The Use and Misuse of Psychiatric Drugs

An evidence-based critique

Joel Paris

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Contents

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An Evidence-Based Critique

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This book is dedicated to the students I have taught (and who have taught me) over the last four decades

Foreword

Forty years ago, whenever new drugs were introduced into medicine they created great excitement and were all the rage. Now, each new agent also creates great excitement but instead just calls the rage. This is especially true of drugs for mental disorders. The rage is directed at those who create new diagnostic groupings that just medicalise normal distress, researchers who distort their findings for every reason apart from wanting to disseminate good science, pharmaceutical companies for doing anything and everything to extend their sales, and doctors for being so gullible to believe the nonsense that is peddled to them by all these other agencies. Are all these claims true and, if they are, who can we believe? Well, you could make a start by reading this book. Dr Paris is not a psychopharmacologist, a creator of diagnoses, an employee of a drug company, or a simple prescriber. He is a sophisticated psychiatrist with many years of experience and an excellent knowledge base. This book represents a well balanced, sober account of a serious issue that affects almost all of us in one way or another. His language is carefully chosen, his research is impeccable and his conclusions based on evidence. We can all learn from sorry chapters in the history of medicine and unless we take corrective action it will not be long before they fill book after book. Patients, health professionals, service planners and drug companies could all gain from the lessons of this text, so please read on – and prepare to be surprised.

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Introduction

WHAT THIS BOOK IS ABOUT

Many books have been written about the use of drugs in psychiatry. Large specialized research texts have probed deeply into the latest scientific data. Smaller books, some of which fit into the pocket of a lab coat, have offered practical hints for daily practice. Most volumes proclaim received wisdoms, celebrating the modern age of neuroscience and chemical therapy. Yet quite a few books have been broadsides *against* drug therapy, based on the idea that psychopharmacology is either a scam, or a conspiracy against social deviance.

This book is different. It will neither celebrate nor attack psychopharmacology. Nor is it designed to be a clinical guide to practice. Instead, it focuses on the *use* and *misuse* of psychiatric drugs. Its thesis is that pharmacological agents are highly effective when used properly, but can do harm when given without sufficient evidence to patients who will not benefit from them. It will argue that while most drugs in psychiatry are valuable, they are being over-prescribed. It will also suggest that most patients do not need to be treated with multiple drugs. In summary, this book will be respectful to good practice, and critical of bad or unproven interventions.

One factor behind the misuse of drugs is that the science behind psychopharmacology has been over-sold. I am as impressed as anyone else by the advances in neuroscience in recent decades. As a student, I was fascinated with this area of research, which was one of the reasons I went into psychiatry. However, neuroscience has not yet explained very much about mental illness. And in spite of the many interesting theories about the relation of drugs to

neurotransmitters, we only have a general idea of how the agents we prescribe actually work.

The practice of psychopharmacology has outrun scientific data, and this book will criticize the “hype” that has come to afflict clinical work. The effectiveness of many drugs has been exaggerated through selective publication of clinical trials. The resulting excess of enthusiasm supports a serious over-prescription of drugs–both to adults and to children.

These problems relate to another theme of this book: how academic psychiatry (and academic medicine as a whole) has been corrupted by the pharmaceutical industry. In recent years, this issue has come to wide attention, both in the medical literature and the media. Senators and parliamentarians have raised public concern about how drugs are being developed and prescribed. While one can now read about these problems in the morning newspaper, there is little reason to believe that they are on the way to being solved.

To assess scientific support for the efficacy of psychiatric drugs, I have had to review an enormous literature. Many thousands of research papers have been published in the last 50 years. Yet only a minority of these studies meet the high standards of modern evidence-based medicine. I have therefore focused on data drawn from randomized controlled trials, sophisticated effectiveness studies, and meta-analyses. Inevitably, the reviews in this book will be selective. But they highlight unanswered questions about the efficacy of commonly prescribed agents.

This book will also look towards a future in which better, more specific psychiatric drugs will be developed. When the first drugs for cancer were developed fifty years ago, their effects were unpredictable, and many patients failed to respond to them. That is more or less where we are in psychiatry today. In future decades, we can hope to have as

precise a therapeutic armamentarium as most other medical specialists.

Drugs for the troubled mind have helped millions. But we must acknowledge their limitations and consider the alternatives. And that is why I have written this book.

