of extrapyramidal side effects with IV haloperidol (172,173). Dosing of this combination should be tailored to the needs of each patient, but it has been suggested that when the haloperidol:lorazepam ratio is tipped to favor the latter, sedation will prevail over tranquilization and clearing of mental status (174). Haloperidol is generally dosed starting at 0.5, 2, or 5 mg, with the next higher dose administered 30 minutes later if agitation is not controlled—usually up to a dose of 10 mg repeated hourly until agitation is controlled (163,174). The needs of the individual patient must be taken into account, however. Single doses of much more than 10 mg are often necessary, and up to 200 mg boluses have been used safely (163). Accompanying doses of lorazepam are given at likewise increasing increments within a general range of 0.5–10 mg (174). There is no clear consensus on subsequent dosing of these agents. Upper limits of daily dosing should be guided by the clinical status of the patient and not by academic concerns regarding side effects. In some instances (e.g., identified toxicity from pharmacological agents, which have since been discontinued), it may be advisable to wait for reemergence of agitation once tranquilization is achieved. In others (e.g., delirium secondary to a new aspiration pneumonia and/or unidentified causes), scheduled dosing based on duration of effect is necessary, with attempts at tapering both drugs on a daily basis as allowed by the patient’s mental status.
Aside from this haloperidol/lorazepam regimen, the polypharmacy of delirium is essentially uncharted territory. Many antipsychotics have been looked at in isolation as treatments of delirium, including the phenothiazines (171,175), droperidol (176), and, more recently, risperidone (177) and olanzapine (178). The latter two are of particular interest as oral treatments with theoretically low likelihoods of inducing extrapyramidal side effects. Unfortunately, their use has thus far been reported on in only 13 delirious patients. Atypical antipsychotics are increasingly being successfully used in the treatment of acute agitation in psychosis (179), and intramuscular preparations of olanzapine and ziprasidone are anticipated to be approved for this indication by the Food and Drug Administration imminently. It should be noted, however, that this sort of agitation is not necessarily diagnostically or therapeutically interchangeable with delirium, and specific study of these agents in the latter population is needed. Flumazenil has also been suggested as a treatment of at least hepatic encephalopathy (180,181).

As of this time, however, no polypharmacy in the treatment of delirium involving these medications has been examined in any systematic fashion.

CONCLUSIONS AND RECOMMENDATIONS

We hope that this chapter has illustrated that polypharmacy is a larger issue than poly(psycho)pharmacy. Caring for the medically ill psychiatric patient can dramatically complicate pharmacological decisions and require additional thoughtfulness in treatment choices. The hope for this chapter was to highlight some of the more common complications of practicing polypharmacy in medically ill patients and to offer some strategies to help alleviate the extremes of either ‘‘dangerous oblivion’’ or ‘‘frustrating obsessiveness’’ in the care of these patients. To be sure, this is no small task as patients live longer, develop medical illnesses and require more and more medications.

Of late, the literature has been filled with revelations regarding the danger of drug-drug interactions in the practice of polypharmacy. While this concern is appropriate, it is not the only concern with medically ill patients, and perhaps not even the most important one. Chief among the necessary principles for treating these patients is not the myriad of possible drug interactions but an understanding of the physiology of the major organ systems, aging, and of the basics of pharmacokinetics and pharmacodynamics. Attention to these principles will inform the psychiatrist about the implications of medical illnesses and drug interactions, help anticipate potential pitfalls in prescribing, and help understand untoward side effects when they occur. It should be noted that this chapter reviews selected organ systems and common but selected diseases. There are many diseases of potential import to the practicing psychiatrist that are not reviewed. Nor have we reviewed the impact of recreational drugs or over-the-counter medicines.
Practicing psychiatrists cannot hope to sustain a perfect understanding of all of medicine, but with vigilance it is possible to remain informed about patients’ medical conditions and prescribed medications. Patients will often not think to bring this to our attention. Therefore it is imperative to regularly initiate discussions regarding changes in health with patients and their providers. This can get complicated when patients have more than one illness and are being seen by more than one specialist. While having a primary care clinician is generally good practice, it is critical for those patients being seen by more than one specialist. Nonetheless, it is often just such a patient who does not have a primary care clinician and may even resist having to see “one more doctor.” Under such circumstances optimally one of the specialists becomes the de facto primary care clinician.

Finally, keeping track of our patients’ medications as well as psychiatric issues can be daunting. The only way to do this is for psychiatrists to incorporate communication with the medical provider into routine care. Having a collaborative relationship with the primary care physician (PCP) makes this task much easier but does not alleviate the need for vigilance. In many ways the psychiatrist becomes a “second” primary care physician. This occurs for several reasons. One is the fact that the complications of polypharmacy are often manifest in the central nervous system (change in mental states). Secondly we must guard against ascribing systemic complications (lethargy) to psychiatric illness (depression). Lastly we tend to see our patients more frequently than most specialists and thus are in the best position to be aware of their overall health.

Recommendations

1. Advocate that patients have a primary care physician or at least that one of their specialists agrees to function as a PCP, coordinating their overall care.
2. Develop a working relationship with your patient’s PCP and specialists.
3. Check all patients’ medication quarterly and after every visit with another doctor. This should include over-the-counter medications.
4. Start low and go slow with medications for medically ill patients, especially for those medications with long half-lives.
5. Avoid the use of psychotropics for ill-defined systemic symptoms (malaise or lethargy) without a thorough medical evaluation.
6. Avoid the use of psychotropics to treat symptoms of underlying medical problems, e.g., benzodiazepines for insomnia secondary to orthopnea or sleep apnea.
7. Avoid the initiation of new drugs until you have referenced possible drug-drug interactions.
8. Adopt a ‘low threshold’ policy regarding the possibility of side effects or toxicity in your medically ill patients.
9. When untoward signs of toxicity do occur in your patients, suspect changes in a medical condition.
10. Consider taper of medication if untoward effects emerge with age or new medical illness.
11. Measure blood levels of psychotropics more frequently in medically ill patients.

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Polypharmacy in the Elderly

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INTRODUCTION

Polypharmacy in the elderly is extremely common (1–3). Older adults in the United States spend billions of dollars each year on prescription medications, and third-party payers reimburse only a small percentage of these medications. Although only 13% of the United States population, the older population fill approximately one third of all prescriptions written each year and almost half of all over-the-counter medications purchased annually. Approximately 90% of Americans over age 65 take at least one prescription medication daily, and most take two or more.

What is polypharmacy in the older adult? By definition, polypharmacy is the treatment with many medicines for the same disease. In psychiatry we refer to polypharmacy as the concurrent use of two or more medications with similar properties to treat a single condition. Why is there an increase in polypharmacy in the population over 65 years of age?

In this age cohort, patients are at higher risk of polypharmacy due to higher rates of chronic and comorbid illness, with each disorder requiring additional medications. Therefore, the concurrent use of many drugs alone is not an accurate measure of appropriateness of therapy; it may reflect either inappropriate or prudent prescribing. Certainly older patients see more specialists—cardiologists, neurologists, psychiatrists, orthopedists—and frequently these specialists prescribe another medication without consulting the primary care physician or reviewing the current list of medications. Specialists prescribe more combinations of medications than general practitioners, which may be confounded by the complexity of illness in referred patients.
This high prevalence of polypharmacy is not easily remedied. Interventions aimed at educating physicians about the risks of polypharmacy in the elderly generally have not led to reduced rates of polypharmacy (4). One randomized trial was able to demonstrate less polypharmacy during the research protocol period, but after the study was over clinicians returned to their earlier practice of more frequent polypharmacy (5). However, in another randomized study, intervention by a pharmacist reduced inappropriate polypharmacy and side effects even up to a year after the study was completed (6).

Although polypharmacy is not always contraindicated, the practice can increase both cost and side-effect profiles through pharmacokinetic or pharmacodynamic interactions.

On average, older patients take approximately three times as many medications as younger patients. In a study in Denmark, polypharmacy (defined as two or more medications) was present in 16% of adults below age 70 and 48% of adults above age 70 (7). In an emergency room study of 300 visits, 91% of the elderly patients received polypharmacy with 2 or more medications, with an average use of 4.2 medications per patient. Medication adverse events accounted for 11% of emergency room visits (8). Thus, polypharmacy is strongly associated with drug-related adverse events based on the number of medications alone (9). These drug-related side effects can sometimes be quite serious, such as an increased risk of falls, which are associated with a high rate of mortality due to hip fracture. In one study, the use of one central nervous system (CNS)—active drug in the elderly increased the risk of falls by a factor of 1.5, and the use of two CNS-active drugs increased that risk by a factor of 2.4 (10). This is intensified by age-related changes in physiology, pharmacokinetics, and pharmacodynamics. The higher incidence of adverse drug events may not only be due to age-related changes but also to comorbidity-related polypharmacy.

Inappropriate prescribing is harmful and expensive. Physicians prescribe potentially inappropriate medications for almost a quarter of all older adults living in the community; the risks of ADEs most frequently include cognitive impairment and sedation (11). Cognitive impairment and sedation place this population at greater risk for morbidity and mortality. The costs of preventable ADEs that occurred during a stay in hospital were estimated to be $2.8 million annually in two large tertiary care teaching hospitals (12).

BASIC CONCEPTS

Key concepts relevant to polypharmacy in the elderly are the “prescribing cascade,” the effects of aging, altered pharmacokinetics and pharmacodynamics (especially the former), and multiple comorbidities (Table 1).
Table 1  Key Associations of Polypharmacy in the Elderly

1. Prescribing cascade
2. Effects of aging
3. Altered pharmacokinetics and pharmacodynamics
4. Multiple medical and psychiatric morbidities

The Prescribing Cascade

In the elderly, polypharmacy increases the risk of an adverse drug event or adverse drug event (ADE) such as falls, confusion, and functional decline (13,14). Changes in physiology and in social and physical circumstances contribute to the risk of ADEs. The elderly are more likely to have poor vision, hearing, and memory in addition to metabolic changes (i.e., renal function decline). An ADE may go undetected as symptoms may mimic age-related disorders, (i.e., weakness, tremor, forgetfulness, fatigue) or may be misinterpreted as medical problems, leading to more drugs and increased polypharmacy (15,16).

This process has been termed the “prescribing cascade,” which begins with an adverse drug reaction misinterpreted as a new medical problem, thereby introducing another drug to treat this condition, placing the patient at additional risk of adverse effects from the new drug (17). The potentially unnecessary treatment places the patient at greater risk when stopping the original drug would eliminate the symptom and reduce risk.

During hospital admissions this prescribing cascade in most preadmission medications may not be discontinued or the patients are not sure if they should continue these drugs when they return home. A common scenario is that at a subsequent outpatient visit a patient may be on two antihypertensives or on both digoxin and lanoxin, not knowing that there is no difference, or worse, the patients may be readmitted due to the ADEs related to taking the wrong medications. During a hospital stay, due to the effort in shortened lengths of stay, medications are often added but not eliminated. A concerted effort must be made to reduce the numbers of drugs and not increase them unless absolutely indicated. Drug-related morbidity and mortality was estimated to cost $76.6 billion in the ambulatory setting in the United States. The largest component of this total cost was associated with drug-related hospitalizations (18).

The Effects of Aging

Aging in itself jeopardizes the older adult. Aging, by definition, is a course of gradual and natural change. A major aspect of change in the elderly is that of
senescence, which is the loss of the capacity for cell division, growth, and function over time. This slow process ends in death, as senescence ultimately leads to a state that is incompatible with life. Not all the changes that occur in late life are detrimental.

Aging is complex, with a diverse development of physiological changes leading to diminished efficiency and decreased capacity. Great variability exists, and deterioration does not proceed at the same rate or extent within each individual. Medical problems can accelerate the aging process, and these comorbid illnesses are more common in the elderly. The outcome of psychopharmacological interventions may be diminished, or there may be higher risks of adverse drug events, resulting in either lack of response or worsening of the psychiatric condition.

Many older patients in hospitals and nursing homes routinely receive drugs that are not essential and can cause harm, either directly or indirectly through interactions with other medications. A thorough review of medications can often reduce the number prescribed and, according to limited data, improve patient outcomes (6).

Side effects of antipsychotic medications are particularly problematic in elderly patients, who experience many age-related changes that may exacerbate medication side effects. Side effects of particular concern in the elderly include anticholinergic reactions, parkinsonian events, tardive dyskinesia, orthostatic hypotension, cardiac conduction disturbances, reduced bone mineral density, sedation, and cognitive slowing.

Persons over 65 years of age experience ADEs at a rate conservatively reported to be two to three times that of younger adults. The higher rate can be largely explained by changes in renal and hepatic function and body composition associated with aging. Approximately 28% of the hospital admissions of older patients are a result of drug-related problems, and almost 70% of these are ascribed to adverse drug events (19).

The variability of the aging process within a cohort of elderly is exhibited in the nonuniform nature of pharmacokinetic and pharmacodynamic changes. The patient’s individual physiological and functional characteristics are more relevant than age.

### Altered Pharmacokinetics and Pharmacodynamics

Clinically significant changes in metabolism, distribution, and excretion occur in the older adult due to changes with aging. It is vitally important to make appropriate changes in drug therapy to account for these age-related changes. Changes in the pharmacokinetics and pharmacodynamics of elderly patients can result in longer half-lives, increased or decreased drug effects, greater incidence of drug toxicities, and possibly more frequent adverse drug reactions.
Polypharmacy in the Elderly

Changes in pharmacokinetics involve four basic areas: hepatic metabolism, renal excretion, absorption, and distribution. Hepatic metabolism is lowered due to reduced hepatic function, blood flow, and mass. Reduced hepatic blood flow slows drug metabolism, and this can be of great significance in drugs with a high clearance. High-clearance drugs, such as lidocaine, propranolol, and verapamil, are dependent only on blood flow, and thus they are not affected by decreased enzyme activity or hepatic disease. Reduced oxidative metabolism in the aged is also thought to be an important contributing factor. Enzyme activity is reduced predominantly in the pathways of phase I metabolism (oxidation, reduction, and hydrolysis). Phase II metabolism (glucuronidation, sulfation, and acetylation) is virtually unaffected in the elderly. Therefore, drugs eliminated via phase II are generally less influenced by age. Most studies reveal little or no reduction of specific activities and substrate affinities of the cytochrome P450 isoenzymes as related to aging (20). Aging alone with regard to enzyme induction and inhibition does not affect the P450 system, but the reductions in blood flow and hepatic mass can alter metabolism. The enzymes are heme-containing membrane proteins located in the smooth endoplasmic reticulum of several tissues. Although a majority of the isoenzymes are located in the liver, extrahepatic metabolism also occurs in the kidneys, skin, gastrointestinal tract, and lungs. Significant inactivation of some orally administered drugs is due to this extensive first-pass metabolism in the gastrointestinal tract by the CYP3A4 isoenzyme. Many drugs have decreased efficacy due to rapid metabolism, but drugs with active metabolites can display increased drug effect and/or toxicity due to enzyme induction. Enzyme inhibition occurs when two drugs sharing metabolism via the same isozyme compete for the same enzyme receptor site. The more potent inhibitor will predominate, resulting in decreased metabolism of the competing drug. For most drugs this can lead to increased serum levels of the unmetabolized entity, leading to a greater potential for toxicity, which is more dangerous in the older patient (20).

CYP3A activity is unaffected by age, suggesting that the aging-related alteration in the clearance of CYP3A substrates is secondary to changes in liver blood flow, size, or drug binding and distribution with aging (21).

Examples of disease states common in the elderly affecting metabolism are hepatic disease, which affects organ function, and congestive heart failure, which causes decreased blood flow to the liver. Drugs known to have decreased hepatic clearance in the elderly are antiarrhythmics, acetaminophen, antidepressants, benzodiazepines, antipsychotics, beta-blockers, coumadin, indomethacin, and theophylline. Poor-nutritional-status and frailer older patients may be at greater risk; the type of diet and supplements or parenteral formulas can influence oxidative metabolism. Protein deficiency might increase the toxicity of certain drugs. Fasting and high doses of vitamin C can inhibit the hepatic metabolism of several drugs. Certain foods, such as grapefruit, cabbage, spinach, onion, and garlic, can induce metabolism. Available figures in elderly populations have been inconclu-
sive on the responses to certain foods and macronutrients that may interfere with metabolism. Smoking can induce certain activity in the CYP 1A2 system. Avoiding or anticipating potential problems and adjusting a patient’s drug regimen early in the course of therapy can provide optimal response with minimal adverse effects. Many pharmacokinetic investigations in the elderly population reveal decreased clearance of lipophilic drugs metabolized by the cytochrome P450 enzymes. Hepatic drug metabolism in this population is more variable than renal drug clearance (20).

Renal excretion is decreased due to reduced blood flow (2% per year after 40), renal mass (10–20% between 40 and 80), glomerular filtration rate (50% between 50 and 90), functioning glomeruli, tubular secretion (7% per decade), tubular absorption, and creatinine clearance. Tubular secretion is the method of elimination of procainamide, benzodiazepines, lithium, and cimetidine (20).

Calculation of renal function is less accurate in the elderly and often overestimates the actual renal function. Due to age-related reduction in creatinine, more specifically reduced lean body mass that produces lower than expected creatinine levels. Congestive heart failure, diabetes, and hypertension impair renal clearance by reduced blood flow and glomerular filtration rate due to vascular damage (20).

Absorption is decreased in the elderly due to reduced gastric acid, motility, gastrointestinal surface area, and blood flow, but it is not usually a significant factor. Distribution is increased due to increased volume of distribution, increased fat, and decreased muscle mass, water, and cardiac output. Decrease in total body water will result in a smaller volume of distribution for water-soluble drugs such as ethanol, lithium, or digoxin. Conversely an increase in body fat increases the volume of distribution of fat soluble drugs such as benzodiazepines, neuroleptics, and salicylates (20).

Plasma proteins are altered in aging; albumin is often decreased and $\alpha_1$-acid glycoproteins increased (22). In delirium plasma albumin drops precipitously; conversely $\alpha_1$-acid glycoproteins, being acute phase reactants, increase. Protein binding of acid drugs is related to albumin, and binding of basic drugs is related to $\alpha_1$-acid glycoproteins. Thus, by changing the amount of free drug available, protein-binding drug interactions can affect mental status. Therefore, eliminating such drugs if possible is an essential step in managing conditions like delirium.

With aging, pharmacodynamics are also altered (23,24). There are fewer receptors, more resistance to drug diffusion, and either an increase or a decrease in important enzymes. Diminished neurotransmitters place older patients at risk for depression, dementia, and sleep disturbances. Changes in the central nervous system (i.e., decreased number of neurons, diminished neural glucose utilization) can lead to difficulty with coordination and balance, alteration in mood, changes in mental status and sensory interpretation, poor dexterity, information retrieval, sleep disturbance. Elderly patients are more sensitive to CNS-acting agents due to these changes.
Multiple Medical and Psychiatric Comorbidities

Elderly patients with psychiatric illness often have comorbid medical illnesses (e.g., cardiovascular disease and dementia of the Alzheimer’s type) and are thus likely to be taking multiple medications. Medically ill patients are more prone to develop depression than the nonmedically ill (25), and depression and dementia are highly related to each other (26). In fact, depression appears to be a risk factor for subsequent development of dementia (27). Hence, the frequent dilemma discussed in the past about whether cognitive problems represented incipient dementia or the cognitive effects of depression (“depressive pseudodementia”) seems less relevant today. Depression is associated with dementia; the two illnesses frequently go together.

As a consequence, it is not uncommon for an elderly depressed patient to also suffer from dementia, cardiovascular disease, or other illnesses. Some research suggests that dementia in particular is associated with lowered response to antidepressants for depression; other medical illnesses may not contribute to treatment resistance (28). Vascular depression, i.e., depression associated with CNS white matter abnormalities, is also associated with lowered response to antidepressants (29). In such situations, where multiple illnesses impede medication response, one is faced with the problem of treatment resistance to depression, which, as discussed in Chapter 3, leads to polypharmacy out of necessity.

Even when treatment resistance to psychotropic treatments does not occur, polypharmacy may still occur due to the need for different treatments for different illnesses (psychotropic medication for depression, antihypertensives for high blood pressure, cholesterol-lowering agents or beta-blockers for cardiovascular disease). Polypharmacy in this setting appears unavoidable, and the clinician’s main role becomes to use as few medications as possible as well as to make sure that those medications are not likely to interact with each other in such a way as to unduly increase the patient’s side effect burden (2).

CLINICAL DESCRIPTIONS

Approximately one half of patients with dementia have at least one coexisting medical illness, and with treatment of the underlying disorder about one fourth of such patients will have noted improvement of behavior and cognition. Often this improvement is transient but may be sustained. A behavioral disturbance, a sudden decline in functional status, or the worsening of confusion may be the initial manifestation of a physical illness in patients with dementia. Pain, dehydration, infection, heart failure, infections, chronic obstructive pulmonary disease (COPD), drug toxicity, constipation, hunger, fatigue, and head trauma are common diagnoses to consider. Such patients usually already receive polypharmacy
and due to behavioral problems are likely to be prescribed even more medications (the “prescribing cascade”) (17).

In treating dementia, few medications exist except for acetylcholinesterase inhibitors, which can improve intellectual functioning by blocking acetylcholinesterase and enhancing cholinergic function. Dementias other than the Alzheimer type may be particularly problematic in polypharmacy. For instance, in Lewy body disease, there is increased sensitivity to various medications, with a higher risk of parkinsonism and visual hallucinations.

There is some evidence that acetylcholinesterase inhibitors (AchEI) can ameliorate behavioral disturbances in addition to enhancing cognition, which gives these agents a broader role in the treatment of a variety of neurological disorders involving cholinergic deficits (30). Behavioral benefits include reduction in vocal outbursts, suspiciousness, delusions, agitation, hallucinations, wandering, fearfulness, compulsiveness, tearfulness, and threatening behaviors.

It is possible that the beneficial effects of acetylcholinesterase inhibitors with regard to emotion and behavior are mediated through cholinergic effects on the limbic and paralimbic brain structures (30). Many other agents have been studied, with minimal efficacy, such as vitamin E, nonsteroidal anti-inflammatory drugs (NSAIDs), ginkgo biloba, and hormone therapy. Currently, research is underway with sex hormones, like estrogen and testosterone. Anticonvulsants demonstrate effects on locus ceruleus, serotonin, and limbic dysfunction in many psychiatric conditions, which may extend to the dementias as well especially in more refractory cases. While most reports have been anecdotal, one controlled study with divalproex exists. In that study of 56 patients with Alzheimer’s dementia, there was a statistical trend for efficacy with valproate for agitation and other behavioral symptoms (68% response with valproate vs. 52% with placebo; \( p = 0.06 \)) (31).

Psychosis in conjunction with dementia is quite prevalent but often not as responsive to antipsychotic medications as in younger adults. Nonetheless, atypical neuroleptic agents have been proven quite effective in the treatment of psychosis as well as agitation in the elderly with dementia. Published double-blind controlled data exist for risperidone in particular (32). In that very large study of 625 patients with mostly Alzheimer’s dementia, risperidone was more effective than placebo in improving behavioral symptoms. This benefit existed at 0.5, 1, and 2 mg/day of risperidone, but 2 mg/day was associated with increased extrapyramidal symptoms (EPS). This important study highlights the important of very small doses of antipsychotic medications for the elderly, even with the newer generation of this class. At higher doses, EPS can be quite prevalent. The risk of EPS is also higher in polypharmacy of risperidone plus serotonin-reuptake inhibitors (SRIs) (33), since both of these types of drugs can produce EPS (34). Tardive dyskinesia is also less frequent in the elderly with atypical neuroleptic
agents, such as risperidone, than with traditional neuroleptic agents, such as haloperidol (35). Special consideration regarding the use of atypical neuroleptic agents in the elderly include a focus on anticholinergic, antidiuretic, and extrapyramidal side effects (36). In that sense, no single medication is ideal. Olanzapine and clozapine have some anticholinergic side effect risk, and quetiapine has significant antidiuretic effect (with risk of falls) and sedation. Ziprasidone appears to have a higher risk than the other agents of cardiac arrhythmias. Risperidone may be overall best tolerated, though it too can cause sedation or extrapyramidal symptoms, especially at doses above or equal to 2 mg/day.

The use of antidepressants for depression in the elderly usually begins with serotonin-reuptake inhibitors (SRIs). Tricyclic antidepressants should generally be avoided due to their potent anticholinergic and sedating side effects, as well as their risk of cardiac arrhythmias. Choosing the initial SRI is more art than science. Some agents purport to be more energizing or sedating, but the individual response in the elderly can vary widely. Nonetheless, certain general statements based on biochemical features of these agents appear warranted (37,38). Citalopram has the fewest other receptor effects in this class and is the most selective for serotonin-reuptake inhibition. Thus, it is frequently well tolerated in the elderly. Paroxetine, being the most anticholinergic of the SRIs, can sometimes pose a problem. Fluoxetine, paroxetine, and fluvoxamine produce the most drug interactions due to hepatic cytochrome effects, and thus are less easy to use in polypharmacy than citalopram or sertraline. As a class, SRIs can be associated with hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone (SIADH), and this hyponatremia can present as delirium. Furthermore, EPS, especially akathisia, can occur with SRIs, and akathisia in particular can be misinterpreted in the elderly as agitation or confusion. Bupropion in the slow-release form also appears to be well tolerated in the elderly, with minimal risk of seizures. Since bupropion has few neurotransmitter effects, it can be useful in the elderly; it is notable, however, that case reports of psychosis with this agent, presumably due to its mild dopaminergic effects, exist. Venlafaxine, mirtazapine, and nefazodone can be useful, but sedation can frequently be a limiting factor with those agents. As noted previously, in so-called vascular depression, i.e., depression with associated brain white matter abnormalities, antidepressant treatment appears to be less effective than in depressive syndromes in younger adults (29).

