PSYCHOTROPIC MEDICATIONS, HEALTH HAZARDS AND RISKS

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Contents

Summary

This chapter provides a review of antipsychotics, benzodiazepines, antidepressants, and mood stabilizers. Each review provides the following information about the medications:

- A brief history of their discovery
- Their mechanism of action
- Evidence of efficacy
- Effect on long-term outcomes

- Hazards and risks

This chapter also includes a review of risks associated with use of psychiatric medications in pediatric populations.

1. A Paradigm for Understanding Psychiatric Drugs

The modern era of psychiatry began with the introduction of chlorpromazine into asylum medicine in the early 1950s. This drug is remembered as the first antipsychotic. Shortly after that, anti-anxiety drugs and antidepressants were developed, and collectively these agents are said to have kicked off a "psychopharmacological revolution" in the treatment of mental disorders.

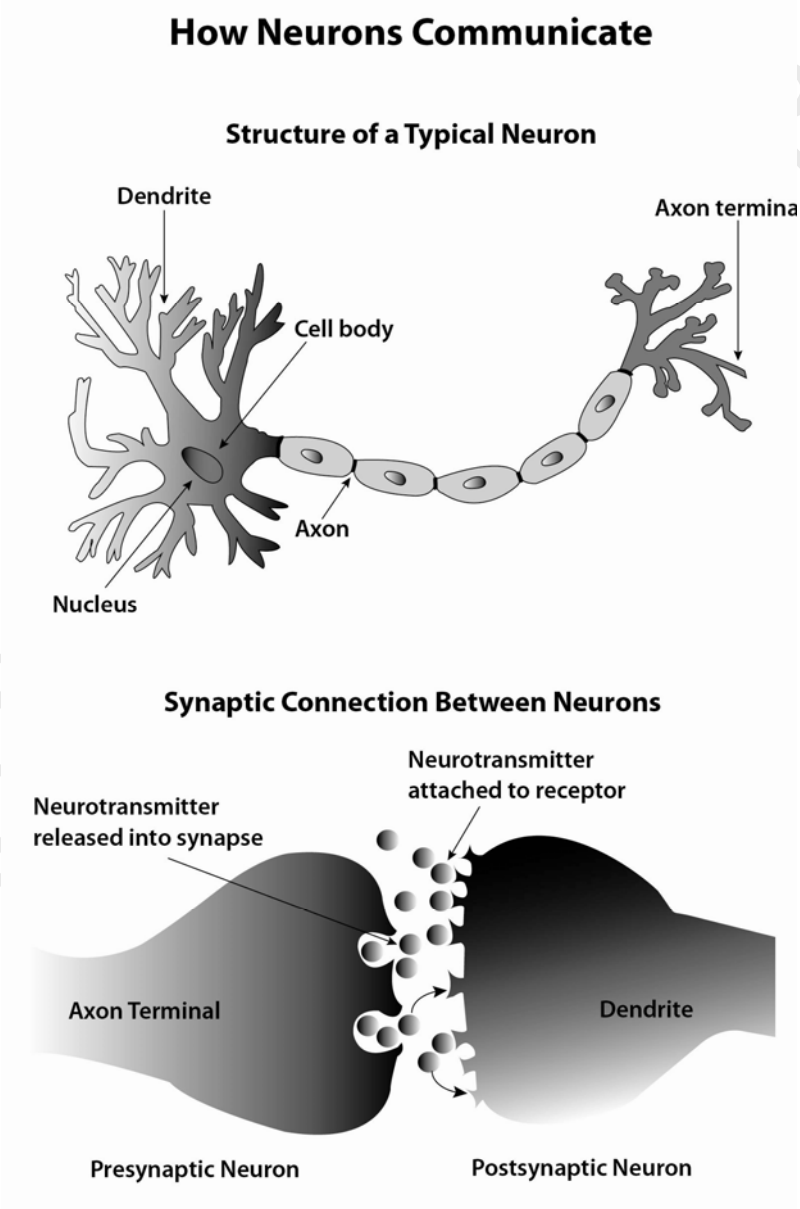

Figure 1. The Disabled Mentally Ill in the Prozac Era

The first of the second-generation psychiatric medications, fluoxetine, arrived on the market in the late 1980s. Since then, societal use of psychiatric medications, both in the United States and globally, has dramatically increased. In 1985, U.S. spending on antidepressants and antipsychotics totaled around $500 million; in 2010, U.S. spending on these two classes of psychiatric medications totaled $28.7 billion. Global spending on psychiatric drugs topped $65 billion in 2010. Despite the widespread use of these agents, the global burden of mental illness has not lessened during the past 30 years. In the U.S., the number of adults on government disability due to mental illness rose from 1.25 million in 1987 to 4 million in 2007.

