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 tricyclics) 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 community psychiatry). Ypsilanti State, the enormous hospital that I had visited in 1958, closed in 1992, and has since been demolished.

### 1.3 AFTER THE REVOLUTION

Revolutions tend to be followed by periods of consolidation. Over the last 40 years, no change of the same magnitude occurred in psychopharmacology. Instead, atypical (second-generation) antipsychotics replaced typicals, specific serotonin reuptake inhibitors replaced tricyclics, and anticonvulsant mood stabilizers partially replaced lithium. While we now had more alternatives, the newer drugs were not always better than older ones (which younger psychiatrists no longer knew how to use). The main advantage was that some of the newer agents (e.g., SSRIs) had fewer side effects than their predecessors and required less careful titration of dose.

For these reasons non-psychiatric physicians became more comfortable with prescribing these agents. Thus, drugs to treat mental symptoms became ubiquitous in general medicine. Today, primary care physicians (and psychologists) treat most patients with less severe mental disorders, while specialists in psychiatry tend to see treatment-resistant cases.
Another caveat about the triumph of psychopharmacology is that in spite of a greater ability to control symptoms, psychiatrists have not been able to cure most of the conditions they treat. There is a big difference between symptomatic improvement and full remission.

For example, in spite of the efficacy of neuroleptics for acute psychotic symptoms, schizophrenia remains a chronic and disabling disease. And in spite of the efficacy of lithium for acute manic symptoms and for prevention of relapses, bipolar disorder remains a serious clinical problem, for which no definitive therapy has emerged. Finally, in spite of the efficacy of antidepressants, many depressions remain treatment-resistant and/or chronic (Fava and Rush, 2006).

In summary, after a period of breakthrough and revolution, progress in the pharmacological treatment of mental illness has been quite slow. The amount and quality of research has greatly increased, and there is little doubt that we know more about how the brain works. However, there is no reason to believe treatment has advanced since the 1970s. In the last decade or so, no drugs have been introduced that even remotely constitute a therapeutic breakthrough.

Even so, there has been a good deal of “hype” around newer drugs. That is mainly due to aggressive industry marketing, as well as the assumption that whatever is newer must be better. In reality, the golden age is behind us. By a combination of brilliance and luck, researchers found ways to manage patients for whom no useful treatment had been available. The last 40 years have been more of a slog than a breakthrough.

We could be lucky again. But I am inclined to believe that future progress in psychopharmacology needs to wait for a better understanding of the causes of mental illness. We still do not know why patients develop schizophrenia, mania, or depression, or whether these conditions need to be classified in a new way (Tyrer and Kendall, 2009). We also do not know how the drugs we are currently using actually work.

The good news is, as the next chapter will show, that we now apply much higher standards for the assessment of new drugs. It is no longer sufficient to try out an agent on 10 or 20 patients and observe results. We have entered an era of evidence-based psychiatry. In the long run, drug treatment is bound to benefit from a scientific approach.