When one examines published controlled data regarding new antidepressant efficacy in the elderly, a few studies stand out. In the treatment of depression with mild-to-moderate dementia in the elderly, double-blind published data supporting efficacy exist for citalopram and paroxetine. Of the citalopram studies, one (n = 336) showed equal efficacy to the antidepressant mianserin (39), and the other (n = 149) demonstrated benefit with citalopram compared to placebo over 6 weeks (40). The study of paroxetine (n = 198, duration 8 weeks) compared
it to imipramine (50–100 mg/d), demonstrating equal efficacy and lower anticholinergic side effects (6% with paroxetine, 13% with imipramine); however, there was no placebo control (41).

Other antidepressants have been studied in the depressed elderly, though not in those with concomitant dementia. In the nondemented elderly with depression, controlled published data support efficacy with sertraline, bupropion SR, and fluvoxamine. One study compared sertraline to imipramine in 55 patients over 6 weeks, demonstrating equal efficacy and better tolerability with sertraline (42). Another study compared bupropion SR with paroxetine in 100 patients over 6 weeks, demonstrating equal antidepressant and anxiolytic efficacy and somewhat enhanced tolerability with bupropion SR (43). Fluvoxamine was also shown to be equally effective to the tricyclic antidepressant dothepin, while being better tolerated in 52 elderly depressed patients (44).

Delirium is a common cause of agitation, aggressiveness, or hallucinations or delusions in the elderly. Delirium is usually due to comorbid medical disorder and/or concomitant medication.

The incidence of psychosis increases with age. A number of factors lead to an increased vulnerability to psychosis in the elderly, including comorbid physical illnesses, social isolation, sensory deficits, cognitive changes, polypharmacy, and substance abuse. Reports of delusions or hallucinations are not invariably an indication for antipsychotic medications. Elderly patients with psychotic symptoms may benefit from social, behavioral, and environmental interventions. When patients require pharmacological intervention, atypical antipsychotics, as noted above, are quite useful.

**SUMMARY OF INTERVENTIONS**

Prevention of polypharmacy is the primary intervention, involving the following measures:

1. Avoid adding a new medication without thoroughly reviewing all current medications, including nonpsychotropic drugs.
2. Fully assess the indications of a medication prior to initiating treatment; there must be a strong indication and strong evidence for efficacy prior to prescribing.
3. Regular medication review with an accurate drug history is essential for the elderly on multiple medications. Often patients do not know nor do they have a list of their medications. Request that patients bring their bottles or a current list of medications prior to the addition of a new medication. Ask patients to include all over-the-counter medica-
Polypharmacy in the Elderly

4. Review dosing, timing, side effects, indication, formulation, and compliance.
5. Educate the patient, family and caregivers about the reason for taking the medication, potential side effects, and possible interactions with other medications.
6. If possible have the patient notify you or their primary care doctor when a new medication is added.

There seem to be more adverse drug events in sicker patients with longer hospitalizations, but relatively few risk factors have been demonstrated (45). Some researchers suggest that prevention strategies should focus on improving medication systems rather than the patient at risk (45).

ADVANTAGES AND DISADVANTAGES OF POLYPHARMACY

Certainly the advantages for judicious polypharmacy are extensive when treating patients with combinations of multiple medications, especially in refractory depression, psychosis, and behavioral problems associated with dementia.

When prescribing for older patients, some physicians are overly cautious, and this strategy can result in a less than optimal treatment outcome. Using the adage to start low and go slow has eliminated many medication interactions, but increasing the dose is paramount to obtain an adequate response. The reluctance to treat aggressively is understandable because the geriatric population is susceptible to adverse drug reactions. The key to maximizing therapy lies in individualizing the intervention as much as possible.

Many newer medications affect multiple receptor sites and neurotransmitters. Use of these medications is not very different, in some senses, from polypharmacy. For example, the atypical antipsychotics can affect dopaminergic, serotonergic, muscarinic, and adrenergic receptors. In the context of delirium, multiple receptor activity may worsen confusion.

Side effects in the elderly often are discounted or overlooked due to age or frailty. For example, abnormal gait, loss of appetite, or confusion may be attributed to aging, whereas medication side effects may be at fault.

In sum, polypharmacy may be necessary in the elderly to maximize efficacy and to treat multiple comorbidities. However, side-effect risks with polypharmacy are correspondingly higher in the elderly than in younger adults. Hence, caution is in order.
SUGGESTED GUIDELINES FOR CLINICIANS

Creating optimal drug regimens that meet the complex needs of elderly people requires thought and careful planning by each physician, working in concert with each caregiver. There should be extensive review of all medications, including medications often overlooked, such as ophthalmic preparations, lotions or creams, herbal or alternative preparations, and over-the-counter medications. Ophthalmic medications are absorbed through the lacrimal duct and may lead to systemic effects. Examples of bradycardia or heart failure due to beta-blocking eye drops are not uncommon. Complementary medications are usually not taken into consideration, because they are natural substances and patients frequently do not list these drugs among their medications. Alcohol use, abuse of prescribed drugs, and illicit drug use are also often overlooked in elderly frail patients.

It is important to assess the appropriateness, that is, the potential benefits of a drug, and to make sure that these benefits outweigh the potential risks. Determining appropriateness requires an evaluation of such potential benefits and risks. Many drugs benefit the elderly, and some can save lives—e.g., antibiotics and thrombolytic therapy for acute illness. Oral hypoglycemic drugs can improve independence and quality of life while controlling diabetes. Antihypertensive

Table 2  Psychoactive Medication Guidelines Under OBRA 1987

1. Limit long-acting benzodiazepines, anxiolytics/sedatives, sleep medications, and antipsychotics. Clinical justification must be provided for initial and continued use.
2. Nonpharmacological interventions should be tried to address behavioral, psychosocial, and mental disorders.
3. Gradual dose reductions of psychoactive medications must be attempted, unless clinically contraindicated, in an effort to eventually discontinue these drugs.
4. Psychoactive medications must be used to treat legitimate medical conditions, not for discipline or convenience. These drugs are considered chemical restraints when used to control mood, mental status, or behavior.
5. Psychoactive drug therapy must not be used unless necessary to treat a specific medical symptom/condition as diagnosed and documented in the clinical record. The care plan must address specific objectives of treatment with these medications, and assess for decline in overall function resulting from their use.
6. Antipsychotic drugs may be used in the patient with delirium or dementia only if there are psychotic or agitated features resulting in danger to the patient or others; continuous crying, screaming, yelling, or pacing; or resident distress or functional impairment. Preventable causes of agitation must be excluded, and the nature and frequency of these behaviors must be documented.
7. Nondangerous agitation, uncooperativeness, wandering, restlessness, insomnia, and impaired memory are insufficient in isolation to justify the use of antipsychotics.
Polypharmacy in the Elderly

Table 3  The Beers criteria

The following medications are considered inappropriate for use in the elderly:
1. Certain antihistamines, anticholinergics, muscle relaxants, barbiturates, and benzodiazepines
2. Certain drugs given above upper dose limits, such as propoxyphene, amitriptyline, doxepin, dipyridamole, ergot mesylates, and gastrointestinal antispasmodics
3. Combination drugs such as chlordiazepoxide and amitriptyline (Libitrol) or amitriptyline and perphenazine (Triavil).

drugs and influenza and pneumococcal vaccines can help prevent or decrease morbidty. Analgesics and antidepressants can control debilitating symptoms. However, adverse effects of many drugs are more common and serious in the elderly.

Clinicians would do well to follow the recommendations of the Omnibus Reconciliation Act of 1987 (OBRA-87), which mandated a standardized national assessment of nursing home residents and included guidelines for use of psychotropic medications. Within 5 years after the guidelines were in effect, the percentage of patients receiving psychoactive medications declined significantly (46). The guidelines are outlined in Table 2. Another set of recommendations is based on a landmark article by Beers (47) outlining a list of drugs designated as inappropriate for use in the elderly (Table 3). A number of other common-sense recommendations may prove useful in appropriate use of polypharmacy in the elderly (Table 4). Table 5 summarizes aspects of the psychiatric interview that are especially important in promoting appropriate polypharmacy but avoiding it where possible.

Table 4  Other Recommendations for Appropriate Polypharmacy in the Elderly

1. Prescribe medications on a regular schedule as much as possible, not on an as-needed (“prn”) basis
2. Prescribe monotherapy as much as possible
3. Plan a finite duration for a medication trial (not open-ended)
4. “Start low, go slow,” but avoid underdosing
5. Continue or initiate nonpharmacological treatments
6. Choose target symptoms and desired/reasonable endpoints
7. Document outcomes
8. Monitor for and document adverse effects
9. Taper to lowest effective dose
10. Attempt periodic drug removal
11. Consider longer-term medication only for recurrent or relapsing disorders and for those with chronic psychiatric illness
Table 5  Aspects of Psychiatric Interview Essential to Promoting Appropriate Polypharmacy

1. Before prescribing, begin by carefully assessing the absolute need for the drug.
2. Establish an accurate diagnosis of a dementing illness (do not accept unconfirmed diagnosis; consider lifelong personality disorder, chronic psychiatric problems).
3. Document the specific behavior:
   - Description (specific)
   - Frequency, timing, location
   - Potential antecedents/triggers
   - Immediate consequence(s) of the behavior
4. What has worked, what has failed?
5. Assess for causative or contributing factors:
   - Anxiety, depression
   - Medications
   - Physical limitations, functional disabilities
   - Medical illness, delirium (infection, drug effect, cardiac disease)
   - Pain/discomfort (fatigue, distended bladder, constipation, bedsores)
   - Hearing impairment, visual loss
   - Boredom, isolation, loneliness
   - Environmental sources (staff interaction, hospitalization, under/overstimulation)
6. Determine whether symptom requires intervention:
   - Patient safety (danger to self or others) vs. staff convenience
   - Distressing to the patient (e.g., some hallucinations or delusions are not bothersome or frightening and may be ignored/observed)
   - Interferes with activities of daily living or socialization
   - Affects placement (e.g., leading to institutionalization)
   - Consider whether behaviors might represent depressive symptoms

In appropriate management of polypharmacy in the elderly, it almost goes without saying that clinicians need to pay careful attention to the wishes and perspectives of caregivers and family members, in addition to those of the patients. It is worth repeating this point, however. Family members and caregivers can often help clinicians to best understand the needs of elderly patients, thus avoiding misdiagnoses or excessive treatments. Close coordination of diagnosis and treatment with caregivers is essential in the elderly.

SUMMARY

The use of multiple medications in a judicious manner, with well thought-out combinations, is helpful in older patients with multiple illnesses. However, it is imperative that clinicians review side-effect profiles and incorporate side-effect
burden in the decision-making process of drug selection. It is difficult to reduce polypharmacy in the elderly, but where such polypharmacy is inevitable, careful selection of treatments can maximize their benefits while reducing their risks.

REFERENCES

INTRODUCTION

In this chapter on polypharmacy, common child and adolescent psychiatric disorders will be addressed. We will highlight what is available in the literature to date on combined pharmacotherapy. Relevant studies, when available, will be referenced, as will the first author’s clinical experience in almost 20 years of prescribing to children and adolescents with complex psychiatric disorders, in inpatient and outpatient settings, in tertiary care facilities, and in community mental health centers. Fortunately, the first author has had patients that have been followed from early childhood into adulthood and has maintained a practice that spans three northeastern states as well as three generations of family members who have complied with treatment and cooperated in clinical research studies.

THE CURRENT STATE OF POLYPHARMACY IN CHILD PSYCHIATRY

Polypharmacy, also called combined pharmacotherapy, has been defined as two or more medications prescribed to an individual for the same disorder. It has also been defined as multiple agents administered to the same individual for the treatment of comorbid conditions or to minimize and/or alleviate side effects.
produced by a medication. Regardless of the definition, in child psychiatric practice over the past decade and a half, the use of multiple medications has become increasingly common, as described in pharmacoepidemiological studies (1). These changes in practice have been outlined by others (2). Proponents have argued that “previously the law of parsimony dictated a single cause for each symptom complex.” This led to the use of large doses of individual agents for a given disorder, often resulting in intolerable adverse side effects. In contrast, the use of combined pharmacotherapy has permitted more targeted treatment and greater efficacy, often achieved with lower doses and fewer adverse effects (3).

Much controversy exists around the safety and efficacy of such practice. There is a paucity of controlled data in young subjects on single agents, let alone multiple agents (4,5). Appropriate concern has been raised regarding drug interactions and metabolism as well as the need for close monitoring (6). The use of algorithms and risk-benefit analysis has been emphasized until scientific data can validate practice (7). In preschool children there has been obvious concern over the effects of agents on the developing brain. This has led to a call for more rigorous testing (8) and pharmacokinetic study (9). The U.S. Food and Drug Administration (FDA) has urged expanded testing of medications in children and adolescents. This remains problematic because of consent issues for minors and their caretakers and the ethical issues inherent in giving a placebo to a child with serious mental illness. Arguments in the literature calling for fewer medications in children with unclear diagnoses also emphasize the adverse effects of medications, e.g., the psychotomimetic effects of stimulants in pervasive developmental disorders (10).

Nevertheless, following adult practices, children and adolescents are prescribed multiple medications in both outpatient and inpatient settings. Combinations of medications have been used to treat disruptive behavior disorders, mood disorders, anxiety disorders, psychotic disorders, and pervasive developmental disorders. Frequently, comorbidity is used as the rationale for prescribing multiple agents for a child or adolescent (Table 1). At a recent conference, Bhatara

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Polypharmacy</th>
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<tbody>
<tr>
<td>Bipolar disorder</td>
<td>Stimulant plus mood stabilizer</td>
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<tr>
<td>Unipolar depression</td>
<td>Stimulant plus SRI</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>Stimulant plus benzodiazepines</td>
</tr>
<tr>
<td>Aggression</td>
<td>Stimulant plus SRI</td>
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SRI = Serotonin-reuptake inhibitor.
et al. analyzed data collected from outpatient practices under the National Ambulatory Medical Care Survey between 1993 and 1998 and found an increase in child polypharmacy (11). The most commonly prescribed combinations were (a) an antidepressant with divalproex or olanzapine and (b) stimulants plus clonidine. Presumably, the combination of mood stabilizer and antidepressant or antipsychotic was for bipolar disorder, a disorder now more commonly diagnosed in young subjects.

In attention-deficit hyperactivity disorder (ADHD) it is not uncommon to prescribe a psychostimulant during the day and clonidine at night for sleep. This practice has come into question after some adverse responses (12) including three deaths (13). Clonidine has been used for pervasive developmental disorders, Tourette’s syndrome, aggression, anxiety disorders, and insomnia. It has also been implicated in worsening depression in combination with a psychostimulant and antipsychotic (14). Adverse reactions have also been reported with methylphenidate and imipramine (15) and with stimulants combined with antidepressants (e.g., methylphenidate and fluoxetine) for ADHD comorbid with depression or anxiety. Toxic reactions to SRIs and tricycles also have been noted. (The first author has two cases in which 10 mg nortriptyline plus 10 mg fluoxetine given to children with ADHD and depression resulted in toxic tricyclic levels, necessitating admission to a pediatric intensive care unit for cardiac monitoring until blood levels waned.) Antipsychotics given for psychotic disorders, bipolar disorder, and aggression often require addition of an anti-parkinsonian agent. In one study, combined pharmacotherapy occurred in 60% of a sample of residentially placed children and adolescents and was significantly associated with the lifetime number of psychiatric placements, lifetime number of psychiatric diagnoses, and nonseizure neuropsychiatric comorbidity. Combined pharmacotherapy was significantly associated with aggression and neuroleptic use. There was no correlation between combined pharmacotherapy and diagnostic comorbidity on admission (16).

**GENERAL CONSIDERATIONS**

Administration of any medication to a child warrants careful monitoring by a clinician. Given the limitations of the scientific data on psychotropic agents in combination in children and adolescents, added caution and close monitoring is necessary. In an effort to help these children without harming them, thoughtful and rational approaches must be practiced. No medication should be administered to anyone without a careful and thorough assessment, risk-benefit analysis, and informed consent. Merely extrapolating from the adult literature can be misleading (17). Before embarking on a recommendation of any medication or combination of medications, a careful, systematic, and comprehensive assessment of a child or adolescent is necessary. Obtaining information from multiple sources
including parents, teachers, pediatrician, neurologist, hospitals, agencies (departments of social services, mental health, youth services and courts) along with the child or adolescent’s self-report in an interview is critical. Structured interviews and rating scales can be helpful, though not always obtainable. Schools often will provide data from Connor’s rating scales when ADHD is under consideration. Mood charts can be filled out by parents and even by children or adolescents in some instances, so that a sense of day-to-day fluctuations in mood can be ascertained. A medical evaluation is essential to rule out any illness or disorder that may contribute to the behavior, mimic it, or complicate treatment. (Such an evaluation might include an EEG, thyroid function tests, toxic screens, etc.). After careful formulation in the context of a multidisciplinary treatment plan, when the decision to prescribe is made it is imperative that the caretaker have the skills to administer approximately the agent or agents. The prescriber must have a solid relationship with the child and the caretakers and must be able to communicate effectively so that there is good cooperation around keeping scheduled appointments and obtaining necessary laboratory studies.

ADHD

Attention-deficit hyperactivity disorder is a common and often disabling disorder that presents in childhood and often is chronic, lasting into adolescence and adulthood. It is an illness that has been better studied and treated than many other disorders presenting to a child psychiatrist, with over 150 studies and 5000 subjects studied and a half century of treatment with psychostimulants; it is also frequently comorbid with other disorders (18).

Initial treatment for simple, uncomplicated ADHD should be with a psychostimulant (methylphenidate, dextroamphetamine in short- or long-acting preparation). Magnesium pemoline (Cylert) is infrequently prescribed due to its potential for hepatotoxicity. If one stimulant such as methylphenidate (Ritalin, Concerta) is not effective or causes an adverse reaction, another class of psychostimulant such as dextroamphetamine should be tried. Monotherapy should be the rule when starting out in treatment. However, in a third or more of children, a psychostimulant may not be effective. Other agents then are considered either singly or in combination. “Complex cases of ADHD may require rational uses of combined pharmacotherapy” (18).

If a child has both ADHD and a seizure disorder, an anticonvulsant may be necessary in addition to a psychostimulant or antidepressant. In a double-blind crossover study, 30 children with epilepsy and ADHD were treated with anticonvulsant and methylphenidate (0.3 mg/kg). Methylphenidate was effective in 70% of the group and did not seem to affect anticonvulsant blood levels (19). In ADHD comorbid with depression, bupropion as a single agent may be indi-
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cated. In children who have an underlying seizure disorder along with ADHD it is important to make sure an anticonvulsant is also prescribed since bupropion in doses above the recommended maximum lowers seizure thresholds and may induce seizures. The risk is often highest in the initial titration of bupropion, and so a very slow introduction of this medicine may reduce the risk of a seizure.

In children who benefit from psychostimulants during the day but have insomnia secondary to the stimulant, ADHD, or a mood disorder, addition of clonidine at bedtime may be helpful (0.05–0.2 mg). It is prudent to not exceed 0.4 mg of clonidine in a 24-hour period. Clonidine is an \( \alpha_2 \)-noradrenergic receptor agonist used as an antihypertensive agent in adults that does not seem to effect blood pressure in young subjects. Its presumed mechanism of action is to act on the presynaptic neurons to inhibit release of norepinephrine from the locus ceruleus (20). The combination of psychostimulants and clonidine is commonly given to children with ADHD (11) despite three related fatalities with clonidine and methylphenidate (13). The etiology of the associated deaths were unclear—possibly an underlying congenital cardiac problem in one and an overdose in another. Other possible adverse reactions to clonidine plus trazodone and clonidine plus dextroamphetamine have been reported (12). It is important to review these possible reactions with families when administering clonidine in combination with an antidepressant.

Prior to the introduction of serotonin-reuptake inhibitors (SRIs) for depression and anxiety, tricyclic antidepressants (TCAs) were used to treat children with mood disorders and ADHD. Due to the sudden deaths of seven children on desipramine and the availability of safer agents, it is less common today to see tricyclics used in young subjects. Rapaport and colleagues studied the separate and combined effects of methlyphenidate and desipramine on cognition (21). In this double-blind, placebo-controlled, crossover design study, methylphenidate alone improved vigilance, both medications positively affected short-term memory and visual problem solving, and the combined medications affected learning of higher-order relationships. In this study the goal was to examine a behavioral-affective spectrum that included ADHD with depressive symptoms, ADHD and major depressive disorder (MDD), and MDD with prominent attentional symptoms. K-SADS-E (22) was administered to the parent and the child admitted to the inpatient unit along with all outside clinical information and the clinical interview. The children (\( n = 16 \)) participated in the study for 16 weeks. None of the children were taking medication at the start of the study. For the first 2 weeks of the study no medication was administered as baseline data was gathered. Subsequently, each child received desipramine, each of three dosages of methylphenidate 10, 15, and 20 mg, combined desipramine and methylphenidate (at each of the three levels) or placebo. Desipramine dosage began at 50 mg and titrated up to a blood level between 125 and 225 ng/mL. Cognitive measures included the Continuous Performance Test (CPT), the Paired Associate Learning Paradigm
Methylphenidate was consistently the most potent medication affecting children’s vigilance (CPT) and ability to learn paired associations (PAL). Methylphenidate also had a significant effect on MFFT and SEP. With the addition of desipramine, MFFT and SEP scores were further enhanced. Desipramine did not effect vigilance and may have caused a blocking of the effect gained by methylphenidate when combined. Desipramine’s strongest effect in this study was on MFFT performance. The study concluded that as more complex tasks are challenged, desipramine should compare to methylphenidate and the combined effect of the two should have a superior effect on performance. In this study the additive effect of the two medications was considered beneficial without evidence of harm. There was a case report (23) in which an ‘apparent additive’ effect of methylphenidate and imipramine caused a blood dyscrasia. Speculation on a possible mechanism for this included a methylphenidate-induced elevation of plasma imipramine concentrations (15).

ADHD comorbid with anxiety and depression bears comment here and will be further addressed later in the chapter. The SRIs have been useful in treating anxiety and depression in youth. They, however, are not good agents for ADHD, and so a combined approach is often required, e.g., stimulant plus SRI. It is important to prioritize the symptoms, addressing the one that may need the most immediate intervention first. Most often a child needs help with attention at school, so a psychostimulant would be the first medication prescribed. However, if a child is school-phobic and cannot even get to school, then medication for anxiety should come first. The attentional difficulty can be addressed later.

BIPOLAR DISORDER

Bipolar disorder in children and adolescents is frequently comorbid with ADHD. After mood stabilization, addition of a psychostimulant such as methylphenidate may be warranted. A case report of a bipolar child with comorbid ADHD showed improvement when lithium was combined with methylphenidate (24). In an open study of divalproex in bipolar subjects aged 7–19 years, many of the subjects had such severe ADHD that the researchers allowed them to remain on their psychostimulants, without which their behavior would have been unmanageable (25). Of 40 subjects entered into the study, 6 (15%) were discontinued because of adverse effects, 6 were discontinued because of lack of efficacy, and another 6 were dropped because of noncompliance. Of the 21 (61%) completing the open trial, all showed a greater than 50% improvement in Mania Rating Scales, a positive response. Side effects included headache, nausea, vomiting, diarrhea, and somnolence. In another 8-week open trial of naturalistic design, researchers followed hospitalized bipolar adolescents (5 males and 5 females, aged 13–18,
all with comorbid conditions). Nine out of the 10 patients received combined pharmacotherapy, which included psychostimulants, lithium, antidepressants, antipsychotics, and antiparkinsonian agents. Though separating the effects of the different medications was difficult, valproate was well tolerated. Moods improved according to measurements on the Beck Depression Inventory and the Clinical Global Improvement Scale. The only side effects reported were transient alopecia in one subject, menorrhagia in one female (which necessitated discontinuation), and sedation in one male (26).

Wozniak and Biederman (27) outlined three basic considerations to take into account when tackling a complex condition such as bipolar disorder, with its frequent comorbidities. They suggest: (a) consider the medications(s) most effective for a child presenting with a particular spectrum of comorbidity; (b) consider the symptoms whose severity demands priority of treatment; and (c) consider the potential interactions of multiple medication and the risk of exacerbating one disorder while treating another. Mood stabilization is usually the first concern, and one or more mood stabilizers should be considered (lithium, valproate, or carbamazepine). If ADHD is prominent, then the addition of a stimulant in very low doses or of bupropion in similarly small doses (e.g., 37.5 mg) may help. If panic and agoraphobia are prominent, addition of a benzodiazepine such as clonazepam may be beneficial in a non–substance-abusing individual. In bipolar patients with anxiety disorders, antidepressants might be added only at low doses.

In the first author’s experience, even low doses of antidepressants in some children and adolescents already on a mood stabilizer may cause adverse reactions. These reactions include hypomania, mania, or worsening depression. Even in patients shown to tolerate the addition of an antidepressant, careful monitoring must continue during titration and maintenance phases.

If a child or adolescent is psychotic, an antipsychotic agent can be added. If aggression is a problem, as it is so often in youth with bipolar disorder, an anticonvulsant, antipsychotic, clonidine, or a beta-blocker may help. Of all the conditions listed here, bipolar illness has the broadest comorbidity and, in the first author’s clinical experience, the greatest number of medications prescribed.

When bipolar disorder is comorbid with Tourette’s syndrome and obsessive-compulsive disorder (OCD), the clinician must again consider the order of treatment. Often in clinically referred children and adolescents, Tourette’s and OCD may be the first presenting symptoms. If a child has episodic rages, sometimes centered around rituals and the need to perform compulsive behaviors, mood stabilization should be achieved first. Once the mood has been stabilized, other agents may be introduced gradually. Clonidine may be used for tics, and then fluvoxamine or clomipramine for the obsessive-compulsive symptoms. In some patients it may be necessary to add an antipsychotic such as pimozide, haloperidol, orquetiapine.
Substance abuse disorders occur comorbidly with adolescents and even latency-age children diagnosed with bipolar disorder. This is a group that is often very difficult to treat. In one double-blind placebo-controlled study of adolescents using lithium, 25 adolescents primarily diagnosed as bipolar with a secondary diagnosis of substance abuse disorder participated. Lithium was found to be superior to placebo in improving mood and reducing substance abuse (28). This study demonstrates the need for appropriate mood-stabilizer pharmacotherapy when treating bipolar patients with substance abuse problems.