Numerous other countries—Canada, Iceland, the United Kingdom, Australia, and New Zealand, to name a few—have similarly reported a sharp rise in the number of adults on disability due to mental illness. The World Health Organization estimates that mental disorders will account for 15% of the "global disease burden" in 2020, up from 9.7% in 1999.

To understand how psychiatric drugs work, it is necessary to first review how neurons communicate (See Figure 1). The cell body of a "typical" neuron receives input from a vast web of filaments called dendrites, and it sends out a signal via a single axon. At its end, an axon branches into numerous terminals, and it is from these terminals that chemical messengers—dopamine, serotonin, etc.—are released into the synaptic cleft, which is a tiny gap between neurons about twenty nanometers wide (a nanometer is one-billionth of a meter.) The chemical messenger then binds with receptors—much like a key fits into a lock—on the cell surface of a second neuron, which is called the postsynaptic neuron. This binding process may excite the postsynaptic neuron and cause it to fire, or it may inhibit it from firing.

After this binding process has occurred, the neurotransmitter must be removed from the synaptic cleft so that the "message" can be crisply terminated. This is done in one of two ways. Either the neurotransmitter is taken back up by the presynaptic neuron and stored for re-use, or an enzyme metabolizes the neurotransmitter and the metabolites are carted off as waste.

Psychiatric medications work by perturbing this messaging process in one manner or another. A drug may block receptors, thereby putting a brake on neuronal activity. A drug may block the removal of the neurotransmitter from the synaptic cleft, thereby accelerating the transmission of messages. There are several other ways that a drug may alter this messaging process, but the usual result is that the drug either puts a brake on the transmission of messages, or it accelerates that process.

In response to this perturbation, the brain undergoes a series of compensatory adaptations. For instance, if a drug blocks the transmission of messages, the brain will compensate by trying to increase that activity. The presynaptic neurons will release more of the chemical messenger and the post-synaptic neurons will increase the density of their receptors for that neurotransmitter. Conversely, if a drug accelerates the transmission of messages, the brain will compensate by trying to put on the brake. The presynaptic neurons will release less of the chemical messenger and the post-synaptic neurons will decrease the density of their receptors for that neurotransmitter. In this

manner, the brain tries to maintain a homeostatic equilibrium (and thus the normal functioning of its neuronal pathways.)