FORCES DRIVING THE USE AND MISUSE OF DRUGS

Psychiatric drugs remain, in many respects, medical miracles. No physician could treat heart disease or cancer without modern drugs, and that is equally true for the treatment of severe mental illness. I am old enough to remember a time when psychiatrists did not have any effective drugs. Until researchers discovered pharmacotherapy for schizophrenia, bipolar disorder, and severe depression, we had little to offer patients with these diagnoses. In the course of my career, I have seen patients respond to drugs in dramatic and heartening ways. There can be little doubt that psychopharmacology has been a boon to humanity, leading to enormous progress in the treatment of disease.

But psychopharmacology is a victim of its own success. Psychiatric drugs are being over-prescribed, and applied to problems they cannot solve. Many of the agents we use today are highly effective–if prescribed in an *evidence-based* way, and given for precise indications. Unfortunately that is far from the case. Many current drugs are prescribed for *off-label* purposes, without research support for these indications.

Psychiatrists may think they know how psychiatric drugs work. The facts do not support that belief. The idea that mental disorders are the result of “chemical imbalances” in the brain (which drugs supposedly put back into balance) is

an over-simplified and misleading view of a complex problem. This theory is not just wrong. It leads to a more serious “imbalance”, in which clinical psychiatry has come to rely almost entirely on pharmacological treatment, to the exclusion of all other options.

For the most severely ill patients, psychiatric drugs have been a very good news story. The news has not been as good for patients with less severe symptoms. For common mental disorders, such as mild depression, drugs sometimes work, but sometimes do little more than a placebo. (As I will show, placebos do much more than most physicians think). The concept of “treatment-resistant depression” implies that all one needs to do is to prescribe the right drugs to treat complex cases. But that concept actually describes a potpourri of problems, some of which will respond to pharmacotherapy, and some of which will not.

Clinicians have been sold the myth of experts who know how to mix and match the right cocktail of medications, and that it is possible to make almost any patient better with an artful prescription. In fact, only a few drug combinations have been properly tested; the mixing of multiple agents is a largely unproven procedure. Intentions are good, but results are often bad. Practices that are not evidence-based can create more problems than they solve.

Naturally, the myth of the therapeutic cocktail has been actively encouraged by the pharmaceutical industry. These corporations earn billions from the prescription of psychiatric medications. Drug companies are not in business to promote health, but to maximize profits for their shareholders. Industry marketing is a powerful driver of prescribing practices. There is little doubt that pharmaceutical companies are misleading physicians (and patients) about the value of their products. But to be corrupted and fooled, you have to be willing. The responsibility for this situation lies squarely with

practitioners and with the academic leaders of psychiatry. It is up to clinicians and key opinion leaders in the field to resist these blandishments, and make decisions based on scientific evidence.

In the modern world, large numbers of people are taking (or have taken) antidepressants or some other psychoactive drug. And that is not only the case for consenting adults. Behaviorally disturbed children are now being given complex combinations of powerful drugs. I will criticize many of these practices, which are based on very little data and a great deal of “hype”. A commitment to evidence-based medicine should lead to a healthy skepticism about current practices.

While this book will be critical of the pharmaceutical industry, I fully recognize that innovative, life-saving drugs have come from that source. But these companies are not charitable organizations, and their marketing departments know how to get physicians to prescribe their products. Ultimately, the responsibility for avoiding treatments that are not evidence-based lies with practitioners.

All these problems can be placed in the larger context of medical philosophy. Physicians are trained to do their utmost for patients. This laudable goal makes us over-enthusiastic. In our zeal to cure disease, we lose sight of what drugs can and cannot do. We are too keen to treat the symptoms of mental illness, but do not understand enough about its causes.

By and large, those of us who chose psychiatry did so out of idealism. We were intensely curious about the mysteries of mental illness, and wanted to help suffering patients. But in recent years, psychiatrists have succumbed to the illusion that neuroscience can solve every problem. Treatment has vastly over-run the understanding of disease, and drugs have come to dominate management. When all one has is a hammer, everything looks like a nail.

Consumers also play a role in the misuse of drugs. Psychiatrists try to meet the perceived needs of those who seek their services. While some patients still seek psychotherapy, most now expect a prescription. As the internet makes information more readily available, some of our more sophisticated patients will request the latest drugs. This problem is not unique to psychiatry. For example, our colleagues in internal medicine tend to prescribe expensive drugs to manage hypertension, even though research shows that “golden oldies” (such as diuretics) do the job just as well. And many physicians give in to patient pressure by prescribing antibiotics for viral infections when they are not indicated.