Newer agents are being introduced even as this chapter is being written, and as with all medications clinicians must proceed with caution. There are few clinical data available on controlled studies in children and adolescents using gabapentin, lamotrigine, or topiramate for bipolar illness. These are agents that have been found to be clinically beneficial. Omega 3 fatty acids are also prescribed adjunctively to bipolar children and adolescents related to positive results in adult research (29).

UNIPOLAR DEPRESSION

All of the antidepressant agents used by adults have been used in children and adolescents [tricyclics, serotonin-reuptake inhibitors (SRIs), monoamine oxidase inhibitors (MAOIs), atypicals such as bupropion, venlafaxine, trazadone, and nefazodone]. Though many of the controlled studies of tricyclics did not find them better than placebo (30) for depression, they have been found beneficial for anxiety, OCD, and enuresis. Augmentation with lithium in treatment-resistant depression was effective in adolescents unresponsive to imipramine (31,32). In a case study of two severely depressed adolescents, lithium augmentation of venlafaxine was followed by a marked improvement in mood and function. Fluoxetine has been shown to be better than placebo in young subjects (33). It is common to use trazodone as a sedative at night if a patient on SRIs has trouble sleeping. Trazodone should be cautiously given to males because of the risk of priapism, but female patients may be helped by this combination.

SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS

Neuroleptics are the most common agents used to treat childhood schizophrenia. With the improved side effect profile of atypical antipsychotics, these agents are taking the place of typical antipsychotics. Clozapine has been used in adolescents with schizophrenia as well as in adolescents with refractory bipolar disorder. Some case reports indicate worsening symptoms of OCD in schizophrenic adolescents on clozapine. This occurred in a dose-dependent manner, so that a reduction
in clozapine led to a reduction in symptoms. The use of lithium plus a neuroleptic has been studied in schizophrenic youth. AIMS (Abnormal Involuntary Movement Scale) must be administered to track any manifestation of adverse side effects whenever a typical or atypical antipsychotic is prescribed to a child or adolescent.

ANXIETY DISORDERS

Anxiety disorders are the most common class of serious psychiatric conditions affecting children and adolescents. In a community-based study, nearly 3% of 9- to 17-year-olds had a diagnosable anxiety disorder that caused serious impairment (34). Children and adolescents with anxiety disorders have been prescribed the following drugs—benzodiazepines, buspirone, tricyclics, and SRIs. Controlled studies of tricyclics alone have yielded mixed results, and given the more desirable side-effect profile of SRIs, tricyclics are used less frequently today. A benzodiazepine (e.g., clonazepam) in small doses (0.125 or 0.25 mg) administered at bedtime and/or in the morning may help children suffering from panic disorder or school or social phobias. Great care is needed when administering a benzodiazepine to children, and the risk of possible disinhibition should be considered.

Failure to treat anxiety disorders in childhood and adolescence may cause developmental problems that result in cognitive impairment and social dysfunction. Anxiety disorders are frequently comorbid with other anxiety disorders, depression, and substance abuse. The lifetime risk of major depression is as high as 70% for patients with social phobia or generalized anxiety disorder. If anxiety is comorbid with depression, the risk of a suicide attempt is elevated by a factor of 2 to 6 (35). In cases of comorbid depression, any of the SRIs (fluoxetine, citalopram, paroxetine, or sertraline) can be added to the anxiety treatment.

TIC DISORDERS

Clonidine is the first-line agent for Tourette’s syndrome. Tics are commonly comorbid with ADHD. Stimulants may precipitate or worsen tics, as may buproprion. Tricyclics and clonidine are alternatives that may benefit some patients and also treat their ADHD. Nevertheless, in some patients stimulants may be more effective and should not be excluded from the armamentarium of drugs used in this disorder. Haloperidol, pimozide, and more recently quetiapine may be antipsychotics that can help reduce tics.

There has been a case report of a child with Tourette’s and severe OCD who, on the combination of paroxetine and haldol, developed an acute dystonic
reaction. The patient was subsequently switched with benefit to clonidine 0.5 mg qid, sertraline 100 mg qd and clonazepam 0.5 mg qd (36). Again, this highlights the necessity of close monitoring but also supports the idea that complex psychiatric conditions with associated comorbidity require more than a single agent for effective treatment.

**OBSESSIVE-COMPULSIVE DISORDER**

Obsessive-compulsive disorder may be treated with an SRI or clomipramine. The frequent comorbidity of OCD with Tourette’s syndrome (TS) and the possibility that both disorders may be different behavioral manifestations of the same underlying disease suggest that SRIs that are effective for OCD may also be beneficial for Tourette’s (36). In a chart review by Hawkridge and colleagues, four out of five cases of OCD comorbid with TS showed improvement with combined SRI and neuroleptic treatment (36).

SRIs may require addition of clonidine or a neuroleptic in the presence of tics, benzodiazepine in cases of severe panic or insomnia, and sometimes an antipsychotic (pimozide, haloperidol or atypical antipsychotic).

**CONDUCT DISORDER**

The most important therapy for conduct disorder does not involve pharmacological intervention. When drugs are used, as is often the case with aggressive disorders, they are only part of a comprehensive treatment strategy. Clinicians should also remember that before evaluating aggression in conduct disorder, it is necessary to first assess other comorbidities. These should include unipolar depression, bipolar depression (especially in adolescents with conduct disorder), and ADHD. For these subgroups, antidepressants, lithium, valproate, and stimulants may be helpful. For nonspecific treatment of aggression with conduct disorder, controlled research supports the use of neuroleptics and lithium. Carbamazepine, trazodone, clonidine, and beta blockers may also be effective, but more controlled research is needed (20).

**PERVASIVE DEVELOPMENTAL DISORDER**

In pervasive developmental disorders, medications should decrease maladaptive behaviors, with minimal side effects and minimal impairment of cognitive function. Psychopharmacology should be seen as adjunct to a multidisciplinary treatment plan. Beta blockers, naltrexone for self-injurious behavior, and psychostim-
ulants may be helpful, but adverse responses have been reported (e.g., the psychotomimetic effects of stimulants in pervasive developmental disorders) (10). Neuroleptics are often prescribed for aggression in this population. Other agents such as anticonvulsants for explosive rage have been studied, though not in a controlled fashion (20).

MENTAL RETARDATION

In mental retardation, neuroleptics are often used for aggression, an extremely controversial topic in child psychiatry. Given the “adverse risk profile” of such agents (e.g., extrapyramidal symptoms, akathisia, acute dystonic reactions, and tardive dyskinesia), there is appropriate concern that these agents are overprescribed and that some children and adolescents could be treated with antidepressants or psychostimulants instead of neuroleptics. In addition to the serious side effects listed above, neuroleptics are also known to have a negative effect on cognition. Stimulants in mentally retarded aggressive children may be underutilized. The use of antipsychotics in nonpsychotic children and adolescents must be carefully thought out, with a detailed analysis of the risks and benefits. Alternative agents such as SRIs, beta blockers, buspirone, lithium, anticonvulsants, α₂-agonists, clonidine, guanfacine, and naltrexone should be considered in treating this population before prescribing conventional antipsychotics (20). Atypical neuroleptics have much lower risks and should be preferred to conventional neuroleptics.

SUMMARY AND RECOMMENDATIONS

Combined pharmacotherapy is becoming an increasingly popular treatment for children and adolescents. As more and more children are being treated with multiple medications, the controversy surrounding this method is growing as well. There are some advantages to polypharmacy in children (Table 2), such as more precise targeting of symptoms and decreases the need for large dosages, thus minimizing side effects sometimes associated with single-agent therapy. It is also beneficial, given the prevalence of comorbidity in many patients. However, de-

Table 2  Advantages of Polypharmacy in Children

1. Appropriately treats certain comorbidities (11,27)
2. May treat side effects associated with high-dose monotherapy (2)
3. May decrease drug dosage in monotherapy (3)
disadvantages of polypharmacy in children

1. Adverse events (6,12–15)
2. Limited database of empirical evidence (4,5,37)
3. Drug interactions (6)
4. Unknown long-term effects on the developing brain (7)
5. Lack of evidence on drug metabolism (6)

Despite these benefits, clinicians should proceed with caution when prescribing multiple agents to children, especially to preschoolers (Table 3). Little controlled data exist on the developmental and metabolic effects of single agents in children and adolescents, and even fewer data are available on multiple agents. Therefore clinicians must carefully monitor behavior, cognitive development, and other developmental parameters when using polypharmacy in children.

As a general rule, initial therapy should be monotherapy. Even in cases of apparent comorbidity, clinicians should make judgments as to which condition needs to be treated first and which condition can wait for reassessment after the introduction of a new agent. For example, when treating a child who suffers from school phobia and ADHD, clinicians should first treat the school phobia and reevaluate the ADHD in the context of the monotherapy. Also, in bipolar disorder with ADHD, mood stabilizer monotherapy is initially preferable. Only after careful evaluation and risk-benefit analysis should additional drugs be introduced.

Once it is determined that polypharmacy is necessary due to comorbidity, inefficacy, or side effects, clinicians should refer to the existing data when determining therapeutic drug combinations. Some of the most commonly prescribed combinations include an antidepressant with olanzapine or divalproex, stimulants with clonidine, stimulants with antidepressants, and stimulants with anticonvulsants. In the use of all combinations in children, special attention should be paid to adverse events (Table 4).

In summary, polypharmacy can be carefully and effectively utilized in children with psychiatric conditions, although polypharmacy needs to be applied judiciously and only where it is necessary.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Adverse Events Reported in Polypharmacy in Children</th>
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<tr>
<td>1. Nortriptyline plus SRI reported to cause cardiac side effects</td>
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<tr>
<td>2. Three cases of fatalities with stimulants plus clonidine (13)</td>
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<td>3. Stimulant plus bupropion lowers seizure thresholds (19)</td>
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<tr>
<td>4. Methylphenidate plus imipramine caused a blood dyscrasia (23)</td>
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Psychosocial Aspects of Polypharmacy: The Social Work Perspective

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While the main emphasis of this book is medical perspectives on polypharmacy in psychiatric disorders, psychosocial perspectives are equally important. There is a growing interest in the relationship of social work to psychopharmacology (1–3), with polypharmacy being a subject of particular importance. In this chapter, we will describe many of the psychosocial phenomena associated with polypharmacy, and we will specifically discuss the role of the social worker in psychopharmacological treatment.

Polypharmacy is justifiably criticized in many settings. Social workers are among those who have perhaps been most vociferous in these criticisms. However, it is all too easy for social workers and other mental health professionals to stand apart from the medication treatment process, disagreeing from afar yet doing nothing constructive. We advocate that social workers need to be active players in the medication treatment of persons with serious mental illness (SMI). Social workers need to be engaged in this treatment process, both to maximize the

* Much of this discussion will have relevance to other nonphysician mental health professionals, particularly psychiatric nurses, but also psychologists, occupational therapists, and other providers. We focus on the role of social work since social workers are increasingly central to the provision of primary psychiatric care in the United States and since social work has a philosophy and tradition that specifically diverges from the medical tradition of physicians and other health professions.
benefit of needed medications as well as to help avoid treatment with unneeded medications. Especially in the case of SMI, traditional models of single provider treatment do not suffice. Psychopharmacology is usually necessary but not sufficient by itself for treatment success. Individual psychotherapy is often helpful, though not usually by itself. Attention needs to be paid to family structures and habits, community links, social supports, occupational abilities, and rehabilitation needs. The best outcomes result from a team approach linking psychiatrists, social workers, psychologists, case managers, occupational therapists, and other mental health professionals with the client. In the last few decades, as new and more effective medications have become available for SMI, it has become essential for all members of this team to contribute to medication management. If the psychiatrist acts alone making medication decisions in a vacuum, uninformed by contributions from other members of the treatment team, then the team approach fails. Often, ineffective polypharmacy is the end result.

It is useful to clarify at the onset of this chapter that two camps of thought and persuasion concerning polypharmacy exist, both in the medical and nonmedical fields of psychiatric practice (with family and other caregivers of mentally ill persons included in the nonmedical realm). One camp holds to a rather pejorative definition when speaking of using multiple medication therapies, and usually the blame falls at the door of the prescribing psychiatrist, as she is the one who actually writes the prescriptions and recommends (or sometimes enforces) that the client take them. Granted, many an ill-informed or lackadaisical physician has employed a haphazard approach to prescribing medications in an attempt to shut off the symptoms a client experiences, or to practically shut down the person’s functioning altogether, as no successful outcome seems within reach. However, it must be said that there have been social workers who have contributed to this uninformed method because of lack of education or complacency.

The use of multiple medications is often appropriate when the symptoms of a client’s condition(s) do not remit sufficiently to allow him or her to return to more positive functioning in all their social roles. When effective medicines that can deliver a positive outcome without harmful or very bothersome side effects are combined well, the client is well served. We will provide empirical data and a case example that suggest that a fine-tuned treatment team is the best vehicle for ensuring the success of a treatment plan that may include multiple medications and psychosocial interventions.

PSYCHOSOCIAL FEATURES OF POLYPHARMACY

Polypharmacy in SMI is sometimes necessary, sometimes not. As discussed in Chapter 4 in relation to schizophrenia, for instance, if an individual takes appropriate doses of antipsychotic medications for adequate durations of time and fails
Table 1  Psychosocial Factors Leading to Polypharmacy in Serious Mental Illness

1. The client is nonadherent with medication trials, leading to the appearance of refractoriness to monotherapy.
2. The client has multiple familial or community stressors that impeded response to monotherapy.
3. The psychiatrist is unaware of some of the client’s symptoms, thus making an inadequate diagnosis (and consequent treatment nonresponse).
4. The client (or psychiatrist) may excessively subscribe to the medical model, seeking a medication for every symptom, rather than recognizing the influence of current environmental circumstances on symptoms.
5. The client and mental health professionals may possess opposing models of mental illness, resulting in sporadic polypharmacy treatment, often in hospital settings.

Medication Nonadherence

Nonadherence to medications is a common occurrence in severe mental illness (4) and a likely major contributor to polypharmacy. Social workers can play a major role in improving medication adherence (5). This nonadherence can have many sources. Patients may lack insight into their illnesses (6); social workers can help promote insight through ongoing psychoeducation and the development of a gradual therapeutic alliance through sustained empathic communication. Nonadherence may also be related to social stigma (7); social workers can help identify sources of this stigma. Frequently, nonadherence stems from particular family members who may reject the use of drugs to treat mental symptoms. Social workers can intervene in such family structures, through education efforts, for instance, to help guide family members about the potential benefits of medication treatment (8). Referrals to community support groups have also helped in this case. Sometimes social stigma stems from a circle of friends or others in the community; social workers can help persons with SMI reorient their social circles toward more supportive persons. Involvement in self-help groups, such as the National Alliance for the Mentally Ill (NAMI), can prove especially helpful in establishing a community support system that combats stigma (9). Indeed, one empirical study found that 86% of participants with mood disorders in the Na-
tional Depressive and Manic Depressive Association group reported improved medication adherence (10). These policy- and advocacy-oriented groups can be excellent referral sources for clients and caregivers who may want additional support from sponsored groups that allow more one-to-one connection with people who are facing similar problems and challenges.

Medication nonadherence also frequently relates to perceived side effects. Sometimes these side effects are more perceived than real; those patients who are very negatively disposed to taking drugs may experience the ‘‘nocebo’’ phenomenon, that is, the reverse of the placebo phenomenon (11–13). In the nocebo response, patients experience medications as being quite distressing, often with dysphoric mood and nonspecific physical symptoms (sedation, headache, nausea, dizziness). Obviously, these are real physical symptoms, not figments of the imagination, but in the nocebo effect, they are driven by a negative psychological mindset about taking medications. The nocebo phenomenon is a strong counterexample to the notion that the mind cannot influence the body. Social workers can help explore the beliefs and attitudes that underlie negative feelings about medications, and they can serve as another professional on whom persons with SMI can rely to help them tolerate and overcome their feared or actual side effects. Frequently, it is the fear of future side effects, rather than the actual present existence of them, that leads clients to stop taking medications. Persons with SMI may be more likely to take their medications if they know that they have a professional advocate, their social worker, who will help them understand the real risks of medications, as well as serve as a separate professional conduit to the treating psychiatrist. Persons with SMI need to know that social workers will also go to the psychiatrist with clear descriptions of clients’ side effects, so as to advocate for the stopping of medications when intolerable side effects occur. Some persons with SMI, often the most poor and uneducated, are unwilling or unable to clearly explain their side effects to their psychiatrists. Often, perhaps more frequently in the era of managed care, psychiatrists may mistake the lack of clear complaints for absence of side effects. It is not uncommon for persons with SMI to live for years with serious side effects or risks that might be unnecessary (e.g., newer medications might have been developed that are safer). Social workers need to advocate for their clients in such cases. Such advocacy for the stopping of harmful medications is the flipside of the social worker’s role in promoting adherence where medication treatment is indicated. Persons with SMI need to know that their welfare is paramount, whether such welfare is enhanced by taking more or less medication. Social workers need to be objective, informed advocates in this setting. This means that social workers need to be knowledgeable about medications and creative in their interactions with psychiatrists, on the one hand, and with clients, on the other.

In summary, unnecessary polypharmacy can result from medication nonadherence (and thus the appearance of nonresponse to monotherapy trials). Social
workers and other mental health professionals can play an invaluable role in promoting medication adherence (14,15), thereby minimizing the need for polypharmacy.

**Poor Medication Response Due to Psychosocial Stressors**

Empirical research is beginning to show that medication response itself is influenced by psychosocial factors. Social workers can play an important role in identifying and alleviating some of these psychosocial influences, thus enhancing the effects of medications and potentially obviating the need for polypharmacy.

For instance, in schizophrenia, a large body of research exists that demonstrates that a high amount of expressed emotion (EE) is associated with diminished antipsychotic medication response (16–18). EE reflects a style of familial interaction in which family members tend to use highly charged statements that increase the client’s anxieties, fears, and guilt feelings. Treatment research using family therapy approaches in schizophrenia shows that such approaches reduce EE and improve long-term outcome of antipsychotic treatment, compared to control groups receiving medication but not psychosocial interventions for EE (17).

In unipolar major depression, an effective type of psychotherapy has been developed that focuses on the traditional context of social work interactions: current interpersonal relations. Called interpersonal therapy (IPT) (19), this approach was in fact explicitly developed by Gerald Klerman and Myrna Weissman, a psychiatrist and a psychologist, as a standardized application of the methods they observed in use by their social work colleagues at the Massachusetts General Hospital. IPT has been proven effective in the acute treatment of unipolar depression even without concurrent medication use. It also seems effective in relapse prevention and is useful in severe acute depression, mainly when combined with medications in the latter settings. IPT focuses on current interpersonal relations, not past experiences. Thus, while familial relations are important and usually are associated with important past experiences, IPT differs from psychoanalytic therapy in not specifically focusing on the past to shed light on the present, as well as in avoiding interpretations of psychological states based on any specific set of theories about the mind.

Similarly, in bipolar disorder, two types of psychosocial interventions are associated with improved outcomes. One approach, family-focused therapy (FFT), was developed by David Miklowitz and colleagues (20,21). It is derived from the EE literature in schizophrenia but is more broadly psychoeducational in its scope for bipolar disorder (22). It seeks to enhance familial communication so as to minimize conflict and stigma (23). Preliminary data suggest better outcomes with FFT added to standard medication treatments for bipolar disorder, as opposed to medication treatments alone (24). Interpersonal and Social Rhythm Therapy (IPSRT) for bipolar disorder (25), developed by Ellen Frank and col-
leagues, derives from IPT for depression. Like IPT, IPSRT focuses on current interpersonal relations, which have been shown to improve depressive symptoms. Further, in bipolar disorder, circadian rhythms appear to play an important role in influencing symptoms. Isolated insomnia, of whatever cause, for instance, can trigger a manic episode, which then takes on a life of its own. Frequently, poor sleeping habits alone, ingrained by years of mood symptoms, can impede medication response, due to the mood-destabilizing effects of irregular sleep hours. The social rhythm component of IPSRT focuses on these and other circadian aspects of daily living habits. The social worker is often most clearly aware of the daily lifestyle of clients and thus can again accurately identify and improve these aspects of the client’s living habits. IPSRT also leads to better outcomes with medication treatment for bipolar disorder compared to medication treatment alone (26,27).

In a way, family-focused therapies, and IPT are types of “polypharmacy” that, combined with a single medication, can produce as good or better outcomes than multiple medication polypharmacy. In other words, where psychosocial conditions impede medication efficacy, “polypharmacy” with adjunctive psychotherapies is preferable to polypharmacy with adjunctive medications.

It is also worth noting that medication response usually does not entail full remission of symptoms in SMI. Residual symptoms usually continue to markedly impair psychosocial function, despite maximal medication benefit (28). Social workers are uniquely positioned to identify problems in functioning and to maintain the treatment team’s focus on such problems, rather than merely symptomatic response (2). These adjunctive psychotherapies may especially serve to remove residual symptoms and enhance psychosocial functioning, which, after all, is the ultimate goal of psychiatric treatment of SMI.

Misdiagnosis

It is an unfortunate reality (perhaps partially a psychoanalytic legacy that continues to exert undue influence) that many psychiatrists and other mental health professionals do not feel a need to obtain any information beyond the clinical interview in making diagnostic assessments. Thus, psychiatrists may solely rely on their own observations (usually in a one-hour slice of time initially, and 15–30 minutes in follow-up visits) and the client’s self-report. However, both of these sources are obviously limited. Many aspects of a patient’s behavior are invisible in the office; certain behaviors occur at work or at home and are elicited by particular persons in these settings. Often, clients are unable to accurately convey their behaviors in those settings. For instance, a client may seem completely asymptomatic in an office interview, while a few days ago she might have demonstrated significant manic symptoms at work and home. The time limits to a clinical interview are also obviously constricting. Further, even the best clinical
interview, performed by the most astute diagnostician, can fail to diagnose many forms of SMI (mainly schizophrenia and bipolar disorder) due to clients’ lack of insight (6). Many clients simply have never been aware that they have experienced psychotic or manic symptoms, and they will deny such symptoms during clinical interviews. The impact of such impaired insight on misdiagnosis is not hard to imagine and is, in fact, supported by empirical data, especially in bipolar disorder. In one study (29), detailed, lengthy (mean 102 min) research diagnostic interviews still underdiagnosed bipolar disorder and schizophrenia compared with adding information from hospital charts. Using medical records as a secondary diagnostic tool increased the frequency and accuracy rates in both conditions twofold. In another study of prodromal symptoms of mood disorders (30), researchers demonstrated that clients report manic symptoms about half as frequently as family members report observing them in the clients’ behavior, while both groups report depressive symptoms about equally. Since the diagnosis of bipolar disorder is based on current or past manic symptoms, this study would suggest that reliance on client self-reports, without consulting family members, would result in an underdiagnosis of bipolar disorder (and consequent misdiagnosis as unipolar depression) by a factor of about one half. Indeed, empirical studies have demonstrated misdiagnosis rates in the 40–60% range for persons with bipolar disorder (31,32).

The obvious consequence of misdiagnosis is ineffective treatment, as discussed in Chapter 2. If a patient fails to respond to a medication for unipolar depression, due to undiagnosed bipolar disorder, polypharmacy for presumed treatment refractory depression ensues. The social worker can play an essential role in bringing familial and community information to the psychiatrist for diagnostic consideration (33). Again, it is unfortunate that there is a tradition in psychiatry that tends to avoid seeking third-party information. This tradition derives from the psychoanalytic habit of believing that all diagnosis and treatment begins and ends at the portals of the office door. Social work brings an opposing tradition that is much needed: diagnosis and treatment is inadequate if it is uninformed by the familial, social, and community setting. We suggest that adequate diagnosis and treatment for SMI cannot occur based on patient interviews alone. Family and other third-party reports are also required, and the social worker can play the lead role in bringing these sources of information together.

What the social worker does with the collected data is crucial to a positive outcome for the client and for the best use of the treatment team’s time and efforts. If she can assimilate and critically analyze the data while employing good communication techniques, then the client is well served by her efforts and the combined efforts of the team. If she is not able to coherently and adequately present the data and offer recommendations based on findings, then the end product is just a load of information that enlightens no one.

Sometimes concerns regarding confidentiality are expressed when we pro-
pose this approach to diagnosis. But our suggestions do not conflict with patient confidentiality. All we are proposing is that the treatment team needs to hear from sources beyond the client; this does not bear at all on the client’s right for the treatment team to refrain from disclosing information to others. In any case, it is our experience that most clients (with the exception of those experiencing severe acute paranoid psychotic states) will agree with this kind of approach once the rationale is explained to them. Often it is harder to convince psychiatrists that their clinical interviews are insufficient for adequate diagnosis and treatment.

**Excessive Adherence to the Medical Model: A Pill for Every Symptom**

As discussed in Chapter 1, contemporary medicine has gradually moved away from using medications to treat symptoms (which resulted in the polypharmacy bemoaned by Oliver Wendell Holmes and William Osler) in favor of using medications to treat syndromes or diseases. Some physicians continue to hold an outdated medical model, and, unfortunately, many members of the general public seem to believe in that approach as well. This attitude is a kind of extreme medicalized approach, in which all psychological states are to be treated by drugs. It almost goes without saying that many psychological states are environmentally driven and respond better to environmental, rather than biological, interventions. For instance, the feelings of grief are almost indistinguishable from major depression, yet grief is clearly the result of an event in one’s life, and grief resolves with time, empathy, and social support. It usually does not require medication treatment. While such facts seem obvious, it is frequently important to remind clients, our psychiatric colleagues, and ourselves, that not every psychological symptom requires treatment with medication.