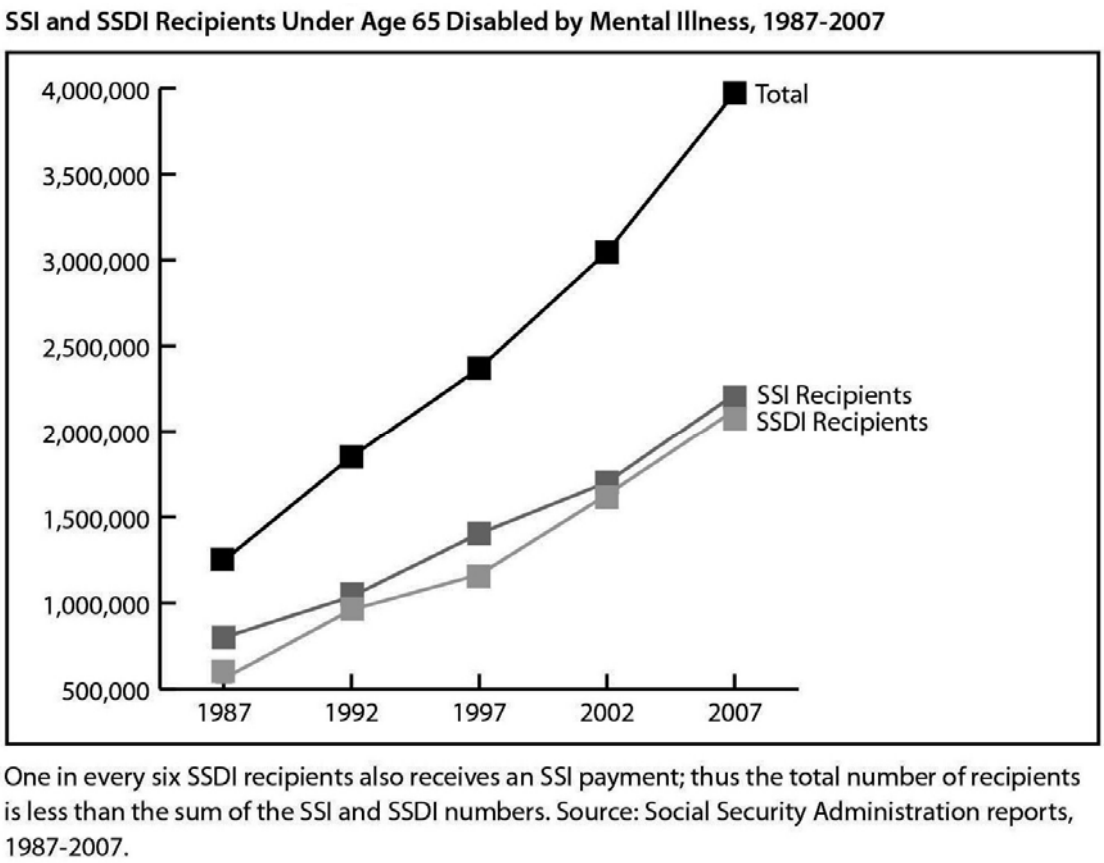

Figure 2. Communication between neurons

However, after a few weeks of drug exposure, these compensatory processes begin to break down, and when this happens, the brain is unable to maintain neurotransmitter activity within pre-existing homeostatic parameters. The "chronic administration" of the drug, explained neuroscientist Steve Hyman in a 1996 paper, causes "substantial and long-lasting alterations in neural function." When this occurs, the brain can be said to be operating in a manner that is "qualitatively as well as quantitatively different from the normal state." (Hyman 1996)

In short, a psychiatric drug perturbs a neurotransmitter system, which triggers a long-lasting change in how neuronal pathways operate. The hope is that this modification of brain function produces a therapeutic effect, both short term and long term.

2. Antipsychotics.

2.1. History of Discovery

The discovery of chlorpromazine as a treatment for psychosis occurred in a serendipitous way. In the 1940s, researchers at a French firm, Rhône-Poulenc, while looking for drugs that might be effective against the microbes that cause malaria and

worm-borne illnesses, synthesized a compound, promethazine, that proved to have antihistaminic properties. This suggested it might be useful in surgery to protect against a precipitous drop in blood pressure. In 1949, a French surgeon, Henri Laborit, tested it for that purpose, and he found that it numbed his patients to physical pain and thus might be useful as an anesthetic. Rhône-Poulenc quickly synthesized a new compound, chlorpromazine, that was more potent in this regard. After testing chlorpromazine, Laborit, while speaking at an anesthesiology conference in Brussels, observed that it quieted his surgical patients and made them emotionally detached. Chlorpromazine "produced a veritable medicinal lobotomy," he said.

At that time, surgical lobotomy, which involved destroying the frontal lobes of the brain, was seen as a helpful procedure for psychotic patients. Lobotomy was known to make people lethargic and disinterested in their surroundings, and this change was judged to be beneficial to asylum patients who were anxious, agitated, and filled with disturbing thoughts. Laborit's observation suggested that a pill had been discovered that could transform patients in a similar way. In 1952, two French psychiatrists, Jean Delay and Pierre Deniker, reported that it indeed made asylum patients quieter and easier to manage. They dubbed chlorpromazine a "neuroleptic," meaning that it took hold of the nervous system.

The use of chlorpromazine spread quickly to hospitals throughout Europe and to the United States. Psychiatrists in the U.S. called it a "major tranquilizer."

2.2. Mechanism of Action

In the 1960s and 1970s, researchers discovered that chlorpromazine and other first-generation antipsychotics block dopamine receptors in the brain. In particular, they block a subtype known as the D_2 receptor. At a therapeutic dose, chlorpromazine, haloperidol and other first-generation antipsychotics block 70% to 90% of the D_2 receptors.

This blockade hinders the transmission of messages along the three major dopaminergic pathways in the brain, which extend to the basal ganglia, the limbic system, and the frontal lobes. The basal ganglia initiates and controls movement, while the limbic structures help regulate emotion. The human capacity for self-consciousness arises from the frontal lobes.

The brain responds to this blockade of D_2 receptors in two ways. The presynaptic neurons release more dopamine into the synaptic cleft, while the postsynaptic neurons increase the density of their dopamine receptors. The first of these two compensatory responses—the release of additional dopamine—may last for only a few weeks, and then the presynaptic neurons may begin firing in an irregular manner.