Some psychiatric patients have an absolute need for pharmacological therapy. Yet many others do not benefit from *any* existing drugs. The underlying problem is that we do not always know what we are treating. Psychiatry is a long way from developing a scientific classification of mental illness. Diagnosis is rarely a specific guide to treatment. Ultimately, pharmacotherapy can be no more precise than our understanding of disease mechanisms. While this problem is not unique to psychiatry, we must acknowledge that our current level of knowledge leaves a great deal to be desired. In practice, we do not know who will respond to a given treatment. The result is that non-responders tend to be treated “aggressively”, leading to drug regimes that do not work and that carry a high burden of side effects. Mental illness is a complex challenge, not a simple problem in chemistry that pharmaceuticals can reverse.

Psychiatrists have been enticed and excited by a wish to cure mental illness, and by the temptation to prescribe “the latest thing”. Wise physicians have always known better. To quote an aphorism attributed to Hippocrates, our true role is “to cure sometimes, to relieve often, to comfort always”.

A NOTE ON NOMENCLATURE

Many psychiatric drugs are marketed using different names in the USA, Canada, UK, and on the European continent. While most practitioners refer to the drugs they prescribe by easy-to-remember trade names, this book will only use generic names.

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I was fortunate to have two highly knowledgeable readers, David Goldbloom and Edward Shorter, who carefully read drafts of this book and made many useful suggestions for improvement. Karl Looper and Roz Paris also helped me by reading sections of the manuscript.

This book is largely based on my experiences as a teacher of psychiatry. In a series of Journal Clubs and Evidence-Based Medicine Seminars, over the last 30 years, psychiatric residents have reviewed the literature with me. I need to acknowledge a great debt to my students – to whom this book is dedicated.

PART I

Overview

CHAPTER 1

The History of Psychopharmacology

Let us begin with a thought experiment. Imagine what it was like to treat mental illness 60 years ago. If psychiatrists in that time were honest, they would have had to admit they had few options for effective pharmacotherapy. Yet they might not have seen the situation in that light. Psychiatrists could not have known that better drugs would appear within a few years. They would concentrate on available options, and convince themselves that these agents were effective.

In 1950, if a patient was anxious or had insomnia, there were barbiturates. If a patient was depressed or complained of fatigue, there were amphetamines. These drugs, though now considered not effective, were very widely prescribed. Moreover, if patients had confidence in their physicians, whatever effects these agents had would be magnified by a placebo response.

Psychiatrists may well have thought they were helping most of their patients, and even congratulated themselves on being more advanced than their colleagues in 1890 would have been. Yet in retrospect, the only important biological therapy that has survived from 60 years ago is electroconvulsive therapy (ECT). Almost none of the other agents are prescribed for the same purposes today (although stimulants are now used to treat attention deficit hyperactivity disorder).

Now imagine the practice of psychiatry 60 years from now. Although we cannot know how much drug development will

advance, it seems likely that by 2070, much more effective agents will be available than those we have today. If so, future psychiatrists could be in a position to provide more consistently effective treatments for depression, anxiety, and psychosis. They will also probably classify these conditions in a different way, allowing them to predict treatment response from diagnosis. If future practitioners were to read about how psychiatry was practiced in the early part of the twenty-first century, they might feel just as sorry for us as we do for our predecessors from 1950.

The point is that every age retains the illusion that the tools at their disposal are effective. There is progress, but it is difficult at the time to realize the limitations of therapeutic options. Taking a historical perspective helps us to be humble about what we can and cannot do for patients.

Psychiatry has come far, but has very far to go. Developing a sense of humility about drug treatment will be the main theme of this book.

1.1 BEFORE THE REVOLUTION

Starting in the early 1950s, psychopharmacology was revolutionized. Like revolutions of all kinds, this is a story of triumph and hubris.

In the years following the Second World War, psychiatrists had few options for the effective treatment of severe mental illness. It is difficult for trainees or young psychiatrists today to imagine what psychiatric hospitals were like in those days.

I had the chance to see the problem in the late 1950s, when I was an undergraduate student in psychology at the University of Michigan. A group of us volunteered to spend weekends at the nearby Ypsilanti State Hospital, which housed over 4000 inpatients. We talked to patients, and learned a little more about them from the staff.

The wards of the hospital were full of seriously ill people who were receiving very little treatment. A stuporous catatonic stood motionless in the hallway. A paranoid schizophrenic sat in the corner writing endless notes about her delusions. A manic patient was confined to bed with cold packs. A young woman who had made a serious suicide attempt had just completed a course of ECT.