**Opposing Models of Mental Illness**

Frequently, we face a related problem: the psychiatrist, the client, and the social worker (the most common treatment triad), may possess competing beliefs about mental illness, confusing the client and leading to inefficient and inadequate treatment (34). Sometimes, the conflict ensues between the psychiatrist and the client. The psychiatrist often subscribes to a medical model of mental illness—some notion of a chemical abnormality, with concomitant need for medication treatment. In this approach, the illness is a physical ailment over which the client exerts no independent influence. The client often holds a common-sense notion of free will, believing that her mental states are, or should be, within her control, thus opposing the standard medical model just described. The presence of these opposing philosophies may lead to miscommunication, disagreement (e.g., breakdown of collaboration between client and treaters), nonadherence, overmedication, and ineffective polypharmacy. A not-uncommon scenario is that the psychi-
atrist prescribes multiple medications that the client mostly does not take. Intermittently, either because of family pressure, worsening symptoms, or hospitalization, the client takes the medications for some time, but then stops them later. The social worker can serve as an important intermediary, a professional who can communicate with the psychiatrist from the medical perspective, but also an advocate who recognizes and values the client’s beliefs and attitudes. Bringing everyone together into a communicative treatment team is an important function the skilled social worker can perform.

Sometimes, the client may not possess strong beliefs herself about mental illness, yet she may become confused by disagreements among her treaters. Again, frequently it is the psychiatrist who upholds the medical model, and a social worker or psychologist may argue for a nonmedical approach. Further, social workers who perform different functions within a team setting may have differing views and values about medication treatments. In this case it is imperative that the two professionals work very hard to not further confuse or alienate the client by openly disagreeing about medication options. If the client is to maintain her own independence and involvement in the decision-making process, all the team members must take care to collaborate in a professional manner. The client may get mixed signals, with the psychiatrist giving medications and counseling patience until the medications “kick in,” while the social worker may tend to be more focused on what feelings, thoughts, or past experiences led the client to her current state. One approach implies no control over her condition; the other implies that she indeed has influence over her condition. One approach may make her feel like a soulless automaton; the other may make her feel even more inadequate and guilt-ridden. In a recent article (34), a social worker with major depression described her experience in this regard:

Depression is not just a mood or a set of symptoms. It is a totality of self during that episode of time, which contributes to the difficulty of describing it and to the difficulty of others in understanding it. This sets the stage for a pendulum of causation and treatment debates utterly devastating to the very subjects of the debates, often without the realization of professionals who are simply doing their best in what they believe will help. . . . Listening to the debate and buffeted by its winds are those in the midst of a severe episode of major depression. What effect does it have on them, if they cannot establish whether the fragile boat they ride in the stormy sea has a pilot, or they are being expected to pilot it? . . . As a research biopsychologist wrote to me at one point later, “I often have the sense that personal philosophies get played out more in the field of mental health than other areas of medicine and that patients are often the unfortunate bearers of these philosophical burdens.” Unfortunate bearers, indeed.

As the above author noted, the reality is that such dogmatically opposing philosophies are simply wrong, in addition to being harmful to clients. We know that the brain influences mental states; we also know that environmental and
psychological experiences produce changes in the brain, sometimes long-lasting alterations (35). Thus, psychotherapy affects the brain, just as medications affect psychological states (36). And it is indeed simplistic to draw conclusions from etiology to treatment. Some conditions, like posttraumatic stress disorder and even schizophrenia or bipolar disorder, have clear environmental precipitants, perhaps early in life or even in utero (37); yet they still may benefit from medication treatments. Similarly, some conditions may have genetic aspects, like panic disorder, and still benefit from behavioral interventions. The tradition of social work is consistent with a biopsychosocial model that allows for all these factors (2,38,39), as well as with a pluralistic model of psychiatry that recognizes that no single perspective (whether biological, psychological, or social) is sufficient to explain or treat mental illnesses (40,41).

SOCIAL WORK AND PSYCHOPHARMACOLOGY

This discussion of psychosocial aspects of polypharmacy has highlighted the important influence social workers can have in avoiding unnecessary polypharmacy while promoting appropriate medication treatment of SMI. We move now to a more general discussion of the relationship between social work and psychopharmacology to give a broader context on these issues.

The Role of Social Work in Psychopharmacology

Social workers in mental health settings serve clients with a full range of presenting problems, from adjustment disorders to chronic schizophrenia. In fact, they have become the primary treatment providers in many outpatient facilities for clients with severe mental and emotional disorders. There are four reasons for this development:

1. The presence of social workers in public mental health settings has consistently increased over the past 20 years in proportion to psychiatrists, psychologists, and nurses (42). Part of this change may be due to the cost-cutting influence of managed care, which has led to increased activity for social workers, as opposed to psychiatrists, in psychotherapeutic treatment.

2. Public policy since the 1970s has emphasized deinstitutionalization and community-based intervention programs, and the number of persons in the community with mental illnesses has increased (43). Many people with mental illness have limited social functioning skills, frequently experience crisis situations, and require continuous mental status monitoring. Psychosocial rehabilitation and case-management in-
Interventions, largely associated with the social work profession, have been found effective in helping these clients adjust to community living (44).

3. As new types of psychotropic medications have been introduced into the market, a broad range of issues has arisen for consumers to consider. These include symptomatic indications for use, choices among drug types and classes, adverse effects, the use of generic vs. brand name drugs, and consumer input into decisions of adherence and refusal of medications. These issues need to be addressed by all practitioners, including social workers.

4. The social work profession has developed an increased emphasis on collaboration with clients and family members (2). Social workers are often the first point of contact for significant others who are concerned about the mental status of their loved ones. Social workers base relationships with clients and families on an appreciation of their strengths and on the assumption that the helping relationship should be active and mutual.

While strong evidence exists for the biological origins of many conditions such as schizophrenia, bipolar disorder, and major depression, the evidence is less compelling for many others, such as some personality and anxiety disorders. From the social worker’s transactional perspective, most problems in living arise from or are perpetuated by a variety of factors, and altering one’s relationship to the environment can significantly ameliorate these. The social work profession values client self-determination and believes that medication should be only one part of comprehensive intervention.

Social workers tend not to classify individuals as abnormal or disordered, but instead consider person-in-environment processes as facilitating or blocking one’s ability to experience satisfactory social functioning. While it is unlikely that members of the medical profession would disagree with this perspective, they might not attend as thoroughly to its implications in practice. Members of the medical profession tend to view problems in living as being within the person, with internal physiological processes as primary targets for intervention. Social workers tend to emphasize individuals’ strengths. One example of a difference in perspective between the professions may be seen in the treatment of social phobia. Paroxetine has emerged as an effective medical intervention for the disorder, although it has been demonstrated that cognitive/behavioral interventions, even without medication, may be more effective for client functioning over the long term (45).

Social work practice, then, is based on biopsychosocial theories of assessment and intervention. The prescription of medications may be an essential component of a client’s intervention plan, but vulnerability and stress factors will
also be moderated by the presence of protective factors such as coping skills, psychotherapy, and social support. Further, though medications affect functioning at a biochemical level, they may also affect the psychological and social lives of clients and their significant others in ways that merit professional attention. When social workers help to build up protective factors, they decrease the impairments experienced by clients and their families, and through psychosocial interventions they can help clients maximize the benefits of their psychotropic medication. This description of the philosophy of social work relative to mental illness is not presented to take issue with that of the medical profession, but to point out that the intervention roles assumed by each profession might reflect this difference. While occasionally giving rise to conflict, this generally enriches the range of outcomes for clients and makes room for more collegial and fruitful interactions between medical and nonmedical colleagues.

**Six Intervention Roles of Social Workers**

The following are six distinct roles social workers can play as they interface with psychiatrists and clients in the process of the psychopharmacological treatment of SMI (Table 2).

**Physician’s Assistant**

In the role of physician’s assistant, the social worker accepts the physician’s decisions about psychotropic drugs and helps clients take their medications according to the physician’s recommendations. The social worker is not expected to offer advice about any decisions involving the prescription and use of medication or any adherence strategy. For many years the role of physician’s assistant was the most common in social work because of its limited legal scope of practice, traditions of authority among the helping professions, a lack of emphasis on psychopharmacology in social work education, and negative attitudes of social

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<td>1.</td>
<td>Physician’s assistant</td>
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<td>2.</td>
<td>Consultant</td>
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Social workers about medication (46). Though social workers are still limited to the role of physician’s assistant in many settings, they have largely moved beyond this role.

Consultant

Social workers and physicians need to actively collaborate with each other, to specify the range of the social worker’s activities in medication management, devise procedures to evaluate each medication’s effectiveness, and record relevant data when monitoring a client’s response. Physicians can provide in-service training to social workers and other professionals on such issues as drug categories, adverse effects, and assessment techniques. Social workers, in turn, can update physicians about effective aspects of psychosocial intervention. Collaborative activities do imply that disagreements may arise among the physician, social worker, and client over some issues, which they must openly deal with toward constructive resolution. This situation itself offers social workers, psychiatrists, and clients a chance to ‘‘model’’ how clients can negotiate, interact, and further enhance their own relationship to medication issues. As a consultant, the social worker needs to be skilled in three areas (47). First, he or she must be able to assess clients for possible referral to physicians. This involves evaluating the client’s level of functioning, the intensity of the observed suffering, and the client’s capacity to manage that suffering. Second, the social worker must prepare clients for active participation in the process of the physician’s assessment. The worker’s responsibilities include articulating the reasons for the referral, reviewing the client’s attitude toward psychiatrists, and discussing the client’s expectations and/or biases about medications. Third, the social worker must assess the client’s ability to pay for medication, the costs of which may be quite high, and assist with practical measures to receive monetary aid. These options include entitlement, insurance benefits, or research study participation.

Counselor

The term ‘‘counselor’’ is often used interchangeably with that of ‘‘therapist,’’ but there are distinctions. Counseling is a process of helping clients cope with normal daily living problems and opportunities (48). In the role of counselor the social worker helps the client problem-solve and make decisions about practical matters related to medication use. Examples of counseling include providing clients with information about where to get prescriptions filled, how to ask questions of the pharmacist, at what times of the day to take the medicines, and what steps to take if certain adverse effects occur. Social workers can devise creative schedules and prompts in cooperation with the consumer to increase adherence and recovery. When social workers help clients with problem-solving related to medi-
cation issues, which are not necessarily related to those of mental illness, they are engaged in the role of counselor.

**Educator**

The role of educator is essential to the social work profession’s maintenance of collaboration with clients and families. A major force contributing to the family advocacy movement was a perceived lack of effort by mental health professionals to help clients and families understand the rationale behind decisions about medication and other interventions. The uses and actions of medication are confusing for many professionals as well as the general public, and there continues to be a need for social workers to address the topic by directly providing educational materials to clients. With the widespread development of client and family psychoeducational and medication education programs, this area has seen progress (49). Social workers can educate clients and families about the purposes, actions, and effects of medication, teach clients and families how to monitor positive and negative effects, teach skills in problem solving regarding medication, and offer practical suggestions to help clients take medication appropriately. Social workers can also help clients and families stay abreast of new medications as they become available. They can also provide ideas about how to access those new medications, even when they might initially be experimental. Activities in the educator role complement the kinds of information generally provided to clients by physicians and nurses.

**Monitor**

To monitor medication, the social worker must observe, and help the client observe, the positive and negative effects of medication and the appearance or persistence of symptoms (5,50). The social worker may also check the client’s use of medications as prescribed. She needs to help evaluate the client’s responses to any discomfort, the relative significance of the adverse physical effects (e.g., dry mouth vs. impotence), and any impairment in family or social function related to medications. The social worker conveys observations from the monitoring process back to the client, perhaps to the family, and to the physician. Obviously, this process requires increased attention and energies from the social worker, psychiatrist, and client/family team when effects are negative, as is often true during periods of relapse, the introduction of new medications, or following hospital discharge. Adverse effects may be physical, psychological, or social. Through self-study and collaboration with medical personnel, the social worker can become educated about adverse physical effects. Adverse psychological effects involve any changes in the client’s self-image and identity that emerge as
a result of using medications. For example, clients may come to view themselves as "sick" or may become overly dependent on medication as a solution to perceived emotional problems. The taking of medication itself may be associated with stigma, especially in certain families or communities. Adverse social effects include any consequences that affect a client's standing with social institutions. For example, clients may overuse psychotropic medications to maintain qualifications for disability benefits. This topic of extraphysical adverse effects merits particularly close attention by social workers because the health professions have largely neglected it.

Advocate

Advocacy is the process of representing the interests of mentally ill individuals and groups to those in the mental health system who have the power to assess how medications are administered (46,51,52). The social worker as advocate participates with the physician in all phases of decision making regarding choices about medications. This role has become crucial because of the increase in community care programs, which makes the responsibility for monitoring a client's medication needs and outcomes difficult for any single person. As an advocate, the social worker must have a sound knowledge of mental illness, psychotropic medications, and laws and regulations about such issues as forced medications and client rights. Client advocacy may at times be based on a perception that medical expertise is not always reliable and that medication can have negative effects that might outweigh its benefits. Social workers need to be aware that their advocacy efforts may lead clients and families to refuse medication or to negotiate extensively with physicians about the types and dosages the client should take. Social workers may find themselves in ethical binds when clients or physicians choose strategies the social workers do not believe will work. Social workers may function as political advocates for clients who cannot access medications (53). This situation developed quite dramatically with the introduction of clozapine in 1991. The cost of the medication, coupled with the need to monitor blood counts, created a financially expensive treatment regimen. Because some clients and families could not afford the drug, they filed suits to gain access to it, and adjustments were made in public insurance policies to broaden its availability (54). Social workers need to serve as advocates in relation not only to physicians, but also to agencies, funding sources, and government regulators.

Case Example: Heidi

Heidi was a 29-year-old university student who came to the mental health center because of stress related to her demanding course load and failing marriage. She
reported a history of sexual acting out and alcohol dependence and demonstrated signs of compulsive behavior. In keeping with the client’s wishes, the social worker focused on behavioral strategies for improving her academic adjustment. Soon, however, Heidi’s coping capacity decreased. The more she reflected on her emotional concerns, the more she experienced feelings of depression and anxiety. Heidi began to experience memories of sexual abuse by her brothers. She suffered from insomnia, nightmares, and an inability to concentrate that made her academic work even more difficult. She also felt like drinking again. The social worker suggested that Heidi meet with the agency physician for a medication evaluation. Heidi was ambivalent. The social worker did not pressure her to take this step, but he did provide her with a detailed orientation to the purposes and procedures involved in such a meeting. As a part of this process he helped Heidi write down questions that she might want to ask the physician.

The social worker and physician always collaborated on medication issues. This is not to say that they always agreed. In fact, the social worker, while understanding the value of medication, tended to favor its use for limited periods of time with clients who experienced fluctuating depression. The physician, on the other hand, believed that medication could often serve as a primary intervention. The two professionals did communicate openly with one another and enjoyed mutual respect. Following his evaluation, which the social worker attended, the physician prescribed two antidepressants for Heidi, fluoxetine and doxepin. The second drug was intended to help her to relax and sleep at night. Heidi’s husband was unexpectedly furious about the new intervention. He and his wife both had substance abuse histories, and he was concerned that Heidi would again become dependent on drugs. His reaction encouraged Heidi to express again her own ambivalence about using medication. The fact that two medications had been prescribed made the situation more disagreeable to them. The social worker was surprised by the husband’s reaction (Heidi had resisted involving him in her therapy), but he met with them both to discuss their concerns. He explained the rationale for the prescriptions, the purposes of the medications, and their benefits and risks. He reminded Heidi that she was in control of her treatment and could terminate the medications when she wished, so long as it was done under the supervision of the doctor. He provided the couple with written material about the medications and agreed to talk with them regularly about their concerns. This seemed to satisfy them. The social worker kept the physician apprised of the issue. Heidi’s husband could not meet with the physician due to his work schedule. Heidi and the social worker met weekly for the next year, as Heidi came to terms with and learned to manage the emotions associated with her posttraumatic stress disorder. She made consistent progress and emerged from the experience with greater self-control and the ability to cope with her depressive episodes. Still, the therapy process often increased her distress for periods of time. Heidi
experienced anxiety attacks, and she experienced five short-term hospitalizations for suicidal ideation.

The social worker met with the physician at least once between each of her scheduled appointments to report on Heidi’s mental status. At one time the physician added lorazepam to the drug regimen to reduce the severity of Heidi’s anxiety attacks. The social worker opposed this decision based on the client’s history of drug dependence, but the physician intended this to be both a PRN and short-term intervention. The social worker did not express his reservations to Heidi. He helped her understand the rationale for the antianxiety drug and monitored her physical and emotional responses to it. He met with Heidi and her husband again to explain the long-range plan for this medication. Her husband was again concerned, but seemed to accept the potential benefit of the strategy, since he could see that his wife was in such distress. Fortunately, Heidi did not abuse the drugs. As medications from two drug classes were now being prescribed, the social worker monitored their interactive effects and their impact on Heidi’s self-image. Using the medicines did affect her self-image negatively. He helped her understand that despite her feelings of inadequacy the drugs had a positive role in her therapy process. The social worker frequently reminded Heidi of her strength and resilience in the face of such painful work. The therapy and medication situations became more complicated when, after a second suicidal threat, the physician discontinued the antianxiety medication and added a small dose of the antipsychotic medication olanzapine. This was intended to reduce Heidi’s agitation and the transient delusional ideas she experienced when deeply depressed. At another time when her compulsive behaviors became more troublesome, he discontinued the fluoxetine and prescribed fluvoxamine in its stead. The physician discussed these changes in advance with the social worker, who supported them. Heidi had been progressing in her therapy and was more accepting of the role of medication in the overall therapy process. She did perceive the drugs to be temporary interventions, however. The social worker suggested to Heidi that long-term use of an antidepressant might be beneficial to her, but that according to her physician it was reasonable to plan for eventual discontinuation of the other medications.

The social worker’s role during Heidi’s hospitalizations must be highlighted here. The physicians from the two facilities (the community mental health center and the hospital) were never in direct contact with each other. It was left to the nurses and social workers to coordinate Heidi’s care. The social worker was present on the unit several times each week (Heidi never stayed more than 8 days), and in the role of advocate he frequently argued against major medication changes suggested by the hospital staff. He was not concerned about dosage adjustments, but he resisted changes in the types of drugs prescribed because they would disrupt the regimen that Heidi’s primary physician had worked hard
to establish. He also felt that avoiding major changes to her drug regimen would likely prevent further anxiety and conflict between the client, her husband, and treatment providers, given previous experience with her reactions in similar circumstances. The hospital’s social worker was supportive of this advocacy strategy. It is likely, however, that in facilities with less of a team orientation, or a stricter professional hierarchy, fundamental medication changes might have been made. Heidi’s psychosocial growth was constant throughout that year. She was able to make better decisions about her life goals and her relationships with family and friends. She had been resistant to involving her husband in the counseling, but his participation around the medication issues served to improve their communication and enhance her sense of importance to him. As she came to terms with the reality of her posttraumatic stress disorder, her mood stabilized. She reduced the frequency and intensity of her psychotherapy experience and, seeing her physician every 2 months, was eventually prescribed only fluvoxamine.

SUMMARY AND RECOMMENDATIONS

In this chapter we have reviewed specific psychosocial contributors to polypharmacy and described how social workers can assist in this regard. These psychosocial factors include medication nonadherence, familial/community stressors, psychiatric misdiagnosis, extreme use of the medical model, and conflicting models of mental illness among clients and treaters. We have also reviewed the general relationship between social work and psychopharmacology and have identified specific roles that social workers can play, including the roles of physician’s assistant, consultant, counselor, educator, monitor, and advocate.

Social workers have historically provided treatments that were more narrowly focused on alleviating clients’ daily living problems that could be addressed outside the medical arena through case management and varying types of counseling. With the initial use of psychotropic treatments, some social workers accepted the challenge of becoming educated about the different classes of medications available and how they might help their clients. In the past 10 years, however, new medications designed to alleviate a plethora of psychiatric symptoms have been marketed at a rate that far surpasses the previous 40 years. Consequently, social workers today must be knowledgeable about a vast array of medications and, concurrently, how those medications may or may not help their clients (2). Obviously, the increase in options naturally creates a subsequent increase in demand for information and understanding on the part of the social work professional who strives to assist clients in achieving maximum benefit from a holistic treatment approach that may include medication.

Polypharmacy has been criticized for years, at times most vehemently within the social work community. Undoubtedly, many psychiatrists have used
multiple medications in ill-conceived treatment plans. Sometimes clients have been harmed by these uninformed treatment strategies, and frequently, nonadherence has resulted from taking too many medications on confusing schedules. Polypharmacy, within this pejorative framework, usually happens when medical practitioners do not have current data on how medications should be appropriately combined, what other medication options may replace one that is clearly not working for a particular client, and when medical practitioners do not avail themselves of the helpful input of both social workers and other nonmedical practitioners who work with psychiatric clients across various settings (home visits, vocational assessments, academic settings). Psychiatrists need to collaborate more closely with informed social workers to enhance the overall treatment process (51), thereby decreasing the occurrence of polypharmacy. Fortunately, interdisciplinary teams offer a formalized context in which colleagues across disciplines can work cooperatively to formulate the optimal treatment strategies for clients. However, active collaboration between the treatment triad of client, physician, and social worker outside a formal group setting should always be the goal of ethical treatment providers. Obviously, medical practitioners and social workers who actively collaborate outside this more formal structure decrease the possibility of poorly chosen options being recommended to clients. It should be emphasized that this kind of collaboration requires a high level of creativity, competence, and flexibility. Social workers need to be pharmacologically knowledgeable and adept, and psychiatrists need to be more psychosocially attuned and open to collaboration (55,56). For clients with SMI, such multidisciplinary collaboration provides the best hope for maximal recovery (Fig. 1).

To assist social workers and physicians in this process, we offer the following set of questions, the asking and answering of which can also serve as recommendations designed to enhance the overall psychiatric treatment of patients with serious mental illness:

Why is medication being prescribed for my client?
Why are these particular medications being prescribed?
What are the specific desired effects of these medications?
What is the full range of their possible positive and negative effects?
Is there a long-range plan regarding my client’s use of medication? That is, when will they be adjusted or discontinued whether they are effective or ineffective?
What is the client’s attitude about taking these medications?
What is the client’s belief system about how medications work?
Do I have a clear role or set of roles related to my client’s use of the medications?
Am I assuming these roles or have others involved in the client’s care articulated them?
How could my client’s use of this medication affect, positively or negatively, other interventions I am providing? Can the client or family afford these medications?

Barkley and colleagues (57) have articulated additional questions for the social worker to consider that are particularly relevant to the interests of both the client and family:
(When the client is a child) Are the medications designed to benefit the child or the child’s caregivers?* Have the behavioral targets of the medication been clearly communicated to all persons involved? How, and how frequently, will the effects of the medications be monitored? By whom? Will the physician be available to the client, family, and other caregivers? Have the risks and benefits of the medications, as well as those of alternate interventions, been assessed and discussed with all relevant parties?

Lastly, focusing on the treatment team triad of the client, psychiatrist, and social worker, we suggest the following questions:

Are there complementary treatment strategies to enhance coping and recovery, like psychotherapy (group or individual), and vocational/educational rehabilitation? Within the family (or a school system) should someone assume responsibility for the client’s adherence to the prescribed doses and schedules? Does the social worker have the opportunity to speak regularly with the physician and other community service providers about the medications (either in a formalized team meeting, or informally)? Has the client been appropriately educated about her role in decision making about medication therapy, and what are her beliefs about her own independence in treatment? Do the physician and social worker invite and accept input by the client in a consistent fashion, and have the two treaters come to agreement about how disagreements will be handled so as to put the client’s interest first? Do the physician and social worker collaborate outside specific cases to the extent that the social worker can consistently glean new information about current medication options and, therefore, use the physician as a mentor in matters of medications?

* This question can have relevance to adult persons with mental illness also, particularly those who still live in a home setting with familial caregivers. Sometimes, these adult clients are given additional medications to control symptoms that do not always adversely affect them personally, but do cause a caregiver distress or disruption in daily life. At times, the course of the illness coupled with the burden brought on by symptoms and loss of functioning wears caregivers down to the point they experience a need for relief. However, it often is the case that if an adult with SMI had the appropriate advocacy efforts afforded him by a competent team, he could actually live outside the home, with varying degrees of supervision. Frequently, in these settings, less medication is required to control symptoms; perhaps due to a decreased level of family conflict, or merely because the burden of care has been shifted to a team of people versus just one or two caregivers who are already exhausted by years of responsibilities.
Do the physician and social worker discuss issues related to medication therapies that directly and indirectly impact a client’s care (e.g., issues of court-ordered treatment, liability, right to refuse medications, drug-free holidays, procedures for negotiating medication changes with the client, current funding sources and procedures for newer medications)?

REFERENCES


INTRODUCTION

Although "alternative" or natural medications have been used for centuries (1), their popularity has been increasing dramatically over the last few years (2–5). The National Institutes of Health (NIH) has recognized that up to 25% of people in the United States seek and obtain nontraditional treatments (6), representing an enormous market for the nutraceutical industry and a potential new field for academic and pharmaceutical research.

While there are natural medications available for almost any physical or medical problem, there are relatively fewer such medications for psychiatric disorders (1). Some of these medications, such as St. John’s wort, kava, and valerian, are derived from plants and herbs. Other medications, such as melatonin, are natural hormones. Additional nutraceuticals include vitamins, such as folic acid and vitamin B₁₂; omega-3 fatty acids, such as docosahexanoic acid (DHA); and homeopathic preparations, which may involve combinations of the above nutraceuticals. Despite the growing popularity of these medications, their actual bene-
fits are not clear, given a relative lack of basic and clinical research data for or against them.

Many individuals nowadays choose to self-medicate with natural over-the-counter treatments, often without informing their physician, a kind of "over-the-counter polypharmacy." Patients may use these remedies in combination with prescription medications or with other natural medications. While there are obvious risks involved in taking this approach, there are cases of patients who have benefited from taking a natural medication in conjunction with a registered medication and/or with other natural remedies. There are even some formulations of the antidepressant St. John’s wort that also contain kava for added anxiolysis (7).