In the late 1980s, the first atypical antipsychotic, clozapine, arrived on the U.S. market. It was said to be "atypical" because it didn't block D_2 receptors with the same potency as the first-generation antipsychotics, but rather was a broad-acting drug that blocked receptors for numerous neurotransmitters. Soon other atypical antipsychotics—risperidone, olanzapine, quetiapine and others—were brought to market. In addition to

binding with dopaminergic receptors, these drugs may interact with serotonergic, histaminergic, adrenergic, and muscarinic receptors. For the most part, atypicals thwart the passage of messages along these various neuronal pathways, triggering numerous compensatory adaptations in the brain.

2.3. Efficacy

In short-term trials, antipsychotics reduce psychotic symptoms, as measured by the Brief Psychiatric Rating Scale, better than placebo. In a 1977 review, Baldessarini determined that the first-generation antipsychotics proved superior to placebo in 83% of the trials. (Baldessarini 1977)

However, many patients fail to respond to the medication in a robust way. In a review of the trials of the atypical antipsychotics, Leucht concluded that 41% of the drug-treated patients had a clinically significant response to the drug, versus 24% of the placebo group. (Leucht 2009)

To investigate how long schizophrenia patients should stay on antipsychotics, researchers conducted drug-withdrawal studies. In a 1995 meta-analysis of this literature, Gilbert determined that in 66 trials, involving 4,365 patients, 53% of the drug-withdrawn patients relapsed within ten months versus 16% of those maintained on an antipsychotic. This is the evidence that supports the long-term use of antipsychotics. (Gilbert 1995)

There are three notable limitations to the relapse studies. One, the studies were mostly conducted in schizophrenia patients who had stabilized well on an antipsychotic, and thus the results don't reflect the long-term relapse rates for all drug-maintained patients with that diagnosis. If the poor responders to antipsychotics were included in those studies, the reported relapse rate for drug-maintained patients would be much higher. Two, in most of the studies, the antipsychotic was abruptly withdrawn, which increases the risk of relapse, and thus the relapse studies don't provide a good measure of the frequency of relapse in never-medicated patients (or patients gradually withdrawn from the drug.) Three, the relapse studies do not provide information about how well drug-maintained patients function over the long-term.

2.4. First-generation Versus Second-generation Antipsychotics

When risperidone, olanzapine, and other second-generation antipsychotics were brought to market in the 1990s, there were claims, based on results from industry-funded trials, that these newer drugs were superior to the first-generation agents. However, government-funded studies did not find that to be the case.

In 2005, the U.S. National Institute of Mental Health's CATIE Trial determined that there were "no significant differences" between the newer atypicals and a first-generation antipsychotic. Seventy-four percent of the 1,432 patients were unable to stay on the medications, mostly because of their "inefficacy or intolerable side effects," and this percentage was the same for both the newer and older agents. (Lieberman 2005)

A study by the U.S. Department of Veterans Affairs came to a similar conclusion about the relative merits of the atypical olanzapine and the first-generation antipsychotics. (Rosenheck 2003) Then, in 2007, British investigators reported that schizophrenia patients, if anything, had a better "quality of life" on the old drugs than on the new ones. (Davies 2007)

The second-generation antipsychotics do have a different side-effect profile than the first-generation drugs. The second-generation antipsychotics may cause fewer extrapyramidal symptoms, but induce more metabolic problems. However, the government-funded trials did not find evidence that the second-generation medications were superior to the older ones in terms of their overall efficacy and tolerability.

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Biographical Sketch

Robert Whitaker is an American journalist who specializes in writing about science and medicine. He has written two books on the history of psychiatry and psychiatric medications. His first, Mad *in America: Bad Science, Bad Medicine and the Enduring Mistreatment of the Mentally Ill,* was published in 2002. His second, *Anatomy of an Epidemic: Magic Bullets, Psychiatric Drugs, and the Astonishing Rise of Mental Illness in America,* won the Investigative Reporters and Editors book award for best investigative journalism in 2010**.** Prior to writing books, Robert Whitaker worked as the science and medical reporter at the *Albany Times Union* newspaper in New York for a number of years. His journalism articles won several national awards, including a George Polk award for medical writing, and a National Association of Science Writers' award for best magazine article. A series he co-wrote for *The Boston Globe* was named a finalist for the Pulitzer Prize in 1998.