Psychotic (or severely depressed) patients could languish on wards for years – unless they were fortunate enough to go into spontaneous remission. There were few specific or effective biological treatments for them. If seriously agitated, they could be sedated with barbiturates or paraldehyde. Neuroleptics had been introduced only a few years before, and psychiatrists were just starting to use chlorpromazine in small doses.

The out-patient management of common mental disorders was equally limited. Depression and anxiety, the most frequent symptoms seen in practice, were not effectively managed with barbiturates and/or amphetamines (Shorter, 2009).

Only a few treatments from this time have survived. Insulin coma therapy had inconsistent results, and fell out of favor entirely after a controlled trial failed to demonstrate its efficacy (Ackner *et al.*, 1957). Prefrontal lobotomy, after being scandalously over-prescribed, vanished almost entirely (Valenstein, 1986). The most effective treatment in psychiatry 60 years ago was electroconvulsive therapy (ECT), which remains useful today. While ECT was over-prescribed in the past (for lack of alternatives), it is an evidence-based option that can pull patients out of psychotic depression, and provide short-term control of acute schizophrenia and mania (Shorter and Healy, 2007; Fink and Taylor, 2007).

In the absence of effective pharmacological treatment, psychotherapies held sway in certain settings, particularly

private hospitals and clinics. The most prominent and prestigious method of psychological treatment, usually provided in office practice, was psychoanalysis. Even then, it was widely known that psychoanalytic therapy was expensive and yielded inconsistent results (Paris, 2005). But this was the only way most clinicians knew how to talk to their patients. Alternative methods, such as cognitive behavioral therapy, had not yet been developed.

It should not therefore be surprising that many patients failed to respond to any form of treatment. In the face of intractable disease, almost anything was worth trying. At McGill University, where I work, a long-lasting scandal ensued when massive doses of ECT were given to patients with many different problems in an attempt to "depattern" them – with the idea of removing mental patterns and starting with a blank slate (Collins, 1988). This misadventure in therapeutics can only be understood in the context of the times, when alternatives were few and when rigorous empirical testing of new therapies had not yet become standard. A revolution in drug therapy was needed. And that is exactly what happened.

1.2 BREAKTHROUGH

One of my most admired teachers was a pioneer in the development of psychiatric drugs. Heinz Lehmann (1911–1999), a refugee from Germany who practiced psychiatry in Canada, always kept up with developments in Europe. That is why he became the first physician to introduce chlorpromazine and imipramine to North America.

A few years before his death, Lehmann (1993) wrote an article entitled "*Before they called it psychopharmacology*." Lehmann observed that the field was created from scratch over a relatively brief period. Developments then moved so rapidly that they came to be called the

“psychopharmacological revolution.” In the 1950s and 1960s, a remarkable series of dramatic breakthroughs occurred.

This was an age of heroic pioneers (Healy, 1998). While madness has always been with us, the discovery of the first effective drugs to treat psychosis has been described as a turning point in human history (Healy, 2008). The introduction of effective antidepressants may have been less dramatic, but there is little doubt that these drugs have helped millions. Within a few years, clinicians obtained access to a whole range of agents that could control most of the major symptoms that psychiatrists treat.

In 1952, the first-generation antipsychotics (FGAs) were introduced (Delay, Deniker and Harl, 1952). Two French psychiatrists, Jean Delay (1907–1987) and Pierre Deniker (1917–1998), studied chlorpromazine, a phenothiazine (chemically an antihistamine variant) that had been developed for anesthesia. Delay and Deniker made the discovery that chlorpromazine was specifically effective for psychotic symptoms. Two years later, in North America, Lehmann and Hanrahan (1954) confirmed its efficacy in schizophrenia.

Within a few years, FGAs dominated the treatment of psychosis. There were various phenothiazines – aliphatics, piperazines, and piperidines – but all had similar effects. One problem was that emergency treatment required a highly potent drug. That was the advantage of haloperidol, which belongs to a different chemical group (the butyrophenones). Haloperidol was used routinely for several decades as the mainstay of management for psychosis. But this agent came with a high risk for neurological side effects. And many patients found these effects sufficiently troubling that they were non-compliant.

The second breakthrough was the development of effective antidepressants. The first group to be introduced

was monoamine oxidase inhibitors (MAOIs). These drugs, developed to treat tuberculosis, turned out to have more dramatic effects on mood. However MAOIs have many problematic side effects, and some have since been withdrawn (Healy, 2008). Today they are rarely used for first-line therapy.