Given the importance and widespread use of augmentation and combination strategies in psychopharmacology (8,9), it is worthwhile to review the state of knowledge regarding polypharmacy with natural remedies as part of the patient’s regimen. The concern about safety is particularly relevant in this setting, given the dearth of information about adverse drug-drug interactions. This chapter will provide background on the indications and mechanisms of the better-known natural psychotropics, review the available data regarding combinations and drug-drug interactions, and propose a framework for clinicians who may be called upon to carry out polypharmacy with these remedies.

POLYPHARMACY AND NATURAL MEDICATIONS

Polypharmacy in psychiatry generally involves using medications with complementary mechanisms of action, sometimes to aggressively treat one condition and sometimes to treat co-existing conditions or symptom clusters. For example, patients with anxiety comorbid with depression may benefit from the combination of antidepressants with anxiolytics, patients with particularly severe depression may require administration of two or more antidepressants with complementary mechanisms of action (e.g., SSRI plus bupropion), depressed bipolar patients may do better with an antidepressant in combination with a mood stabilizer; and so on.

While augmentation and combination strategies with registered psychotropics have been studied in research settings and reviewed in the literature (9), there is a paucity of data regarding the effectiveness, safety, and drug-drug interactions of combinations of natural psychotropics, either with other natural remedies or with registered medications. Using principles adapted from our experience with registered medications, it is possible to develop some reasonable strategies to approach the patient who may require (or desire) polypharmacy with natural remedies.

Effective polypharmacy strategies generally rely on an understanding of how the medications work. Unfortunately, our understanding of the mechanisms
of action of natural remedies is limited. Mechanistic data, where available, are largely speculative. I will therefore focus on selected natural medications, review their efficacy and putative mechanisms of action for treatment of different psychiatric disorders, and use this information to illustrate potential augmentation and combination strategies. Where relevant, I will highlight adverse interactions with other natural medications and with registered medications.

MOOD DISORDERS

St. John’s Wort

The extract of the flower of St. John’s wort (Hypericum perforatum L.) has been used in the treatment of depression for centuries (1). Physicians in Europe have typically prescribed hypericum for mild-to-moderate depression with generally positive outcomes. In the United States, St. John’s wort is sold in health food stores and over the counter in drugstores, and thanks in part to the recent increase in media coverage about this remedy, more American physicians are now aware of hypericum’s putative antidepressant effect.

Hypericum has been reported to have greater efficacy than placebo and equal efficacy to active controls, based on more than 10 double-blind placebo-controlled studies and five studies that compare hypericum to an active control, usually the tricyclic antidepressants imipramine and maprotiline (10–14), all conducted in Europe since 1979 (1). It must be emphasized that doses of tricyclic antidepressants in European clinical practice tend to be lower than those considered adequate by U.S. psychopharmacologists, and in these clinical trials, typical doses of imipramine and maprotiline are on the order of 75 mg daily. The duration of most of these studies was short (4–6 weeks), and no information about longer-term outcomes was available. The placebo response rate appears comparable to that observed in many outpatient studies of antidepressants conducted in the United States (15).

Hypericum has recently been compared against sertraline and against fluoxetine. In a 6-week double-blind, randomized study with 30 patients, hypericum (900 mg/d) and sertraline (75 mg/d) were compared. Clinical response was noted in 47% of patients receiving hypericum and 40% of those receiving sertraline. The difference was not statistically significant (16). In a similar trial against fluoxetine, 240 patients with mild-moderate depression were compared. After 6 weeks of treatment, the mean endpoint HAM-D scores were comparable for hypericum and fluoxetine, but mean Clinical Global Impression (CGI-severity) was significantly superior on hypericum, as was the responder rate. The incidence of adverse events was 23% on fluoxetine and 8% on hypericum (17). Although hypericum demonstrated a somewhat better responder rate, the authors believed that the main difference between the two treatments was tolerability. A major
limitation of these two studies is the lack of a placebo control arm; this makes it difficult to assess the degree of placebo response, which is known to be high (up to 15–20%) in antidepressant trials. Additional trials comparing hypericum to SSRIs are currently underway in the United States.

The mechanism of action of hypericum is not as well understood as that of the traditional antidepressants. Hypericin, believed to be one of the main active components in hypericum, may inhibit monocyte cytokine production of interleukin-6 and perhaps interleukin 1β (beta), resulting in a decrease in corticotropin-releasing hormone, thus decreasing the production of cortisol and regulating the hypothalamic-pituitary-adrenal axis (18) (Fig. 1). Hypericin is also thought to inhibit reuptake of serotonin, norepinephrine, and dopamine (19) and may be followed by downregulation of beta-adrenoreceptors and increased 5HT2 and 5HT1a receptor density (20). Finally, hypericin may also have affinity for GABA receptors (1).

More recent studies have suggested a role for hyperforin (a phoroglucinol derivative) as a key component in the antidepressant effect of hypericum (21–23). Laakmann and colleagues (22) performed a randomized, double-blind, placebo-controlled 6-week study of two different extracts of hypericum on a sample of

Fig. 1 Possible hypericum mechanism. (Adapted from Ref. 163.)
147 patients. The two extracts varied only in hyperforin content (0.5% vs. 5%). Patients who received the hypericum extract with 5% hyperforin showed somewhat greater improvement in their HAM-D scores than the group that received the extract with 0.5% hyperforin, and the latter group showed only slightly greater improvement than the placebo group. Chatterjee and colleagues (21) have demonstrated that hyperforin is a potent uptake inhibitor of serotonin, dopamine, norepinephrine, GABA, and L-glutamate.

Other components of hypericum, including the flavonoids, are MAO-A irreversible inhibitors, but the concentrations of these compounds in the extract are so small that they are unlikely to be involved in the antidepressant mechanism (24). Nonetheless, it is recommended that St. John’s wort not be combined with SSRIs, as cases of ‘‘serotonin syndrome’’ have been reported with this combination (25–27).

Adverse drug events with hypericum have generally been mild. Patients have complained of dry mouth, dizziness, constipation, other gastrointestinal symptoms, and confusion (1). Cases of mania and hypomania resulting from St. John’s wort (SJW) have been reported (27–33). Many of these individuals had no documented bipolar disorder or prior history of mania or hypomania. One patient was taking SJW with sertraline and testosterone replacement, so it was not clear which of these agents was the prime contributor. The protective role of mood stabilizers in cases of polypharmacy of bipolar depression (i.e., mood stabilizer plus SJW) is relevant here. On the one hand, if SJW is a ‘‘milder’’ antidepressant, it might present a lesser risk of mania induction in bipolar depression and might be preferable over registered antidepressants such as SSRIs, which can induce cycling; on the other hand, SJW may unmask undiagnosed bipolar disorder in depressed individuals who self-medicate and result in potentially disastrous consequences. Further research will be necessary to clarify the risks and benefits of SJW in bipolar depression, but physicians should warn bipolar patients of the risk of using SJW without supervision and without concomitant mood stabilizers such as lithium. Phototoxicity has been associated with hypericum in grazing cows. It has therefore been suggested that patients who take an overdose of hypericum should be isolated from UV radiation for 7 days, but this caution may not necessarily apply to patients on regular doses. One study (34) found that doses of hypericum as high as 1800 mg caused minor increases in sensitivity to UV light in humans but no phototoxicity. So far there are no published data assessing the effects of a hypericum overdose (35).

With regard to drug-drug interactions, hyperforin has been shown to induce CYP-3A4 expression but has no effect on CYP-2D6 (36). Combinations of hypericum products with warfarin, cyclosporine, oral contraceptives, theophylline, fenprocoumon, digoxin, and indinavir have led to reported interactions and reduced therapeutic activity (27,36–39). Caution is therefore required in HIV-positive patients receiving protease inhibitors, as well as in transplant recipients.
In summary, hypericum has been shown to be more effective than placebo and equivalent to registered antidepressants (though often in low doses), and it appears to have a benign side effect profile. Hypericum has been combined with kava safely and effectively (7,15) in some preparations that are made up of SJW plus low doses of kava in a single pill form. This suggests that hypericum may be combined safely with other anxiolytics. Care needs to be taken when attempting to combine hypericum with other antidepressants. Potentially harmful drug-drug interactions have been demonstrated, and hypericum should therefore be used with caution in the patient who is on multiple medications.

**S-Adenosyl Methionine**

S-Adenosyl methionine (SAMe) is a major methyl donor in the brain. It functions by donating methyl groups to hormones, neurotransmitters, nucleic acids, proteins, and phospholipids (40). It is particularly dependent on levels of folate and vitamin B₁₂ in the nervous system (Fig. 2). Deficiencies of the latter are also associated with development of depression and/or refractoriness to treatment (41).

SAMe has demonstrated a mood-elevating effect in depressed patients. A small number of clinical studies show that parenteral (IV or IM) SAMe is superior to placebo and as effective as standard antidepressants (TCAs) (42). More recent trials of oral SAMe suggest efficacy comparable to TCAs and superiority to placebo at doses up to 1600 mg/day (42). Some studies, however, are questionable due to problems with dissolution and stability of the oral SAMe (42).

SAMe may have a relatively faster onset of action than conventional agents. Some patients improve within a few days, and most within 2 weeks (43–51). The combination of SAMe and low-dose TCA may result in earlier onset of action than TCA alone (52,53).

Other psychiatric uses for SAMe include the reduction of cognitive deficits in dementia (54), relief of distress during the purpuerium (55), and the reduction of psychological distress during opioid detoxification (56). SAMe may also be

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**Fig. 2**  SAMe-related metabolic pathway. MTHFR = methylene tetrahydrofolate reductase; MTHF = methyltetrahydrofolate; 1-Met = methionine; MAT = methionine adenosine transferase; DA = dopamine; 5HT = serotonin (5-hydroxy tryptophan); NE = norepinephrine. (Adapted from Ref. 164.)
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useful to the depressed alcoholic (57) and in medically ill depressed patients for whom conventional agents may be contraindicated (58).

SAMe is well tolerated, free of adverse effects, and has no apparent hepatotoxicity (42). Its side effects include mild insomnia, lack of appetite, constipation, nausea, dry mouth, sweating, dizziness, and nervousness (42). There are some reports of increased anxiety, mania, or hypomania in bipolar depression (42), and some of the SAMe clinical trials demonstrated a higher rate of mania with SAMe than with placebo. Carney et al. (59) found that 3 of 12 responders to IV SAMe underwent an early switch to mania or hypomania. Further, in an open trial of oral SAMe, Carney reported that three of the first six patients treated (500–1600 mg oral SAMe daily for 14–42 days) experienced 1–3 days of euthymia followed by hypomanic switches with symptoms including increased speech and activity, grandiose ideas, and, in one subject, increased libido (60).

As observed with SJW, it is important that research be carried out to clarify the risks of cycling in bipolar disorder with SAMe treatment, particularly in those individuals not on mood stabilizers, such as in cases of undiagnosed bipolar disorder. In view of the above, SAMe should be used with caution in individuals with documented or suspected bipolar disorder and probably with a concomitant mood stabilizer.

Recommended doses of SAMe range from 400 to 1600 mg/day (61–63), though anecdotes suggest that some patients may require higher doses to respond. So far, there appears to be no evidence of adverse drug-drug interactions, and SAMe can generally be safely combined with other medications. The combination of SAMe with TCAs suggests that additional combination with antidepressants and/or anxiolytics may be safe and effective.

Omega-Fatty Acids

The naturally occurring omega-3 and omega-6 fatty acids (FAs) are referred to as essential polyunsaturated fatty acids (PUFAs) (64,65). They are classified according to the position of the first double bond with respect to the methyl (CH3-) end of the molecule (the omega-carbon) (Fig. 3). The predominant omega-3 fatty acids include docosahexanoic acid (DHA) and eicosapentanoic acid (EPA), which are found primarily in fish (66), and α-linolenic acid (ALA), obtained from land-based plants such as flaxseed (67,68). Omega-6 fatty acids include linoleic acid (LA) and arachidonic acid (AA), which are derived primarily from vegetable oils.

The omega-3 fatty acids have been studied primarily as a treatment for bipolar disorder. Stoll and colleagues (69) reported a 4-month, prospective, double-blind, placebo-controlled trial of omega-3 FA mix in a sample of bipolar patients. High-dose omega-3 fatty acids (6.2 g of EPA and 3.4 g of DHA per day) was compared to placebo (olive oil) in subjects who had experienced a
recent mania or hypomania. The omega-3 fatty acid group performed better than the placebo group (64.3% vs. 18.8% response rate), and this difference was statistically significant. The duration of remission was also significantly greater in the omega-3 group compared to placebo. Limitations of this study included the lack of long-term follow-up on the study drug and the lack of control for concomitant pharmacotherapy.

Stoll and colleagues have also reported treating 16 patients with refractory unipolar depression with omega-3 FAs (70). While only five of these patients responded at least partially, this may nonetheless represent an improvement over response rates typically seen in refractory patients, and nonrefractory patients may respond at a higher rate. Omega-3 and omega-6 FAs may also help alleviate psychotic symptoms in schizophrenic populations. Case reports involving neuroleptic supplementation with EFAs have shown variable results (71). No controlled dose-response studies have yet been performed, and it is not clear at this time whether EPA, DHA, ALA, or all three omega-3 fatty acids are psychotropically active.

Mild gastrointestinal distress, generally loose stools, has been reported in some individuals taking omega-3 FAs, but no other significant adverse effects were noted, and overall the treatment appears to be well tolerated (69). There seems to be no toxicity associated with the omega-3 FAs.

The mechanism of psychotropic action of the omega-3 fatty acids has been investigated and appears to be multifold. Omega-3 fatty acids are typically incorporated into the phospholipid bilayer surrounding the cells (64). The double bonds in the omega-3 FA carbon chain render the membrane more fluid (72), affecting the conformation and activities of membrane-bound receptors and enzymes that regulate neurotransmitter signaling (73).

Membrane phospholipids containing omega-3 FAs may regulate intracellular signal transduction (74) by inhibiting the G-protein and phospholipase C–mediated hydrolysis of phosphatidylinositol (PI) into the second messenger molecules inositol triphosphate and diacylglycerol, a step in a putative cascade...
mechanism of antidepressant action (74,75) (Fig. 4). Mood stabilizers, such as lithium and valproate, also appear to inhibit different aspects of signal transduction related to the PI system (75). Therefore, the mood-stabilizing action of the omega-3 FAs may be related to this effect on signal transduction.

Omega-3 FAs also regulate calcium ion influx through calcium channels (76,77). This effect may be due to phospholipase A2–mediated hydrolysis of omega-3 FA–containing phospholipids and may explain the cardioprotective effects of the omega-3 FAs. Since calcium channel blockers such as verapamil and nimodipine have demonstrated some efficacy in mania (78,79), it is possible that omega-3 FAs exert some of their mood-stabilizing effect via calcium flux inhibition.

A third potential mechanism of action for the omega-3 FAs involves the inflammatory and immune pathways, which have been implicated in the development of mood disorders (80–82). Omega-3 FAs decrease secretion of inflammatory cytokines (83) and may thus decrease hypothalamic secretion of corticotrophin-releasing factor, which stimulates the pituitary and adrenal glands to release ACTH and corticosteroids (84), the latter of which can cause mood abnormalities and also impair immunity (85) (see also Fig. 1).

The data reviewed here suggest that omega-3 FAs may have psychotropic effects. At this time, omega-3 fatty acids, unlike most other natural agents, have been studied as part of polypharmacy of bipolar disorder, and early data are encouraging. So far, a lack of reports of adverse events in the clinical literature and lack of basic science or clinical evidence for drug-drug interactions suggests that omega-3 FAs are safe to combine with other psychotropics. However, there are not yet enough data to say with certainty whether the omega-3 FAs are truly effective antidepressants and/or mood stabilizers.
Inositol

Inositol is a naturally occurring isomer of glucose. It appears to function as an intermediate of the phosphatidylinositol cycle, a second-messenger system involving noradrenergic, serotonergic, and cholinergic receptors (86). It has been shown that inositol in the cerebrospinal fluid (CSF) may be decreased in depression (87). The mood stabilizer lithium may treat mania via reduction of inositol levels. Pharmacological doses of peripheral inositol were therefore shown to reverse the behavioral effects of lithium in animals and the side effects of lithium in humans. This suggested that inositol might possess antidepressant properties (86). Its mechanism of action may also involve the reversal of desensitization of serotonin receptors (86). Inositol has been studied for various indications, primarily by Belmaker and colleagues, who have published a series of clinical trials with about 15–20 patients each (86).

In depressed individuals, a double-blind controlled trial of 12 g/day inositol for 4 weeks showed superiority to placebo (88). A related study of combination of inositol with SSRIs showed no significant difference between groups (89). In panic disorder, a double-blind controlled trial of 12 g/day inositol for 4 weeks showed decrease in frequency and severity of panic attacks and agoraphobia (90). In obsessive-compulsive disorder (OCD) a double-blind controlled trial of 18 g/day inositol for 6 weeks resulted in alleviation of symptoms (91). Similar trials showed no effect in schizophrenia (92), ADHD (92), Alzheimer’s disease (93), autism (94), or ECT-induced cognitive impairment (95). There are currently no published studies of inositol for bipolar disorder.

Inositol has no apparent toxicity and a mild side effect profile (86), though some patients have complained of the poor taste of the compound, particularly in the large doses that appear to be necessary to achieve the clinical effect.

Overall, inositol appears to be a promising treatment, particularly attractive because of its multiple possible indications and its apparent safety in combination with other antidepressants. However, clinical trials so far are small, and larger patient samples are required for a better understanding of this drug’s safety and effectiveness, both by itself and in combination with other medications.

ANXIETY AND SLEEP DISORDERS

Kava

Medicinal use of the kava shrub (*Piper methysticum* Forst) appears to have originated in the Polynesian islands. Natives typically drank a kava beverage reported to have a calming and relaxing effect (96). Kava (also called kava-kava) has become increasingly popular in the United States during the past few years.
Controlled double-blind studies indicate that kava may be effective for mild anxiety states (1). A 25-week multicenter randomized placebo-controlled double-blind trial with a special extract of kava assessed 101 outpatients suffering from different types of anxiety disorders including agoraphobia, specific phobia, generalized anxiety disorder, and adjustment disorder with anxiety. In the main outcome criterion, the Hamilton Anxiety Scale (HAM-A), as well as in various secondary criteria, there was a significant superiority of the test drug from week 8 onward (97).

In a second randomized, placebo-controlled, double-blind study, two groups of 29 patients with anxiety syndromes were treated for 4 weeks with kava extract 100 mg tid or a placebo preparation. The HAM-A total score of anxiety symptomatology revealed a significant reduction in the active drug group after only one week of treatment. This difference between drug and placebo increased over the course of the study (98).

A third randomized, placebo-controlled, double-blind study treated two groups of 20 patients with climacteric-related symptomatology for 8 weeks with kava extract 100 mg tid or a placebo preparation. Those who received kava improved more in terms of both anxiety and depression than the placebo group (99).

Kava’s effect appears to be due to kavapyrones, which act as central muscle relaxants (100,101) and anticonvulsants (102). The agent reduces the excitability of the limbic system, perhaps as effectively as benzodiazepines, but without evidence of physical or psychological tolerance or dependency (103). For this reason kava has been recommended for individuals with low degrees of anxiety or who have abuse or tolerability problems with standard agents (104). Postulated mechanisms include GABA-A receptor binding (105), though this is controversial (106,107). Three kava pyrones, (+)-methysticin and (+)-kavain and the synthetic racemate (+−)-kavain, were shown to inhibit uptake of [3H]-noradrenaline, but not the uptake of [3H]-serotonin, in the cerebral cortex and hippocampus of rats (108). This mechanism may, at least in part, contribute to the psychotropic properties of kavapyrones. Other studies (109) suggest that kawain and dihydromethysticin may enhance the effects of the anxiolytic serotonin-1A agonist ipsapirone and that activation of NMDA receptors and/or voltage-dependent calcium channels may be involved in the mechanism of action of some kavapyrones.

Suggested doses of kava are between 60–120 mg daily. There are reports of adverse interactions between kava and benzodiazepines (1) and between kava and alcohol (110). These combinations resulted primarily in excessive sedation. Side effects from kava are rare and may include GI upset, allergic skin reactions, headaches, and dizziness (1,111). Toxic reactions with high doses have been reported; ingestion of up to 300–400 g per week of kava stem (rhizome) powder may result in anorexia and subnormal weight, ataxia, hyperreflexia, facial edema, scaly skin rash, hair loss, yellowing of the skin, abnormal liver function tests,
hematuria, poorly acidified urine, abnormal blood indices, redness of the eyes, problems with visual accommodation, and respiratory problems associated with tall P waves on a resting electrocardiogram, suggesting possible pulmonary hypertension (112,113). These dose levels were at least 100 times higher than the usual clinical doses. Because of the evidence of long-term toxicity, the duration of use of kava is not recommended to exceed 3 months (1).

In summary, kava may be more effective than placebo for mild anxiety states. More studies comparing kava to the more conventional anxiolytics such as benzodiazepines or buspirone are needed to determine kava’s place in the pharmacological armamentarium. As mentioned previously, kava has been successfully combined with hypericum and is likely also combinable with other remedies. However, given the myriad of possible medical complications that may result from its use, particular care needs to be taken with patients who are on multiple medications or have underlying medical illness.

Valerian

The root of valeriana officinalis has been in use as a drug for over 1000 years (114) and is very popular around the world as a sedative and mild hypnotic (115), especially among the Hispanic population (116).

The CNS activity of valerian has been attributed to its valepotriates and sesquiterpene constituents. Its mechanism may be similar to that of benzodiazepines or barbiturates (117,118). EEG studies suggest that valerian results in minor but significant changes in sleep architecture (119–121), though changes in EEG patterns have not conclusively demonstrated therapeutic efficacy. In vitro studies suggest that valerian may decrease the degradation of GABA (122) and increase its concentration at the synapse (123). Its metabolism is not well understood.

About 10 controlled trials have been performed with various types of valerian preparations, some of which are not specified in the published reports (1). Some studies were performed on healthy subjects and others on symptomatic individuals. One three-armed trial looked at nonsymptomatic individuals who received valerian, placebo, or another natural product for 3 nonconsecutive nights (124). Valerian was found to improve sleep quality, particularly for those self-described as poor sleepers. No serious adverse effects were described from valerian, and individuals who received valerian reported less residual daytime sleepiness. A smaller placebo controlled trial with symptomatic patients showed that 450 mg per night of valerian significantly decreased sleep latency compared to placebo. Doses of 900 mg had no statistically significant advantage over 450 mg (125). Valerian has been combined with propranolol with no significant adverse effects (126). Valerian has been compared to flunitrazepam in efficacy, but with fewer adverse effects on cognition (127). Vorbach et al. (128) performed a placebo-controlled double-blind study in 121 patients with significant sleep distur-
The main limitations of these valerian trials are the relatively short duration and small sample sizes. Another major limitation to an effective double-blind clinical trial with valerian is the powerful and distinctive smell of the medication, due to isovaleric acid, a breakdown product of valepotriates (1). Recommended doses of valerian are 450–600 mg, approximately 2 hours before bedtime. Valerian appears to be benign in overdose (129). Adverse effects may include headaches or GI complaints. Rare toxic reactions may include blurry vision, dystonias, and hepatotoxicity (130), although some have argued against such an association (131,132). Products based on Mexican or Indian valerian are not recommended, as they contain higher levels of valepotriates (up to 8%) and baldrinals, which present a mutagenic risk (1,133,134).

The reviewed studies suggest that although valerian may not be ideal for active treatment of insomnia, its value may be in the promotion of natural sleep after several weeks of use with no risk of dependence or residual daytime sleepiness (1). Valerian has been combined with a beta-blocker successfully, and it is likely that it is safe to combine with other psychotropics.

Melatonin

Melatonin is a hormone derived from serotonin, made in the pineal gland. It is involved in the organization of circadian rhythms (135). It is used by travelers to reset their biological clock when traveling across time zones. This represents its main source of popularity. However, studies have disagreed on the degree of efficacy of melatonin compared to placebo, and there is limited consensus as to the appropriate dose, which may range from 0.5 to 10 mg/day (136).

In general, melatonin appears to be an effective hypnotic, which works within one hour of administration regardless of time of day. It may be more effective for people with insomnia due to circadian disturbances (137,138). Its mechanism of action may involve interaction with the suprachiasmatic nucleus, by which it resets the circadian pacemaker and attenuates alerting process (139). It may also have a direct soporific effect (140).

Doses of 0.25–0.30 mg/day can decrease sleep latency, but many preparations have as much as 10 mg of melatonin. Interestingly, a recent randomized double-blind study of 257 Norwegian physicians suggested lack of efficacy for jet lag. No significant differences were found between placebo and three different regimens of melatonin (doses varied from 0.5–5.0 mg) (141). High doses may cause daytime sleepiness or confusion (142). Serious adverse effects, though rare, may include inhibition of fertility and decreased sex drive (143), hypothermia (144), and retinal damage (145,146); the latter case involved coadministration of
melatonin with sertraline (146), but in view of another case of retinal damage with melatonin alone (145), it seems unlikely that the sertraline played a significant role in the latter case. Because of potential interactions with the HPA axis and thymus, which may result in immunosuppression, it should be used with caution in individuals taking steroids (147,148).

In summary, melatonin is a promising hypnotic, which is generally accepted as safe and effective. There appear to be no adverse interactions in combination with other drugs, except perhaps with immunosuppressants. It is likely safe to combine with antidepressants and other psychotropics.

DEMENTIAS

Ginkgo biloba

_Ginkgo biloba_, the seed from the ginkgo tree, has been used therapeutically in eastern Asia for at least 2000 years (1). The primary indication for ginkgo extracts is the treatment of cognitive deficits found in organic brain diseases such as Alzheimer’s and vascular dementia. Its active components are flavonoids such as quercetin, kaempferol, and isorhamnetin, and terpene lactones including ginkgolides, bilobalide, and ginkgolic acids (1).

It is generally thought that ginkgo stimulates populations of nerve cells that are still functional and protects them from pathological influences such as hypoxia, ischemia, seizure activity, and peripheral nerve damage. Its mechanism of action may involve membrane stabilization (149). It may also involve the inhibition of platelet-activating factor by ginkgolide B; for this reason, ginkgo should be avoided in patients with bleeding disorders (150). The flavonoid fraction may protect nerve cells by free radical scavenging (150) and appears to decrease capillary fragility. Other functions may include inhibition of age-related decline in muscarinic choline receptors and \( \alpha_2 \)-adrenergic receptors, as well as promotion of choline uptake in the hippocampus (1).

Over 30 placebo-controlled double-blind trials have been conducted since 1975 to assess the efficacy of ginkgo in patients with cognitive deficits (1). These trials suggest that dementia symptoms and their progression seem to improve with ginkgo treatment. However, the standards for testing the efficacy of ginkgo and other nootropic (cognition-enhancing) drugs have changed over the years. In 1991, for example, the German Federal Health Agency established guidelines requiring that nootropic therapy must improve not only dementia symptoms (such as memory, abstract thinking, and psychomotor function), but also the patient’s functioning in daily activities and need for care (1). Most of the older studies would therefore not meet adequate methodological criteria, and despite the evidence in favor of cognitive improvement, they provide no solid evidence that
overall functioning in daily activities improves or that need for daily care is reduced.

A recent study by LeBars and colleagues (151) assessed the efficacy and safety of ginkgo in Alzheimer’s disease and multi-infarct dementia. In this year-long, randomized double-blind, placebo-controlled, parallel-group study, 309 outpatients with Alzheimer’s disease or multi-infarct dementia were treated with ginkgo (120 mg/d) or placebo. Of the 202 completers, those treated with ginkgo achieved a statistically significant improvement on various cognitive scales, and no significant adverse events were reported compared with placebo. The changes induced by ginkgo were modest, but objectively measurable, and observable by the caregivers.

Gingko has been compared with synthetic nootropic drugs such as piracetam, pyritinol, ergot alkaloids, nicergoline, and nimodipine. While they all appear to be comparable in efficacy (152), ginkgo’s advantage may lie in its lower incidence of side effects (1.69% vs. 5.42%) (153), and for this reason many physicians favor it over the synthetic nootropics (154).

The suggested daily dose of ginkgo is 120–240 mg, divided into two to three doses. A minimal 8-week course is recommended in patients with dementia, and the patient should be reevaluated after 3 months to determine if continuation is appropriate. Assessment of the impact of ginkgo on social functioning may require at least one year of observation (1). Side effects are rare and may include mild GI upset, headache, irritability, dizziness, or allergic reactions. Its toxicity is very low, and there are no known interactions with other drugs (153), though care needs to be taken in patients on anticoagulants. There is no evidence of mutagenic, carcinogenic, or genotoxic effects from ginkgo (155).

Recent studies have suggested a role for ginkgo in the treatment of antidepressant-induced sexual dysfunction (156,157). In an open trial of Ginkgo in 63 patients with sexual dysfunction secondary to various antidepressants of different classes (SSRIs, SNRIs, TCAs, MAOIs) (157), 91% of women and 76% of men reported improvement in all aspects of the sexual cycle (desire, excitement, orgasm, and resolution). Effective doses were between 60 and 180 mg twice a day. The mechanism for this improvement may involve ginkgo’s interaction with platelet-activating factor (PAF), prostaglandins, peripheral vasodilatation, and central serotonin and norepinephrine receptor activity.

Overall, the data regarding ginkgo’s effectiveness suggest a modest but measurable improvement in dementia symptoms, with a benign side effect profile. The full extent of its role in the attenuation or prevention of dementia, as well as its role in the reversal of antidepressant-induced sexual side effects, remain to be clarified. Apart from the risk of hemorrhage in people with bleeding disorders or who take anticoagulants, ginkgo appears to be safe to combine with other medications.
SUGGESTED STRATEGIES INVOLVING POLYPHARMACY AND COMBINATION TREATMENTS

Psychiatrists who are considering recommending natural medications to their patients should proceed with caution (158). Given the limited data on these remedies, the best candidates may be those for whom a delay in adequate treatment would not be devastating, specifically the mildly symptomatic patient with a strong interest in natural remedies. At the other end of the clinical spectrum, patients who have failed multiple trials of conventional medications (because of nonresponse or side effects) may also benefit from natural remedies. However, this population is often the most difficult to treat, and natural agents appear to be most suitable for mild-to-moderate illness (1). Further, clinicians should be aware that many patients are engaging in OTC polypharmacy, adding natural medications to their prescribed treatments, often without informing their treaters (159–161). Clinicians should therefore ask carefully about natural medication use with all patients and then discuss the risks and benefits of polypharmacy. Finally, because of the lack of data regarding safety in pregnancy, it is not advisable for pregnant women to use these remedies.

As with registered medications, we can, in principle, use natural remedies in combination with other natural (or registered) remedies to treat concurrent disorders, to get a more robust effect on one disorder, or to counteract adverse effects of one medication with another medication. Possible combinations are summarized in Table 1; a few representative examples include:

1. Ginkgo plus antidepressants in cases where there is antidepressant-induced sexual dysfunction.
2. Hypericum plus valerian (or melatonin) for depression with insomnia.
3. Hypericum plus kava for depression with generalized anxiety.
4. Omega-3 FAs plus hypericum for bipolar depression. The mood-stabilizing effect of the omega-3 could protect from cycling. However, extreme care must be taken with bipolar patients, and concomitant treatment with a standard mood stabilizer should always be in place.
5. Omega-3 plus omega-6 FAs for schizoaffective disorder might control some mood and psychotic symptoms, though usually as an add-on to standard antipsychotics and mood stabilizers.
6. Inositol could be combined with clonazepam for treatment of refractory panic attacks.

While adverse interactions appear to be relatively uncommon with natural medications, it is important for clinicians to warn patients about the lack of data on the risks of using these remedies, particularly in combination with other medications. As outlined in the chapter, there have been documented interactions with registered medications, some of which can be of grave consequence (e.g., hyperi-
<table>
<thead>
<tr>
<th>Medications</th>
<th>Fatty acids</th>
<th>Ginkgo</th>
<th>Inositol</th>
<th>Kava</th>
<th>Melatonin</th>
<th>SJW</th>
<th>Valerian</th>
<th>SAMe</th>
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</thead>
<tbody>
<tr>
<td>Fatty acids</td>
<td>BPD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>BPD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Bipolar&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td>Depression</td>
<td>Psychosis</td>
<td>OCD</td>
<td>Panic</td>
<td>Psychosis</td>
<td>Psychotic</td>
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<tr>
<td>Ginkgo</td>
<td>X</td>
<td>Dementia</td>
<td>Psychosis</td>
<td>Anxiety</td>
<td>Insomnia</td>
<td>MDD</td>
<td>Dementia</td>
<td>Depression</td>
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<td>biloba</td>
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<td>Inositol</td>
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<tr>
<td>Kava</td>
<td>X</td>
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<td>X</td>
<td>MDD</td>
<td>Anxiety</td>
<td>MDD</td>
<td>Insomnia</td>
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<tr>
<td>Melatonin</td>
<td>X</td>
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<td>X</td>
<td>Anxiety</td>
<td>MDD</td>
<td>Severe insomnia</td>
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<td>OCD</td>
<td>Panic</td>
<td>OCD</td>
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</tr>
<tr>
<td>SJW</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>MDD</td>
<td>Insomnia</td>
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<td>Valerian</td>
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<td>Severe insomnia</td>
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<tr>
<td>SAMe</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MDD</td>
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</table>

BPD = Bipolar disorder; OCD = obsessive-compulsive disorder; Sex dys = sexual dysfunction; MDD = major depressive disorder.

<sup>a</sup> All patients with bipolar disorder should also be treated with standard mood stabilizers, such as lithium.

Source: Adapted from Ref. 165.
Table 2  Summary of Interactions and Suggestions for Combination

<table>
<thead>
<tr>
<th>Medication</th>
<th>Summary of interactions, suggestions for combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty acids</td>
<td>Probably safe to combine with other psychotropics</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Avoid combinations with anticoagulants</td>
</tr>
<tr>
<td>Inositol</td>
<td>Probably safe to combine with other psychotropics</td>
</tr>
<tr>
<td>Kava</td>
<td>Probably safe to combine with most psychotropics</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Be careful with patients on benzodiazepines</td>
</tr>
<tr>
<td>SJW</td>
<td>Be careful with patients on multiple medications and/or underlying medical illness</td>
</tr>
<tr>
<td>Valerian</td>
<td>Avoid in individuals taking steroids or sertraline</td>
</tr>
<tr>
<td>SAMe</td>
<td>Probably safe to combine with anxiolytics</td>
</tr>
</tbody>
</table>

Source: Adapted from Ref. 165.

SUMMARY

Natural medications represent a growing field in the pharmacology of mental disorders and may eventually prove to be a valuable addition to the psychopharmacological armamentarium. Clearly, the public at large is using these treatments, with or without clinical supervision, and often combining natural with prescribed medications. In order to say with more certainty just how effective and safe these medications are, controlled studies on larger, rigorously diagnosed patient populations are needed.

As we have seen, care should be taken with patients who are on multiple medications, as drug-drug interactions have not yet been clearly elucidated for many of these remedies. The combining of alternative with registered medications is still not well documented, but anecdotes and preliminary studies suggest usefulness for some difficult to treat patients.

The NIH and NIMH have acknowledged the need for systematic research on the effectiveness and safety of natural medications (6,162), and academic
Polypharmacy of Alternative and Herbal Medications

Institutions are now undertaking multicenter studies on herbal medications such as St. John’s wort, kava, and the like. It is hoped that these studies will help answer some of the yet unsettled questions about natural medications, particularly with regard to drug-drug interactions and the risks and benefits of combination treatments with these remedies.

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Polypharmacy of Alternative and Herbal Medications


The decision to engage in polypharmacy is presumably made after consideration of a number of factors such as current indications, diagnosis, literature on treatment, prior clinical use and results, and knowledge of algorithms. The question of whether “psychological” factors are involved asks if factors “of the psychology” or “related to knowledge of the psyche” relate to polypharmacy. There is in this question a certain controversial conceptualization that this “psychology” does not involve the brain or that, being less obvious, it is also less true.

Evidence abounds in the literature for the existence of less obvious factors contributing to behavior (2). Whether we call these less obvious factors “the unconscious” or “defense mechanisms,” it is likely that they are metaphoric conceptualizations of brain function, and distinguish themselves from other factors involved in polypharmacy only by virtue of the language medium in which they are expressed, and the more subjective feel to the overall texture of their meaning. These metaphoric conglomerations of meaning also appear to have judgments implicit in their nuclei and do not appear to comply with the scientific intention of “removing responsibility” and viewing things as “the way things are.”

To imagine that any decisions involving polypharmacy do not involve “psychological factors” would imply either that the notion of a psychology is
erroneous, that “psychological” factors are not mediated by the brain in decision making, or that “psychological” factors can be somehow isolated from other mechanisms of decision making. All of these assumptions are difficult to justify: to call anything erroneous implies that we know the “truth”; to imply that psychological factors are not mediated by the brain seems implausible as evidence exists against this view; and to imply that psychological factors can be isolated from “other” factors in decision-making implies a certain stonewall of functioning not consistent with leading theories of neural circuits and neural activation (3,4).

We would say, then, that we are approaching this discussion from the point of view that a human psychology exists, that it is likely mediated by the brain, and that in some cases it may not be possible to isolate such factors from the physiology of “choice,” “decision,” or “implementation.” Thus, polypharmacy, insofar as it is a “way” or “choice,” a decision, or an implementation, likely interacts with pathways involving “the psychology.” We will then describe “the psychology” through the lens that decision-making circuits are not isolated from ideas related to personality, the past, and the subjective circumstances of the “relationship” between the prescriber and patient.

The idea of using more than one drug to treat a patient relies on one or more of the following assumptions:

1. The prescriber wants to prescribe more drugs.
2. The prescriber needs to prescribe more drugs.
3. The patient wants more drugs.
4. The patient needs more drugs.
5. More drugs are better for the patient.
6. More drugs do not compromise the safety of the patient.
7. We know what we are affecting when we prescribe one or more drugs.
8. It does not matter that we do not know all of the effects of prescribing more drugs.
9. There are no other ways to preferably help the patient.
10. A psychopharmacological approach can only be supplemented within the frame of this approach, and not by other approaches.

This set of assumptions, when phrased in this way, appears to be a dangerous scaffolding for decision making. If ignored, they become invisible; if considered, they may be integrated into decision making. A consideration of these factors leads to a consideration of psychology.

HANDING OVER THE PILL AND ORAL PSYCHODYNAMICS

The pill is a condensation and physical manifestation of the power of the clinician (5,6). The sharing of this power is presumably based on a shared belief in the
power of modern pharmacology. The clinician handing over more pills possibly suggests handing over more power, and how the patient feels about this may affect the treatment outcome. If the patient has every reason to believe that she can handle more power, she will be more comfortable with more pills. If not, she will reject this burden and therefore this treatment strategy. The psychology of this is clearly more complicated. Numerous dialogue lines potentially underlie this exchange and may be the "meaning circuits" that are activated. Some possibilities include the following:

1. "Take this from me and put it in your body. It will make you feel better."
2. "Take this from me. It will complete you and supplement your deficiencies."
3. "Take this from me. It will add to your being and complement what you already have."

The first consideration involves a metaphor that has strongly sexual associations. The notion of "inserting" or incorporating relates to both the penis and the breast, but also to a more overarching notion of "parental introjects." As such, any dynamics arising from the polypharmacy may relate to this.

The experience of combined pills causing "too many" side effects may relate to the experience of being overwhelmed in the formation of identity through introjecting "too many" parental characteristics. In addition, recognizing the libidinal aspects of the pill in terms of power and sexual function also points to the potential "meaning" that the receiving of the pill may have for the patient, and having an increased sensitivity to this may help compliance and improve therapeutic alliance. The suggestion here is not to crudely offer these perspectives to patients, but to add this to an overall understanding of what is happening in order to influence decision making.

Furthermore, if it becomes a habit, the "dependence" on the medication may be a mask for the "dependence" on the sexual connotations of "pill ingestion." This relates to the Winnocottian notion of "good-enough mothering" whereby the patient and clinician become involved in a parent-child model of interaction (7).

From a Freudian perspective, it generates "oral" associations and therefore, possibly, "oral" fantasies (8,9). It cannot be underestimated how strongly a patient may feel about getting "more" medication. This needs to be appraised in the context of the patient's life. "More" could be experienced as reinforcing an earlier trauma of "there is no other alternative" or a feeling of being forced to take more despite not wanting to, or it may be experienced as an additional gratification by the patient. These considerations may end up being irrelevant when considered in association with other factors, but are certainly a more inclusive perspective of the notion of giving.

As such, "pill giving" may work for the patient in "healing" the disrup-
tions in the oral phase or may contribute to crises in attachment. If in being on a mother’s breast a child experiences a ‘‘oneness’’ of being, and if in later being given food this ‘‘oneness of being’’ is continued, and if, later on in life, there is movement toward independence and giving of food to another (perhaps a child of the original child), then pill giving allows a certain reliving of attachment to oral reward and a permission to be a child again. This is not an insignificant function of the clinician in general; medicine is a socially sanctioned method of caring for adults in significant ways. The gratification of a patient’s needs should probably be assessed with regard to the advantages and disadvantages. Often clinicians will respond by either gratifying or withholding, and it is important to realize that the interaction is more complicated than that. For example, if a patient says: ‘‘I think I need something more,’’ the clinician may say yes or no in the following ways:

No:
1. ‘‘I don’t think so.’’
2. ‘‘No, you don’t.’’
3. ‘‘Why do you think so?’’
4. ‘‘More is not always better.’’
5. ‘‘I know better than you know what’s good for you.’’

Yes:
1. ‘‘Sure. What do you want?’’
2. ‘‘I agree.’’
3. ‘‘Perhaps, but let’s see if this will really be helpful.’’
4. ‘‘Well, we could target these other symptoms . . .’’
5. ‘‘I worry about the additional side effects, but let’s do it.’’

Each of the above responses will elicit a different response and, in different interpersonal contexts, may have different results. Choosing a response may be informed by a psychodynamic understanding of pill giving.

Here is a case example of how not giving a pill was interpreted as withholding: One of us (NG) saw a patient with complex bipolar disorder for an initial evaluation. Much as discussed in Chapter 2, a good deal of time was spent discussing the effects of antidepressants on the patient, and, as is frequently the case, the suspicion arose that antidepressants may have been consistently destabilizing the patient’s moods. Thus, after much discussion, the clinician recommend tapering off the patient’s current antidepressant and then continuing the mood stabilizer that the patient was already taking. After some time on the mood stabilizer alone, the patient might improve sufficiently so as not to need other medications, or he might need a second mood stabilizer. About an hour after the interview had finished, the clinician received a phone call from the patient. ‘‘Doc, I was halfway home before I realized that I came in for a consult, you took me
off half my medications, and then you sent me home!’’ The patient felt as if he had not been treated: he had not been given the ‘‘better’’ medication which presumably should have replaced those that were stopped. In this case, the clinician’s message was ‘‘More is not necessarily better,’’ which clearly was not consistent with the patient’s belief.

TRANSFERENCE AND COUNTERTRANSFERENCE

The ideas involved in the contemplation of transference and countertransference relate to many of the ideas discussed under ‘‘pill giving.’’ Outside of the Freudian notions related to ingesting a pill, the ‘‘object-relations’’ perspective has some relevance. In Mahler’s original conceptualization of object constancy (10,11), the process of separation-individuation was a central idea in the development of independence. In psychopharmacology, patients presumably often need to take medications for life. This raises many questions regarding dependence and may give rise to recurrent conflicts related to the separation-individuation phase in the development of object permanence. The position of dependence that patients land up in raises questions as to how a dependent relationship is best handled without compromising the health of the patient. These often unconscious elements may bear heavily on the treatment relationship. For instance, a patient who gives in to this dependence may never want to come off medication and, in order to ensure this, may develop a symptom cluster that promotes polypharmacy. Alternatively, patients who resent this dependence may express their anger toward the clinician in the form of conveying that whatever the clinician does is not enough, also promoting polypharmacy. These are just two of many examples of how polypharmacy may be affected by psychological factors relating to the object-relations paradigm.

From an Eriksonian perspective (12), the tasks of autonomy, identity, and ego integrity are all relevant. Autonomy versus shame and doubt, identity versus role confusion, and ego integrity versus despair are all conflicts that need to be negotiated for optimal psychological development. The message in polypharmacy may relate closely to these conflicts in that the underlying message of polypharmacy may be one or more of the following:

1. You are very ill.
2. You will probably not be cured.
3. You are different.
4. You are complex.
5. You need extra.
6. You are deficient.
7. You will never be independent.
8. You need the pill to maintain your identity.
These are just some of the constructs that define how patients may respond at overt or subliminal levels. These constructs are all potentially depression-inducing notions that then add to the burden of suffering that the patient initially presented with. Clinicians should be careful not to replace one presentation of suffering with another. In the latter form (the paradigm of ‘‘you must suffer by taking these pills.’’), what initially started as a shame-avoidant function of the medical model (‘‘it’s not you, it’s the way your brain is’’) may be replaced with a new brand of shame (‘‘I deserve to have to be on all these medications. I’m ill.’’).

Furthermore, the countertransference-related notions may adopt one or more of several emotional flavors. These include the flavors of authority, care-taking, judgment, kindness, guilt, and generosity. Each of these flavors needs to be considered for individual patients. The overt intentions of the clinician may appear to be kind, but they may in fact stem from a feeling of guilt about not providing to a significant other in the past. This may promote an aggressive generosity, a flavor sometimes seen in clinics where clinicians may respond to the request for more help from patients in a time-restricted setting with the unconscious construct of ‘‘well, ok; if that’s what you want, that’s exactly what you’ll get.’’

**THE THERAPEUTIC ALLIANCE**

Therapeutic alliance has been shown to be an extremely important determinant of outcome (2).* As such, the relationship between the clinician and patient is of paramount importance. One of the points to consider is what becomes of the relationship in the face of making decisions based on ‘‘objective evidence.’’ From the perspective of polypharmacy, evidence-based explanations of mechanism of action are limited, but clinicians are left to integrate the incomplete database we have in order to make the best possible decisions. The problem here is that despite numerous clinical trials demonstrating efficacy, clinical trials subjects often differ from more realistic clinical presentations, including comorbidity, substance use, and medical illnesses. For these and other reasons, it is usually impossible to determine how any particular person will respond to an agent. Probability statistics give overall meaning to the efficacy of a medication but have little direct patient-specific meaning. Despite this, within the medical model, patients become drawn into the ‘‘objective’’ paradigm. In effect, they become ‘‘objects.’’ In so doing, they lose their ‘‘subject’’ status and the subjectivity that often relates to their perceptions of the truth. This change in patient status from ‘‘subject’’ to

* Ronald Pies has even suggested that the therapeutic alliance can be conceived as a ‘‘mood stabilizer,’’ since it helps improve mood when depressed, and reduce impulsivity when manic (2001, personal communication).
The Psychology of Polypharmacy

‘‘object’’ is a dynamic and fluid process and an ongoing one, back and forth. Sensitivity to this may enhance communication and therapeutic alliance, as well-being is often intricately connected to agency, which is in turn usually connected with freedom of the subjective self. This needs to be considered in combination with the safety that the ‘‘object’’ status allows, for ‘‘agency,’’ despite its connection to freedom, is also intricately connected to fear and the fear of being alone or out of control. For example, providing patients with knowledge about available medications, risks and benefits, and a revelation of the clinician’s thought processes in combination with allowing the patient to choose from a menu of options combines these concepts of agency and safety. As the relationship progresses, further consideration may be given to this balance.

COMPLIANCE

The therapeutic alliance ties into the issues of compliance and insight. Compliance is perhaps the single most relevant psychological variable in pharmacological treatment. Frequently, polypharmacy occurs because a patient is not compliant enough with the first medication so as to experience full benefit.

Compliance is influenced by many factors, but ultimately, if a patient does not want to take a pill, she will not. Most clinicians recognize that noncompliance is the rule rather than the exception in real-world clinical practice, and this problem generates a great deal of concern on the part of clinicians. Besides limited pharmacological approaches (such as long-acting injectable antipsychotics for schizophrenia), this problem turns around psychological questions. We suggest that two key components are the therapeutic alliance and insight.

If the patient does not have trust and confidence in the physician, if the alliance is weak, then the patient is unlikely to take a medication as prescribed. How does one strengthen a weak therapeutic alliance? Among psychotherapists, one who has written about this issue in relation to major mental illness is Harry Stack Sullivan (3). Sullivan’s techniques can be quite helpful in improving a therapeutic alliance and improving medication compliance (even though Sullivan did not have medications in mind at all when he introduced these techniques in the 1940s and 1950s).

Sullivan possessed a special psychotherapeutic sensitivity to paranoia, the antithesis of the trusting therapeutic alliance. Paranoia is rife in severe psychiatric illness. In severe personality disorders, it may take the form of projective identification and rage directed toward the doctor. In severe psychotic disorders, it may be directly reflected in paranoid delusions and hallucinations. And in severe affective disorders (especially psychotic depression), it may be expressed in a distrustful rejection of the empathic approaches of the doctor.

Counterprojection is one idea developed by Sullivan to handle paranoia.
In its simplest form, as described by Leston Havens (4), it involves the following logical process: the patient says ‘‘You are Jack,’’ which is a projection of his own feeling about an internal object-representation of a man named Jack. The doctor, when counterprojecting, needs to convince the patient of the following proposition: ‘‘No, I am not Jack. I’m Jim. Jack is out there.’’ Jack is out there, in the world, not in the doctor (where the projection places him), nor in the patient’s mind (where he truly resides). At this point in treatment, the severely ill patient is unable to tolerate the idea that Jack resides within him or her as an internal object-representation. Only through repeated counterprojection can the doctor begin to convince the patient that the doctor, at least, is not Jack. If the patient can accept that fact, then psychopharmacological treatment can begin. Only then can the patient divert the paranoia that lives with the concept of Jack away from the doctor, and towards all those Jacks in the external world. Colluding against those other Jacks, the doctor and the patient are free to form some kind of therapeutic alliance. This alliance is to some extent superficial, but in the context of psychopharmacological treatment, it may create just enough of a wedge in the patient’s paranoid world view to allow a pill to enter. With the acceptance of medication treatment, the paranoid world view might be biologically shattered, thus making counterprojection no longer necessary and allowing further psychotherapeutic work to proceed.

INSIGHT

Another important influence on compliance is insight. Insight is defined basically as awareness that one is ill, although much research has shown that there are a few different dimensions of insight, including recognition that one needs treatment and recognition of the social consequences of one’s behavior as stemming from an illness. Over the last decades, a number of psychometrically rigorous insight scales have been devised and used in large clinical studies. One of us has reviewed much of this material elsewhere (5). What is relevant here is the relationship between insight and compliance, and, at least in psychotic disorders, poor insight seems to be associated with poor medication compliance (6). This association likely contributes to poor outcome.

How does one handle the patient with poor insight so as to maximize compliance? One factor that is important is to remember the multidimensionality of insight: some patients will adamantly refuse to accept that they have a mental illness, but they will accept medication nonetheless (often on behavioral grounds, e.g., ‘‘I do not have bipolar disorder, but that pill does help me sleep’’). In those cases, it is self-defeating for the clinician to try to convince the patient that she indeed has an illness. Taking the pill is more important than agreeing on a diagnosis.
In general, our experience is—and limited psychotherapy studies support this notion (6)—that it is more effective to focus on behaviors than on more conceptual constructs, such as mental illnesses or disease entities. Patients are more likely to agree to take a medication for a behavior than an illness. If a mood stabilizer is couched as a medication that helps with moods and improves sleep, a patient is more likely to take than if it is labeled “‘mood stabilizer’” and described as the treatment for the illness “‘bipolar disorder.’”