The second group of antidepressants had a more enduring impact. The tricyclics (another chemical variant of antihistamines) remain an important (but currently less often used) part of our armamentarium.

The Swiss psychiatrist Roland Kuhn (1912–2005) was the first to report on the effectiveness of imipramine (Kuhn, 1958). This agent was (and is) particularly useful for severe depression. Chapter 6 will examine whether it has been superceded by any of the alternatives introduced since. Within a few years after its introduction, imipramine (and several other tricylics) were very widely prescribed, leading to a decline in the use of ECT (Shorter and Healy, 2007).

The third major development of the 1950s was the introduction of anxiolytics (originally called “tranquilizers”). The first agent to be introduced, meprobamate, was widely prescribed for a number of years, but fell out of favor. This was partly out of concern about side effects, but mainly because it was replaced by the benzodiazepines (Shorter, 2009; Tone, 2008).

Like many other drugs in medicine, “benzos” are derived from chemical dyes. A pharmacologist, Leo Sternbach (1908–2005) noticed that these molecules made him drowsy, and went on to develop both chlordiazepoxide and diazepam. These drugs (and their variants) continue to be in standard use today.

Another major breakthrough of the psychopharmacological revolution took place some years later – in the late 1960s, when lithium was introduced for the treatment of mania. An Australian psychiatrist, John Cade (1912–1980), made the

first observations on the effectiveness of lithium (Cade, 1949). However concern about side effects on the heart discouraged its wider use. Lithium was rediscovered and systematically investigated by the Danish psychiatrist Mogens Schou (1918–2005). This research (Baastrup and Schou, 1967) led to its wide use, both for acute mania and for the prevention of relapse in both phases of bipolar disorder.

Thus by 1970, psychiatrists could choose from a pharmacological armamentarium that included antipsychotics, antidepressants, anxiolytics, and antimanics. That toolbox (along with ECT) was almost as good as what we have 40 years later. With a few modern additions, these groups of drugs are the backbone of management for most severe mental disorders today.

In the modern world, we tend to assume that progress is inevitable, and that one breakthrough will inevitably follow another. In the age of neuroscience, research on the brain has been expected to produce rapid and dramatic progress that can be applied to clinical problems. Many of us have come to believe that when it comes to drugs, newer is better.

In fact, psychopharmacology is not much more effective than it was in 1970. New drugs have been introduced with fewer (or different) side effects. But we are not doing that much more for patients. We are much like internists who treat hypertension with expensive ACE inhibitors instead of diuretics. Psychiatry can be practiced effectively using drugs that were available 40 years ago.

Moreover, drug development has been more the result of luck than of planning (Healy, 2002). Phenothiazines were originally introduced for sedation, and their antipsychotic effects came as a surprise. Tricyclics are chemically similar to phenothiazines, and were originally thought to have the same indications – their efficacy in depression came as

another surprise. Lithium, originally developed as a cardiac drug, turned out to have much more useful antimanic effects.

Moreover, breakthroughs mostly arose from careful clinical observation. The effectiveness of new drugs was only confirmed later by randomized controlled trials. This was an era when formal research in medical science was relatively undeveloped. While standards for evidence-base medicine were primitive, talented psychiatrists who were willing to try out new agents could make a real mark on their field.

Moreover, pharmacological treatments for mental illness revolutionized practice. Within a few years, older drugs were forgotten, and resistance from older clinicians melted away. A large body of research confirmed that there was no substitute for the new drugs. For example, neuroleptics were definitively shown by a controlled trial to be superior to either talking therapies or ECT in schizophrenia (May, 1968). Tricyclics were found to be superior to either cognitive or interpersonal psychotherapy for severe depression (Elkin *et al.*, 1989). Lithium was (and remains) superior to any alternative for preventing relapse of bipolar disorder (Goodwin and Jamieson, 2007).

It became widely accepted in psychiatry that patients with mental illness usually need drugs. Expertise in prescription became central to the identity of psychiatrists (Paris, 2008a). In the USA, a failure to prescribe antidepressants for severe depressive illness (in a patient named Raphael Osheroff, himself a physician) became the basis of a famous lawsuit (Klerman, 1990). After the Osheroff case, fewer psychiatrists were willing to treat depression with talking therapy alone.

The period from 1952 to 1970 was the golden age of psychopharmacology, a time of continuous triumph for psychiatric drugs. Mental hospitals emptied out and closed entirely – largely due to drug therapy (but also to better