In handling impaired insight, it may be also worthwhile to bring to light patients’ beliefs about mental illness and the mind/brain in general (7). Patients come to treatment with (often covert) theories about the nature of mind and brain. So do doctors. When these theories conflict, it appears to the doctor as if the patient lacks insight, and to the patient as if they doctor is not empathic. It is not the job of the doctor to convert the patient to a specific view; what the clinician needs to do is to reach some consensus with the patient, so as to improve the therapeutic alliance and thus enhance compliance.

It is worthwhile recalling that sometimes patients’ mind/brain theories do not impede compliance but in fact contribute to polypharmacy. Recall Oliver Wendell Holmes’s speculation (8) that many patients seek drugs because they have a belief, which we might term unconscious, that illness has to do with evil spirits, and noxious medications drive those spirits away. Also, some persons may believe that they have a mental illness, when in fact they do not. And by this scenario we do not mean a Münchausen’s-like near-psychotic syndrome; we refer to cultural and social beliefs that certain behaviors may represent an illness. Clinicians probably do need to do some educating in these cases about which behaviors are not mental illnesses, probably an easier task than clearly defining which ones are.

In this respect, we are on the strongest ground if we stick with the truth, that is, to say that we know some things in psychiatry, but there are a lot of things we do not know. As accepted as the whole notion of psychiatric “‘illness’” is, definitive proof of the validity of any psychiatric disorder may be said to await the discovery of genetic/biological etiologies that correspond to the clinical syndromes. To date, no such clear correspondence has been established. There are many studies on the reliability of disorder categories, and we certainly have some clue as to the underlying neurobiology, but we cannot claim certainty in this regard. Clinicians seem to often be in a bind with regard to this concept, as they fear that admitting to this reality will reduce hope in patients, reduce the placebo-component of response, and that they will seem too shaky and not hope- or confidence-generating. Although these fears are realistic, it is possible to present the dialectic as it is, so that patients know what we know (as limited as it may seem), and that they both accept and reject their diagnoses as they are treated. Promoting this mentality helps prevent the negative effects of stigmatization and the long-term side effect of “‘becoming one’s illness.’” In order to do this, clini-
cians involved in psychiatry would have to come to terms with the nebulous nature of many of the notions we deal with, without feeling invalidated or pressured by evidence-based medicine in order to heal or reduce suffering. By the same token, having some hope about evidence-based medicine also goes a long way to helping clinicians feel more confident and possibly more effective.

**PSYCHOTHERAPY DURING PSYCHOPHARMACOLOGICAL TREATMENT**

As this discussion may suggest, a good deal of psychotherapeutic interaction goes on in the act of prescribing medications. Some patients in fact may seek medications in part to interact with their psychiatrist. Today, managed care companies frequently limit appointments described as psychotherapy sessions, but they less frequently curb appointments that are labeled psychopharmacology sessions. These visits are not really "med checks," in the weird coinage one often hears, except perhaps in the hands of those who are either so overworked or so greedy that they wish to spend as little time with a patient as possible. In reality, in many cases, a good deal of psychotherapy goes on in "psychopharmacology" sessions. At minimum, this psychotherapy is of the supportive variety, and frequently it can be much more complex. The supportive psychotherapy that occurs in the context of 20 to 30-minute psychopharmacology visits should not be underemphasized.* Some of this support is similar to what can also be called existential psychotherapy (9). There is a great benefit to simply being there with a patient. Sometimes, if a patient experiences this existential benefit as a primary source of comfort, she may seek to make more "psychopharmacology" appointments so as to receive this support. If the visits are tied into describing symptoms and taking medications, such visits may evolve into a polypharmacy that may be less important than the underlying existential support. This factor may account for much of the placebo response observed in antidepressant and other clinical trials, where appointments tend to be longer than real-world clinical appointments, and where research staff are strongly incentivized to hold onto and satisfy their research subjects.

**SUMMARY**

We have not intended to imply that polypharmacy in psychiatry is always, or even frequently, the result of certain psychological variables. We have sought

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* In fact, it is quite important to all medical visits, often termed "bedside manner." Recall Osler’s view that the nonspecific aspects of medical care were perhaps more important than drug treatment.
instead to identify some of the psychological aspects of polypharmacy and to
describe those that reflect psychological issues that need to be handled by psycho-
therapeutic methods. Psychopharmacological practice is still psychiatric practice,
and it still requires experience with psychotherapeutic issues and techniques.
Much more than “med checks,” skilled psychopharmacology includes psycho-

therapeutic technique, both to identify symptoms and to promote compliance.
Unless the psychological aspect of care is attended to, the pharmacological aspect
may not be optimally effective.

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Benjamin Rush is generally considered to be the founder of American psychiatry. His likeness is on the seal of the American Psychiatric Association, and most psychiatrists are aware that he not only wrote the first psychiatric text in American medicine, but was also a signer of the Declaration of Independence. Thus, the founder of American psychiatry was also a founding father of the nation, and a political revolutionary. How apt that this activist discipline, American psychiatry, should have such an activist forefather.

For Oliver Wendell Holmes, Rush exemplified the "can-do"* approach of American medicine, its optimism, and activism, all of which predisposed Americans in particular to polypharmacy. Given that Rush is the role model of American psychiatry, Holmes’s comments are even more relevant to understanding cultural aspects of polypharmacy in American psychiatry (1):

There are . . . special American influences which we are bound to take cognizance of. . . . If I wished (a student) to understand the tendencies of the American medical mind, its sanguine enterprise, its self-confidence, its audacious handling of Nature, its impatience with her old-fashioned ways of taking time to get a sick man well, I would make him read the life and writings of Benjamin Rush . . . . Dr. Rush must have been a charming teacher, as he was an admirable man. He was observing, rather than a sound observer; eminently observing, curious, even, about all manner of things . . . . He taught thousands of American students, he gave direction to the medical mind of

* Frederick Goodwin has pointed out to me the influence of this activist attitude in American culture on the beliefs and practice of American psychiatry (personal communication).
the country more than any other one man; perhaps he typifies it better than
any other. It has clearly tended to extravagance in remedies and trust in reme-
dies, as in everything else.

Introducing Rush thus (‘‘the most conspicuous of American physicians’’),
Holmes leaves no room for doubt that the founder of American psychiatry was
also the founder of American medicine. And he connects Rush’s activist tempera-
ment to the tendency of American physicians to use medications aggressively.
He then goes on to connect the tendency to polypharmacy to the activism of the
larger culture that Rush exemplified (1):

How could a people which has a revolution once in four years, which has
contrived the Bowie-knife and the revolver, which has chewed the juice out
of all the superlatives in the language in Fourth of July orations, and so used
up its epithets in the rhetoric of abuse that it takes two great quarto dictionar-
ies to supply the demand; which insists in sending out yachts and horses and
boys to out-sail, out-run, out-fight, and checkmate all the rest of creation;
how could such a people be content with any but ‘‘heroic’’ practice?

‘‘Heroic’’ measures, trying as many treatments as necessary, come naturally to
the American physician. Patience, letting nature heal slowly, does not. Recall
that for Holmes, as well as Osler, most of the advances in medicine came from
the understanding of disease and its prevention, not treatment of symptoms. This
is a major philosophical difference. And what Holmes is trying to say here is
that the American temperament, if one can be allowed to generalize about it,
veers toward treating symptoms with drugs rather than toward understanding
disease.

Frederick Goodwin has suggested that the pragmatic frame of mind of
American culture has been influential in the history of psychiatry (personal com-
munication). It is widely recognized that the one school of philosophy that dis-
tinctly originated in the United States is the pragmatic school, whose founders
are generally acknowledged to be Charles Sanders Peirce and William James. I
will discuss James and some of his ideas because I think they are relevant to the
mindset of many American patients and physicians in relation to polypharmacy.

James was a physician first before he ever became a philosopher. In fact,
he once remarked that the first philosophy course he ever took was the first one he
ever taught. James graduated from Harvard Medical School but never practiced
medicine, instead turning his attention in the 1880s to the newly minted field of
psychology. He became a professor of psychology, writing the 1890 text Princi-
pies of Psychology (2), which continues to be read as a marvel of descriptive
psychology. He then began teaching philosophy, and until his death in 1911 he
published a number of works on pragmatism, an approach to philosophy that was
uniquely his. James continued to maintain an interest in medicine and psychol-
ogy, too, meeting Freud on the latter’s lecture trip to Clark University in Worces-
ter, Massachusetts in 1909.

James’s pragmatism is suffused with optimism. Yet, at the same time James was quite aware of the tragedies of life. He likely suffered from severe episodes of depression (3), and he wrote an essay on suicide, “Is life worth living?” (4), as well as writing about other somber subjects, like war. Thus, those who write off pragmatism as rose-colored and simplistic do not do justice to the depth of James’s thought. His optimism was a response to the tragedies of life, not an attempt to ignore them.

Be that as it may, there is no doubt that James’s approach to life was action- oriented, perhaps, as some have suggested, a reflection of how he managed to overcome his own depression. The following excerpt gives a flavor to this aspect of James’s thought (4):

> It is only by risking our persons from one hour to another that we live at all. And often enough our faith beforehand in an uncertified result is the only thing that makes the result come true. . . . The part of wisdom as well as of courage is to believe what is in the line of your needs, for only by such belief is the need fulfilled. Refuse to believe, and you shall indeed by right, for you shall irretrievably perish. But believe, and again you shall be right, for you shall save yourself. . . . For my own part, I do not know what the sweat and blood and tragedy of this life mean, if they mean anything short of this. If this life be not a real fight, in which something is eternally gained for the universe by success, it is no better than a game of private theatricals from which one may withdraw at will. But it feels like a real fight. . . . For such a half-wild, half-saved universe our nature is adapted. The deepest thing in our nature is this Binnenleben (as a German doctor* has lately called it), this dumb region of the heart in which we dwell alone with our willingnesses and our unwillingnesses, our faiths and fears. . . . Here possibilities, not finished facts, are the realities with which we have actively to deal. . . . These then are my last words to you: Be not afraid of life. Believe that life is worth living, and your belief will help create the fact. (italics original)

Thus, James is dealing with serious and weighty matters, like suicide and death and God and war, and in all cases he is recommending belief, optimism, and an action-oriented approach to life. I find James quite convincing and thoughtful as a philosopher. What I wish to point out here is that, as America’s most prominent philosopher, James’s approach reflects an activism that, in medicine, predisposes to polypharmacy. Belief in the unknown, a willingness to risk, a preference for doing over being—all these aspects of James’s philosophy, when applied to medicine, lead to an emphasis on more and more treatment.

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* I have often wondered whether James is referring to Freud here; it is too bad he did not identify his source.
In American psychiatry, the pragmatic attitude, rooted in James, has manifested itself in two different epochs: the rise of Adolf Meyer’s school of thought and contemporary empirical psychiatry (exemplified in particular by DSM-III).*

Meyer was a Swiss psychiatrist who had emigrated to the United States in the late nineteenth century and would later be chairman of the department of psychiatry at Johns Hopkins University Hospital for decades. Meyer taught and influenced more leaders in American psychiatry than probably any other single academic psychiatrist. Probably the other major American psychiatrist in the middle twentieth century was Karl Menninger, and his views thoroughly agreed with those of Meyer.

Meyer’s influence quickly waned after the rise of empirical psychiatry in the 1970s, but the pragmatic vein that ran through Meyer’s thought is worth highlighting. Meyer had been thoroughly trained in neuroanatomy; he was also quite familiar with psychoanalysis. Unwilling to give up one or the other approach, Meyer advocated “psychobiology.” In practice, Meyerians put much more emphasis on the “psycho” than on the “biology,” partly because Meyer conceived of psychiatric syndromes as “reactions” to life events, in which a biological susceptibility interacted with environmental events to produce psychopathology. Since the biological aspects of life seemed unchangeable, Meyer, and his pragmatic and optimistic American students, focused on the changeable psychological and environmental aspects (55): “I am not particularly interested in data concerning which I have to accept the fact that the dice have already been cast and that life is practically nothing but the dance of factors largely settled by heredity and constitution.” Meyer avoided putting much emphasis on diagnosis and did not see diagnoses simply as diseases, as had Kraepelin and his school (5): “I put my emphasis on specificity. It is ‘the story’ that counts in a person.”

Meyer’s approach is stamped all over the first two handbooks of psychiatric diagnosis, DSM-I (1952) and DSM-II (1968), which spoke of “manic-depressive reactions” rather than disorder or diseases.

Meyer did not write much about somatic treatments in psychiatry, but the gist of his pragmatic philosophy tended toward intervention and treatment. He certainly repeatedly criticized Kraepelin and the German schools for pessimistic resignation and a hands-off attitude to treatment (referred to by others as “therapeutic nihilism”).

This aspect of Meyer’s approach to psychiatry is still present today, even when the overt Meyerian ideas about psychobiology and reactions are not as commonly accepted. Meyer’s fight against Kraepelinian nosology was a short-lived success, for the “neo-Kraepelinians” of the 1970s in American psychiatry succeeded in replacing Meyerian definitions with a return to many of Kraepelin’s perspectives in DSM-III.

* Meyer in fact called himself a pragmatist and was a close friend of John Dewey, dining with him weekly at one point in his life (5).
The proponents of DSM-III sought to make psychiatry more empirical, and much of this drive came from the need to diagnose entities that could be treated with the newly emerging psychotropic drugs (see Chapter 1). Thus, one of the major changes in DSM-III was an allegiance to an "atheoretical" nosology. Unlike the psychoanalytic and Meyerian theories underlying DSMs I and II, the neo-Kraepelinians proposed that DSM-III was to be purely descriptive, not based on any theory. Of course, Kraepelin himself had a theory, as Meyer put it (5):

The superstition about the value of a diagnosis of a disease prompts many to believe that a diagnosis once made puts them into a position to solve the queries about the case not with the facts presented by it and naturally considered in the light of principles based on experiment and on clinical experiences with concrete series of cases, but by a system of rules and deductions from the meaning of the newly defined disease entities, with their prognosis and autotoxic or other origin held out to the believer as sufficiently settled for practical purposes. . . . It may be that even Kraepelin exposes himself to misinterpretations of his rather peremptory propositions, notwithstanding his occasional confession of the provision nature of his groupings, because he speaks so often of disease process in the sense of disease unit, and of the necessity of arriving at some sort of diagnosis at as early a date as possible. But with all this it would probably be a misinterpretation of his inspiring help in shaking up effete conceptions, should it be turned into a revival of scholasticism and of the diagnosis notions cultivated by the ordinary medical tradition. . . . Why not regard the 'diagnosis' as merely a convenient term for the actually ascertained facts which do or do not tell a clear and plain story, and, accordingly, are or are not especially gratifying data of medical insight?

I believe that what has happened is that both Meyer and the DSM-III–oriented neo-Kraepelinians have implemented an American pragmatic attitude to psychiatry, which has tended to both polynosology and polypharmacy. The spirit of pragmatism, introduced to American psychiatry by Meyer, still lives in the "neo-Kraepelinian" world of contemporary psychiatry; in fact, neo-Kraepelinian American psychiatry differs in some essential respects from Kraepelin’s school as it existed in the founder’s lifetime.* Let me explain.

Kraepelin believed that the diagnoses he described probably corresponded to disease entities. He did not think that psychiatrists would be able to treat those disease entities until the etiologies were discovered. In this general approach, the reader might note that he was in the tradition of Osler and Holmes, what we might call the tradition of scientific medicine. As a result, as Karl Jaspers later noted, Kraepelin and his school were "therapeutically hopeless but kind" (6).

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* This seems almost a general rule of intellectual history: "neo" follower of any founder differ in important ways from the founder. Hence, Freud’s comment that ‘Moi, je ne suis pas Freudiste.’
Kraepelin was no pragmatist. Meyer felt that the Kraepelinian emphasis on diagnosis and disease was not useful, and he introduced the pragmatic notion that each case should be examined for its specific characteristics and action should be taken wherever possible. In Meyer’s day, treatment consisted mainly of psychotherapies and rehabilitative services. With the arrival of the psychopharmacological revolution, the proponents of DSM-III combined these two historical sources. They returned to Kraepelin’s emphasis on nosology and an implicit belief in disease entities underlying diagnoses, but they also retained Meyer’s activist interest in intervening in each case wherever possible. By the 1980s, however, drugs were as easily available as psychotherapies for treatment, and today we can probably say that managed care restrictions make drug treatment much easier than psychotherapies. Combining an activist approach to treatment with the easy availability of psychotropic drugs, and with the renewed focus on identifying many diagnoses, American psychiatry has reached a point where psychiatric practice consists of aggressive diagnosing and aggressive treating (mainly with medications).

I have traced a few lines predisposing American psychiatry to polypharmacy: the activist frame of mind of American medicine (exemplified by Rush), the pragmatic approach to life that suffuses American culture, and the specific combination of these factors in the American incorporation of psychiatric influences (especially Meyer and Kraepelin). Readers may need to be reminded that I am not implying throughout this process that polypharmacy is an inherently undesirable outcome (unlike Holmes and Osler). I will provide my own perspective on the desirability of polypharmacy in the next chapter. In this chapter I have been trying to outline the cultural characteristics of American psychiatry that predispose it to the prevalent polypharmacy that exists today.

But now I will turn to a larger view of what predisposes American culture to polypharmacy in psychiatry, focusing less on the profession of psychiatry and more on the attitudes of the lay public, who request and want medications.

First, there is the question of “pharmacological Calvinism,” a phrase originally coined by Gerald Klerman (7) to describe “a general distrust of drugs used for nontherapeutic purposes and a conviction that if a drug ‘makes you feel good, it must be morally bad.” Peter Kramer relates it to “our society’s aversion to prescribed medication” and asserts that “study after study has shown that when it comes to prescribed drugs, Americans are conservative. Doctors tend to underprescribe (relative to the recommendations of academic psychiatrists) for mental conditions, and patients tend to take less medicine than doctors prescribe. . . . Relative to the practice in other industrialized countries, prescribing in the United States is moderate” (7). He supports this statement with studies on the underprescription of antianxiety and antidepressant drugs in the United States as of 1993. As I discussed in the first chapter of this book, David Healy has made a good argument that the question of underdiagnosis and undertreatment is a complicated
one, with economic as well as clinical sources. If the claim of the anti-Calvinists is correct, then the premise of this chapter is wrong: there is little polypharmacy in psychiatry today, and the bias of American culture is against psychopharmacology rather than towards it. Yet this view is contradicted by the entire history of American medicine over the last two centuries. As we reviewed it in Chapter 1, in the nineteenth century the leaders of American medicine worked quite hard at convincing their colleagues and the lay public to adopt a more skeptical attitude toward medications. Skepticism towards medications today is the result of that evolution of American medicine from the nineteenth-century pragmatic attitude that fostered polypharmacy to the twentieth-century scientific attitude that focuses on understanding disease and preventing rather than curing diseases. In this sense, what Klerman identified was not an underlying Calvinistic attitude that is part of America’s cultural fabric, but the hard-won evolution of scientific medicine. Further, it is hard to believe that psychotropic medications like antidepressants are underused when the class of antidepressant medications is the second largest class of medications prescribed in the United States (after the histamine-2 blocker class of antiulcer drugs).*

Thus, I believe that the concern about pharmacological Calvinism is a bit confused. There likely is a part of the population that is conservative about taking psychotropic medications for vaguely philosophical reasons, and perhaps an almost Calvinistic guilt about not being in pain has something to do with it. But most Americans are naturally inclined to take medications, to intervene actively if they are ill or suffer from painful symptoms, and this inclination has mainly to do with the inherently pragmatic bent of the American mind.

Perhaps pharmacological Calvinism, to the extent that it is real, may explain the reluctance of some Americans to take medications specifically for mental symptoms. Some persons might be rather willing to take medications for physical symptoms but not mental ones, which presumably reflects the stigma associated with mental illnesses. In this sense, there may be an influence of a specifically psychopharmalogical Calvinism on American culture, rather than a larger distrust of medications per se.

Also, it should be noted that Klerman was referring to the distrust that people might feel toward medications that make them feel better, whereas Holmes pointed out that people seemed to have a special inclination to take “noxious” substances that made them feel temporarily worse, in the apparent belief that such harsh medicine would eventually kill off the illness. There is a larger issue here, which has to do with pleasure and pain.

In American schools of psychotherapy, many have believed that a certain amount of psychic pain (anxiety, depression) is necessary for psychotherapy to

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* In fact, there is some evidence that antidepressant agents are overutilized in some psychiatric conditions, like bipolar disorder (8).
proceed with any benefit. In other words, “affect tolerance,” the ability to tolerate some anxiety or depression, is an important part of a healthy personality and a necessary component of psychological growth. This perspective has been identified most closely with the work of Elizabeth Zetzel, “one of the most beloved and influential American psychoanalysts” (7). This is the same person quoted at length in Chapter 1 who took Dr. Sargant to task for trying to treat schizophrenia with drugs.* Clearly, some of the controversy within psychiatry about the use of drugs has to do with this ambivalence about pleasure and pain and about the role of pain in psychological growth, as well the continuing antagonism between psychotherapy and psychopharmacology.

There is another way of looking at this topic that suggests that Americans might be particularly inclined to take at least some psychotropic drugs (like antidepressants) (7):

Prozac highlights our culture’s preference for certain personality types. . . . On the one hand, Prozac supports social stasis by allowing people to move toward a cultural idea—the flexible, contented, energetic, pleasure-driven consumer. In the popular imagination, Prozac can serve as a modern opiate. . . . On the other hand, Prozac lends, or creates, confidence. It catalyzes the vitality and sense of self that allow people to leave abusive relationships or stand up to overbearing bosses. The impact of such a medicine remains unclear. . . . Certain intellectuals at mid-century—those who tried to combine the thoughts of Karl Marx and Freud, such as Erich Fromm and the literary critic Norman O. Brown—believed that industrial capitalist society instilled and rewarded the ‘anal character,’ a style marked by dampened enthusiasms, compulsive control, and conformist rigidity. The success of Prozac says that today’s high-tech capitalism values a very different temperament. Confidence, flexibility, quickness, and energy—the positive aspects of hyperthymia—are at a premium.

Someone once remarked that it would be unlikely that there would ever be a best-selling book titled “Listening to Lithium.” There is a sense in which some persons are inclined to take psychotropic medications that they feel will enhance their normal functioning, even if they do not suffer from a diagnosable illness. Even before the newer antidepressants, amphetamine stimulants were frequently used for this purpose. What has been unique about drugs like Prozac is that they are nonaddictive and relatively safe.

Culture seems to influence which form this enhancement takes. In the United States, as noted above, one could argue that there is a premium on energy, action, and vitality. Thus, drugs like Prozac would seem destined for popularity, as would in fact any antidepressants, since the term “antidepressant” really does

* The historian of psychoanalysis Paul Roazen informs me that Zetzel herself was fond of alcohol and sleeping pills (personal communication).
not distinguish effects on depressive illness versus mood-elevating effects in general.* In contrast, in other cultures where these personality traits are not as widely valued, there would not be similar interest in taking such psychotropic agents. For instance, in China, patients are more likely to be hospitalized and treated for mania than for depression (9), suggesting that depressive symptoms are rather tolerated and often go untreated, whereas even mild hypomanic or hyperthymic symptoms tend to be brought to medical attention. In contrast, in the United States, manic and hypomanic symptoms are probably underrecognized (8), patients are more likely to be hospitalized for depression than for mania (9), and, as stated previously, antidepressants are the second most commonly prescribed class of medication.

So common use of antidepressants like Prozac may have a special attraction in the American culture. Why is this so? The allusion (7) to Marxian assessments of psychiatric ideologies may be relevant here. The person whose work in the Marxian tradition most directly relates to issues of psychopharmacology and polypharmacy is Herbert Marcuse, however, not Fromm or Brown. Marcuse was a Marxist who developed a growing interest in Freud over time, and eventually Marcuse became identified with the “Freudian left” of the 1960s counterculture. While many of his ideas are abstruse and ridden with the intricacies of internal Marxist debates, some of Marcuse’s ideas provide other perspectives on cultural influences on American psychiatry.

Marcuse did not write specifically about pharmacotherapy, but his line of reasoning, expressed most clearly in his 1968 book One-Dimensional Man (10), can apply to concerns that are sometimes expressed about the common use of psychotropic medications. Marcuse begins with the basic Marxist concept of “alienation,” which refers to the idea that individuals in capitalist societies are alienated from each other and from themselves (due to their lack of control over the means of economic production and distribution, according to classical Marxist theory). Individuals do not feel “whole” or fulfilled in capitalist society. This alienation is reflected in the consumerization and the “reification” of life, which is promoted by capitalist society since consumer spending supports the capitalist order. Reification refers to the process whereby everything appears as “things,” as separate from oneself and alien to oneself. If one is alienated and unhappy,

* Kramer prefers to use the term “thymoleptic” to indicate that Prozac has effects on the personality beyond “antidepressant” effects. David Healy’s work, as discussed in Chapter 1, emphasizes the rather arbitrary nature of the assumption of specific “antidepressant” effects. While some persons think that the special effects of drugs like Prozac on personality, as opposed to the older tricyclic antidepressants, may have to do with the serotonin-specific effects of Prozac, I think the experience with special benefits with the newer serotonergic antidepressants mostly reflects the overall lower side-effect burden with these agents. Less ill people were able to take them and the effects on normal personality were observed. Had the tricyclic antidepressants been more tolerable, I believe that similar personality effects would have been observable.
then turning to a reified thing, a pill, would seem to be natural and consistent with the capitalist order of things. In this sense, taking psychotropic drugs would seem to support the social order.

Marcuse also argued that modern capitalist society manufactures desires so as to ensure sufficient consumer demand for its products. He detailed the extent to which commercials and advertisements are a ubiquitous part of modern American culture. The immense amount of money spent by the pharmaceutical industry on the marketing of psychotropic medications could be construed as consistent with Marcuse’s thesis.

Marcuse called this process of manufacturing desires and then satisfying them with specific products, while continuing the alienation that is inherent in capitalist society, “desublimation.” By using this phrase, Marcuse is playing on the Freudian concept of “sublimation,” the defense mechanism whereby raw instincts are expressed in culturally acceptable ways (thus, aggressive drives are expressed in sport). Marcuse argues that “postindustrial” capitalist society has converted sublimated drives back to their instinctual roots, but at the service of the capitalist order (thus, sexuality is expressed in advertisements for clothing).

One need not accept much of the Marxian ideology underlying some of these notions to take seriously part of Marcuse’s line of reasoning, which I am here applying to psychopharmacology. It is not just that capitalism rewards vitality and thus promotes the taking of antidepressant medications, but it may be that some of the unhappiness that persons in modern American culture experience has to do with the economic uncertainties of life, and that taking psychotropic medications is a culturally approved form of dealing with that unhappiness.

There are other more straightforward cross-cultural differences in the propensity to polypharmacy in psychiatry. I have discussed in some detail how polypharmacy in the United States has been influenced by many factors: in the nineteenth-century, it was prominent; it declined with the rise of scientific medicine; it has risen again in contemporary American psychiatry for a variety of medical, economic, and cultural reasons. In other cultures, polypharmacy is also prominent, though for different reasons.

In Asian cultures, for instance, pharmacology is more or less identified with polypharmacy. When a patient goes to the doctor, she expects to leave the office with not only one prescription, but three or four, preferably one being for a shot of some kind or other. Asian patients tend to take a “more-is-better” approach to medications. Further, herbal treatments in Asian culture are usually compounds of many active agents, polypharmacy in one treatment.

* Marcuse’s descriptive work on the commercialization of American society is supported by recent data, such as the Consumer Reports observation that “the average American is exposed to 247 commercial messages each day” (January 2001, p. 8).

† I am indebted to Ming Tsuang, M.D. (personal communication) and my father Kamal Ghaemi, M.D. (personal communication), for some of this information.
It is also notable that Middle Eastern culture, for one, is characterized by a high degree of somatization. Patients frequently are not able or willing to discuss mental symptoms in mental terms, and even diagnosed depression tends to be associated with more somatic symptoms than in the West.

Taken together, these anecdotal observations on Asian and Middle Eastern culture suggest that the lay public in these civilizations prefers polypharmacy and that it tends to prefer specific medications for symptoms, rather than the preference of Western medicine to avoid polypharmacy and to use medication for disease complexes rather than symptoms.

At one level, nineteenth-century Western medicine seems quite similar to the basic approaches taken today in Asia and the Middle East. And indeed, the Western lay public still has a tendency to use medications for symptoms, as can be seen with the large symptom-oriented over-the-counter and herbal/alternative drug sectors of the economy. So perhaps there are more cultural similarities than differences here. My own view is that the differences are less at the level of the culture of the lay public than at the level of the culture of mainstream medicine. In the West, the mainstream medical establishment has evolved along the lines promoted by Holmes and Osler, and it has, to some extent, modified the views of the lay public accordingly. In Asia, this medical evolution has not happened, for better or for worse.

In sum, the cultural aspects of polypharmacy are varied. I think the bulk of American medical and cultural history suggests that American culture is predominantly pragmatic and disposed toward polypharmacy. This natural inclination has been retarded by the evolution of twentieth-century scientific medicine, which has tended to limit polypharmacy, but has reasserted itself with the psychopharmacology revolution and the attendant changes in the practice of psychiatry. Making diagnoses has become more important and more central to modern psychiatry, with a frequent implication of a specific pharmacological treatment to follow. The recognition of diagnoses and treatments is partially influenced by economic and political factors. The pragmatic desire to help, and optimistic attitude toward action, has combined with these other factors to make psychiatrists and patients much more likely to use psychotropic medications than in the past. The question remains as to whether, or to what extent, polypharmacy in psychiatry is desirable, and I pick it up in the next chapter.

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It cannot be denied that we have learned more rapidly how to prevent than how to cure diseases, but with a definite outline of our ignorance we no longer live now in a fool’s paradise, and fondly imagine that in all cases we control the issues of life and death with our pills and potions (1).

William Osler

The widespread use of polypharmacy raises a clinically important question. Either the . . . negative judgments are not entirely valid, or else we are seeing incompetent pharmacotherapy practiced on an enormous world-wide scale (2).

If many cures are given, the disease is incurable (3).

Anton Chekhov

There has never been a book on polypharmacy in psychiatry. Perhaps the increasing relevance of polypharmacy in psychiatric practice tells us something about how far the field has come since the early days of psychopharmacology a half century ago. Are we going too far? Does the resurrection of polypharmacy in psychiatry mean that psychopharmacology has run amok? Have we gone from a period of too little use of psychotropic drugs to too much?*

* My colleague Ronald Steingard, M.D., a child psychiatrist, suggests that this is the case, especially in child psychiatry. He describes the field in the 1970s, when he trained, as too little oriented to using medications, and now he refers to himself as a “postmodern pediatric psychopharmacologist” to indicate his current reticence to overprescribe medications for children (personal communication).
In this book, I have tried to collect clinical and research information that can give some empirical perspective to why and when polypharmacy is used in contemporary psychiatry. I have also tried to provide some conceptual discussion of how we can think about the issue of polypharmacy in the larger context of the status of psychopharmacology in general psychiatry. By now, I would hope that readers would have enough of a sense of the empirical literature as well as the conceptual background to be able to make their own judgments about polypharmacy in psychiatry. Before proceeding to my views, I want to briefly assess the few psychiatric authors who specifically have written about this subject.

The earliest paper on polypharmacy in psychiatry that I identified on Medline search is from 1970, a fascinating study in which Sidney Merlis and colleagues examined the nature of polypharmacy in 500 psychiatric patients (4). They identified that 28% of 4820 patients treated at a state hospital were receiving two or more psychotropic medications. Five hundred from this group were randomly evaluated, divided into unequal male ($n = 125$) and female ($n = 375$) groups. This was an era in which chronically psychotic patients remained in the state hospital for decades, and thus it is notable that the average length of stay for this sample was 12 years for men and 16 years for women. Most of these patients likely would be diagnosed today with schizophrenia or a major mood disorder (bipolar disorder or severe recurrent unipolar depression). The researchers ensured that all patients had been on their current medications for at least 30 days to allow a minimal therapeutic trial, and they were followed for another 30 days. Blind raters assessed outcome using the Brief Psychiatric Rating Scale (BPRS). In a National Institute of Mental Health (NIMH)–funded methodology that today would not likely be accepted by most institutional review boards (IRBs), the researchers took one third of the sample off all active psychotropic medications and replaced them with placebos. A second third maintained one active psychotropic medication, and all other medications were replaced with placebo. The psychiatrists stopped what they considered to be the least helpful medications in the combinations used. The final third remained on their active treatments. This was essentially a randomized, double-blind, placebo-controlled, discontinuation study of polypharmacy in psychiatry—the only one of its kind, to my knowledge, in the psychiatric literature.

In the male sample, the two groups who were switched to placebo (and thus either off all psychotropic medications or only receiving one active psychotropic medication) improved at 30-day follow-up compared to the polypharmacy group: they had less interpersonal disturbance, depression, and psychomotor retardation scores on the BPRS. In the female sample, the group switched to only one active psychotropic medication did just as well as the polypharmacy group, but the group taken off all active treatments experienced more depression and psycho-
motor retardation. Unfortunately, the authors did not identify the specific medications used, although it is likely that most of the medications used were either antipsychotics or antidepressants. Since mood disorder is more common in women and schizophrenia is equally common in both genders, it is possible that more women received antidepressants for depression and more men received antipsychotics for schizophrenia.* If this were the case, the findings would make some sense, in that men with schizophrenia on fewer antipsychotic treatments would experience less depression and interpersonal/psychomotor withdrawal, which have been associated with conventional antipsychotics. Women with unipolar depression on fewer antidepressants, on the other hand, would be expected to relapse into depression.

The investigators seemed aware of these possibilities and highlighted a few aspects of polypharmacy that take us back to Osler and Holmes: “The present study demonstrates that polypharmacy, while at times satisfactory, is often inappropriate to the patient’s needs. The use of multiple drug therapy is based more on a clinical ‘feel’ than a scientific basis.” This was essentially Holmes’s point: polypharmacy based on clinical intuition is insufficient; there should be empirically justified research studies to support it. In this rather amazing study, the researchers were able to show, in a randomized, double-blind, placebo-controlled fashion, and regardless of the specific drug or diagnosis, that stopping polypharmacy in 1970 and replacing it with monotherapy led to better outcomes! It would be quite fascinating to see what a similar study would find today, but it would be unethical to conduct. The investigators continued: “Because we generally consider schizophrenia a wastebasket diagnosis—comprised of a number of syndromes of infinite variety—we attempt to deal with symptoms individually rather than the disease as a whole, thus polypharmacy.” This is Osler’s point: even if empirical studies of polypharmacy are conducted, polypharmacy is erroneous if it is based on treating multiple symptoms rather than focused on treating an overall syndrome. Syndromes are based on diseases, and appropriate treatment seeks to affect the underlying disease. Symptomatic treatments that focus on the many features of a syndrome will lead to polypharmacy and will not lead to long-term cure, as Osler highlights in the citation at the start of this chapter. In fact, Osler believed, most diseases can best be prevented, rather than cured. Psychiatry has moved toward syndrome-based diagnosis, partly as a result of the innovations of DSM-III, partly as a result of the FDA’s influence in requiring syndrome-based indications for treatment. Nonetheless, there is enough overlap among DSM syndromes, and enough comorbidity, that polypharmacy is frequently promoted by the current nosological schema. In fact, we are not yet near enough to

* The authors comment in the discussion that more women had affective disorders than men in the sample, although they do not provide the raw data.
Osler’s ideal level of knowledge to be able to effectively devise specific treatments for psychiatric diseases. The genetic revolution, as will be discussed below, may get us there.

Another aspect of polypharmacy in psychiatry that Merlis and colleagues (4) describe is also important:

The general concept of clinical therapeutics currently in vogue is the tendency to add a second drug to the treatment program in the face of unremitting symptoms instead of increasing the initial drug of choice to maximum potential. This in part can be justified by the clinician’s desire to avoid undue side effects by using two drugs in lesser amounts to reach a therapeutic response instead of one at a higher and therefore potentially dangerous level. There is as yet no firm evidence to support this contention. It may be that the use of combinations of psychoactive drugs in lower doses may produce more side effects than the use of one drug in higher doses.

This is a clinical point of some importance. As discussed in Chapter 3 the first step before one even considers polypharmacy should be to maximize the dose and duration of treatment with the first medication chosen. Then, in the case of depression, one might choose to switch to another antidepressant, and thus continue to avoid polypharmacy. Usually, if two full trials of an antidepressant are ineffective, then the combination of two treatments would make sense to most clinicians and researchers. In other words, if one wishes to take a strict and conservative approach, polypharmacy should be reserved for treatment-refractory patients. This important clinical point was raised rather clearly in 1970 by Merlis and colleagues (4).

Thus, a number of conclusions might be drawn about polypharmacy in psychiatry. First, as Holmes taught (see p. 30), combination treatments should be based on empirical evidence, as much as possible on controlled and randomized studies. This is now a rather straightforward point, but unfortunately the controlled empirical literature in psychiatry is quite limited for a number of economic and other factors, as reviewed in Chapter 1. Since most controlled clinical psychopharmacology studies are sponsored by the private pharmaceutical industry, they are directed towards the requirements placed by the federal government (mainly the FDA) on that industry. Because the FDA requires mostly monotherapy studies for drug registration, polypharmacy studies are uncommon in psychiatry. Thus, in making treatment decisions after initial monotherapy, psychiatrists are generally little better off than Holmes’s generation a century and a half ago.

Second, since most of the research literature pertains to polypharmacy, clinicians should use maximal doses and durations of single medications initially, before proceeding to combination treatments. In other words, polypharmacy should generally be synonymous with treatment resistance. Only refractory patients should receive polypharmacy. This does not necessarily mean that a minor-
ity of patients in general will require polypharmacy. This issue is disease-specific. In the case of bipolar disorder, only a third or less of patients respond to mood stabilizer monotherapy; thus, a majority of patients will be treated, and appropriately so, with polypharmacy (Chapter 2).

Third, as Osler emphasized, treatment should generally focus on syndromes, not symptoms, and wherever possible on prevention. Unfortunately, psychiatric syndromes overlap, comorbidity is frequent, and thus polypharmacy is still common. In some cases, however, a concerted effort to focus on treating syndromes rather than symptoms will avoid unnecessary polypharmacy. It should also be emphasized that psychiatric syndromes are defined and generally studied in adults between the ages of 18 and 65. Consequently, in those younger and older, both the syndromes are murkier and the available empirical database is more limited. Thus, in children and in the elderly, psychiatric diagnosis is less accurate and involves more controversy than in adults. Given Osler’s dictum, it is perhaps not surprising, then, that treatment decisions tend to be symptom oriented in these groups, leading to polypharmacy. As Salzman and colleagues showed in a somewhat depressing review of this topic (5), the average elderly patient treated in a hospital in 1981 (not a psychiatric unit) receives seven medications, and in 43% at least one psychotropic agent was in the mix. The use of antidepressants was not generally accompanied by a syndromic justification, nor were antidepressants adequately dosed to treat depression. Anxiolytics and neuroleptics were commonly used for agitation. The treatment of the elderly today is likely little different.

Thus, fourth, besides the general issues around polypharmacy in psychiatry, special problems exist in the treatment of children and the elderly, where we suffer from ignoring both medical traditions, which I called in Chapter 1 Holmes’s rule and Osler’s rules. We suffer from little empirical research on psychopharmacology in these groups and thus base treatment decisions on pure clinical intuition (breaking Holmes’s rule), and we do not have well-defined syndromes in these groups and base medication decisions on symptoms instead (breaking Osler’s rule). It is noteworthy that the circumvention of Osler’s rule also applies to adult conditions in which the syndromes or disease entities are not well delineated or are otherwise controversial. This may explain why personality disorders and posttraumatic stress disorder tend to be treated with polypharmacy geared toward relief of symptoms rather than syndromal response (Chapter 6).

In a 1980 review, Gardos et al. (2) provide a clinical philosophy for polypharmacy: “This review does not advocate the wholesale prescribing of many different psychotropic drugs. We do advocate, however, a flexible clinically oriented approach, where a trial-and-error pragmatic method of drug prescribing has to supersede dogmatic rules.” Readers will note the term “pragmatic” and perhaps relate it to the previous discussion of pragmatism as a philosophical approach that tends to increase the likelihood of polypharmacy. Is there any other
approach to psychopharmacology other than trial-and-error pragmatism? Sometimes, when patients bring up their concerns about the choice of medications seeming to be simply trial-and-error, I emphasize to them that I will try to make decisions, wherever possible, based on empirical research, the more controlled the better. But there are, no doubt, decision points at which trial-and-error is the only approach. As a researcher, when I reach such points, I think about ways studies can be done to answer those questions. In general, Gardos and colleagues are correct that at some point, psychopharmacological practice consists of trial-and-error, but one of the goals of psychopharmacology research should be to push those points and further and further down the treatment algorithms for the various psychiatric diagnoses. As each chapter in this book shows, trial-and-error from the start of a treatment for a specific condition is unnecessary and unscientific. And in some cases, a significant number of treatment decisions can be made based on empirical evidence. The need for trial-and-error pragmatism is less a philosophical value than a brute unfortunate fact.

If one views polypharmacy as most appropriate in treatment-refractory patients in psychiatry, one might wonder whether it might also be appropriate in the other extreme—those who are not ill with diagnosable psychiatric disorders, but who may benefit from psychotropic medications. These include those persons with unhappy lives due to certain personality traits who may benefit from serotonin-reuptake inhibitors (SRIs). Often such treatment is monotherapy, but sometimes it may involve polypharmacy. As discussed in Chapter 13, there are cultural components of polypharmacy that need to be kept in mind. In principle, if one is willing to allow for such uses of medical science as cosmetic surgery,* it indeed does not seem inherently wrong to use medications for mild mental symptoms that usually get treated with psychotherapy. However, as with cosmetic surgery, it is important to rule out diagnosable psychiatric illness, and I think the ability and willingness of the patient to pursue psychotherapy should be carefully explored. As noted previously, some aspects of what patients want is influenced by social and cultural factors, which perhaps themselves deserve to be discussed in a thoughtful form of psychotherapy, rather than simply accepted as valid. In any case, following Holmes’s dictum, any prescription for mild symptoms must be even milder in side effects and risks, and thus polypharmacy for the “worried well” should be infrequent, though not in principle invalid.

In those cases where polypharmacy is less justifiable—where it is not based on empirical studies, not limited to refractory patients, not associated with a syndromal focus of treatment—in those cases, one might ask what practical methods exist to reduce polypharmacy. As noted earlier, one study found that didactic courses in psychopharmacology given by a pharmacist with specialization in

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* Peter Kramer has made this comparison and called the psychiatric version “cosmetic psychopharmacology” (6).
psychiatry was helpful in reducing polypharmacy (7). In another study, computer-generated lists that highlight polypharmacy and report those situations to physicians resulted in a change in prescription in 25% of cases (while in the rest physicians maintained polypharmacy treatment for various reasons) (reviewed in Ref. 8). These measures, while appropriate for large medical centers, would not be able to influence the many physicians who practice in small groups or private offices, however. Even as far back as 1975, polypharmacy with psychotropics in nonpsychiatric patients (i.e., given by nonpsychiatrist physicians) was identifiable in about 20% of outpatient practices (9). This use is undoubtedly higher today, given the increased availability of new psychotropic medications over the last two decades.

To address this large group of practitioners, I believe the basic mechanism must be greater education. There need to be more books, articles, and conferences in which the benefits and drawbacks of polypharmacy are specifically discussed. I would hope that the pharmaceutical industry would be willing to sponsor many of these conferences, as the effective use of their medications, alone or in polypharmacy, ultimately is to their benefit, as well as to the benefit of patients.

I think that patients and their families, as well as clinicians, should lobby their elected representatives to influence the FDA laws so as to encourage research on combination treatments in psychiatry, rather than only monotherapy. There is no need for a twentieth study of a drug versus placebo in mania; we could use a second or third study of two mood stabilizers for refractory bipolar disorder. If the FDA includes polypharmacy studies as part of the registration process, the pharmaceutical industry will conduct them. Similarly, there is no scientific justification for the FDA’s insistence on parallel-design studies; crossover designs will provide empirical polypharmacy data that clinicians can use. The NIMH itself also should fund more clinical psychopharmacology research, especially in polypharmacy of treatment resistance, so that the current status quo of only FDA-oriented research changes. Research funding from private foundations should also be encouraged.

Sometimes polypharmacy results from sheer clinical laziness. It is worth mentioning this real, albeit somewhat embarrassing, problem. Hollister (10) commented briefly on this matter in 1975: “Combinations of psychopharmaceuticals are used far more often than experimental evidence or common sense dictates. Often awkward combinations of drugs arise because no one has taken time to evaluate the changing goals of treatment in a patient, but has simply added new drugs to old. Treatment with psychotherapeutic drugs requires thought, not reflexes.”

One would hope that today polypharmacy is more frequently based on empirical studies that support it in certain circumstances, but it likely is true that in many circumstances, especially community mental health settings where psychiatrists see many patients, a careful reexamination of cases as they are passed from
one psychiatrist to another may not occur. The influence of managed care in reducing the likelihood of continuity of care may also be contributing to unnecessary polypharmacy in this manner. It is important, though sometimes difficult to achieve, for each psychiatrist to reexamine the entire history, including diagnosis and all treatments, in every new patient transferred from another psychiatrist. It is all too common for old diagnoses to be continued and old treatments maintained on the basis of habit alone.

About 15 years ago, one investigator (8) suggested that polypharmacy was undergoing a major change:

The word 'polypharmacy'—an ill-defined pejorative term—will likely disappear from use, as attention shifts to the evaluation of specific drug-drug combinations. This attention shift represents a paradigm shift. The early literature shows that the first hope of elimination of multiple drug use lay in epidemiological surveys, detection methods, and to some extent, moral suasion. The focus is now narrowing on the specific biological effects of drugs. This re-focusing from broadly social to the narrowly biological, is in keeping with the Zeitgeist in Psychiatry, which is moving in the same direction.

As discussed in Chapter 1, and as is obvious throughout this book, neither the term polypharmacy nor the practice of it has declined. I think that now, almost a century and a half after Holmes's famous "all the worse for the fishes" speech, it is probably accurate to state that polypharmacy will never completely go away. It can only become more and more scientific, so that it is used more and more effectively to treat refractory diseases. As new and more effective medications are developed, and as our understanding of psychiatric disease entities advances, the proportion of practice that involves polypharmacy likely will decrease. But it will never go away entirely.

Culture also has its grip, which it will not let loose. To hope that more biological approaches to understanding psychiatry will reduce polypharmacy extensively is a false hope. The act of prescribing involves much more than biology, and those psychological and cultural factors will continue in some cases to promote polypharmacy. In recognizing those factors, psychiatrists will continue to need to be more than pure psychopharmacologists and use the full repertoire of psychotherapeutic skills in which they continue to be trained. Further, psychiatrists and patients need to be aware citizens and recognize the cultural and social factors that push and pull them in the maelstrom of decision making about psychiatric medications.

Criticisms of polypharmacy should not be mistaken to be, or provide cover for, more general criticisms of psychopharmacology. Frank Ayd made this point in a 1975 symposium (11):

Psychopharmaceuticals are hailed as blessings by those who see the good their proper use can accomplish. They are damned by those who fear the
evil they believe their intentional misuse may cause and by those who are horrified by the harmful consequences of injudicious prescription. Some of the latter group of individuals, among whom are physicians who should know better, would have all psychopharmaceuticals banned or at least have their use severely restricted.

And the problem is not as simple as general overuse of psychotropic medications leading to polypharmacy, as Dr. Irving Taylor (12) described at the same symposium. “Dr. Ayd and I also have seen the underuse, overuse, and other injudicious prescriptions of psychopharmaceuticals.”

In fact, to use bipolar disorder as the ideal example of the complexities of polypharmacy (Chapter 2), I believe that antidepressants are overused and mood stabilizers underused. Further, typical neuroleptics are probably still overused and atypical neuroleptics underused, especially for long-term treatment. Also, mood stabilizer monotherapy is effective in a minority of patients, making polypharmacy the rule, rather than the exception, and justifiably so. However, a type of polypharmacy that would make Oliver Wendell Holmes cringe appears to be the rule, breaking both Holmes’s and Osler’s rules. Psychiatrists tend to use antidepressants frequently, despite the incredible paucity of studies of antidepressants in bipolar disorder (breaking Holmes’s rule); even when they are studied, in general they are marginally effective and there is clear evidence of significant risks (with short-term mania and long-term mood destabilization). Psychiatrists also tend to get caught in the acute-treatment tail-chasing scenario: when the patient is depressed, they focus on antidepressants (often causing mania), and when the patient is manic, they focus on neuroleptics (often causing depression). They lose sight that the overall syndrome, the bipolar disorder, is the object of treatment (Osler’s rule) and mainly responds to mood stabilizers in the long run. Thus, while polypharmacy is necessary in treating bipolar disorder, it is an informed, scientific polypharmacy, observing Holmes’s and Osler’s rules, that we need.

To the extent that Osler’s rule is not followed because of the limitations of psychiatric nosology, we can be hopeful that the genetic revolution, following up on the psychopharmacology revolution that we have already witnessed, may provide a breakthrough. If genetic susceptibility to a psychiatric syndrome is able to be tracked to a few genes in at least a subgroup of persons, as with the apoE4 gene for Alzheimer’s disease (13), then the functions of those genes can be identified. Treatments can then be developed to target those functions or to target transcription or translation of those genes themselves (14). Potentially, these treatments could be as or more effective than our current best polypharmacy regimens, thus reducing the need for polypharmacy. Further, those genetic findings may translate into genetic or biological markers, which might increase the specificity of psychiatric diagnosis. Certain subgroups of patients with bipolar disorder, for instance, might be more confidently diagnosable with an associated biological
marker. The search for biological markers is an aspect of psychiatric nosology that has been part of the framework of validation of psychiatric diagnoses since 1970 (15). Yet it has been downplayed recently because of the lack of any consistent neurobiological data that correlate with clinical diagnoses (16). Genetic discoveries could change this suboptimal state of affairs. And if diagnoses become more solid, then treatment can with more justification be disease rather than symptom focused. It is hazardous to predict the future, but it is not improbable that if the genetic revolution produces on its promise as the psychopharmacology revolution has, then together they will completely remake the face of psychiatry.

In 1891, 30 years after he first stepped into that hall where he spoke to the Massachusetts Medical Society, an elderly Oliver Wendell Holmes commented on his earlier oration, which he had republished in a collection of his medical essays (17):

My attack on over-drugging brought out some hostile comments and treatment. . . . Some of my more lively remarks called out very sharp animadversion . . . (like) my statement of my belief that if a ship-load of miscellaneous drugs, with certain very important exceptions,—drugs, many of which were then often given needlessly and in excess, as then used “could be sunk to the bottom of the sea, it would be all the better for mankind and all the worse for the fishes.” This was too bad. The sentence was misquoted, quoted without its qualifying conditions, and frightened some of my worthy professional brethren as much as if I had told them to throw all physic to the dogs. But for the epigrammatic sting the sentiment would have been unnoticed as a harmless overstatement at the very worst. (original italics)

And later: “It is true that some suppose . . . that there may yet be discovered a specific for every disease. Let us not despair of the future, but let us be moderate in our expectations.”

The future has probably fared better than Holmes expected in 1891, partially because of the influence of his scientific caution on twentieth-century medicine. Polypharmacy lives on, but increasingly we can hope it will be a more and more scientific polypharmacy, more restricted in scope, more specific in effect, obeying the rules laid down by our two great medical forebears, and moderate in expectation.

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