CHAPTER FOUR

Psychopharmacology

If you talk to God, it is called praying. If God talks to you, you have schizophrenia.
(Thomas Szasz, author of *The Myth of Mental Illness (1961).*)

Psychopharmacology is the study of the effects of drugs on the nervous system and behavior. Drugs are chemicals not necessary for normal cellular function that are exogenous (not manufactured within the body). Neuropsychology is concerned with those classes of drugs that affect behavior. These include: (a) legal recreational drugs like caffeine, alcohol, and nicotine; (b) illegal recreational drugs like marijuana, cocaine, methamphetamine, ecstasy, heroin, and ketamine; and (c) prescription drugs like anti-depressants (e.g., effexor, prozac, paxil), mood-stabilizers (e.g., depakote), anti-anxiety agents (e.g., buspar; valium; xanax), neuroleptics (e.g., haldol; risperdal), anti-convulsants (e.g., dilantin; tegretol), barbiturates (e.g., barbital; phenobarbital), amphetamines (e.g., adderall; ritalin), and narcotic analgesics (e.g., morphine; oxycodone). These drugs are often collectively called *psychoactive* drugs.

Psychoactive drugs alter the transmission of messages between cells by affecting chemical signaling within the brain. To get to the brain, drugs must be absorbed and distributed within the body through the blood stream. Different routes of drug ingestion mean a drug can enter the blood stream more quickly with more potent behavioral effects (an effect well known to drug addicts). The differing routes of drug ingestion include: (a) intravenous (IV): injection into the blood stream is the fastest way, but the entire dose reaches the brain at once and this may prove dangerous with drugs that have adverse side effects; (b) inhalation: this allows drugs to rapidly enter the bloodstream via the respiratory track; and (c) oral: the drug is absorbed through the lining of the stomach or small intestine and then enters the blood stream. As a general rule, about 10 times an inhaled dosage is needed to be taken orally to give the same behavioral effect.

Blood-Brain Barrier

Within the brain astrocytes stimulate cells in the blood vessels to form tight junctions in the blood vessel walls that are smaller than exist within the peripheral nervous system. This prevents many chemical molecules from exiting the blood stream and entering the brain and is known as the *blood-brain barrier.* It serves to protect the brain from toxic and infectious organisms in the blood stream. Substances that have very small molecules and/or are fat soluble can pass through the blood-brain barrier. This includes prescription psychoactive medications like anti-depressants, recreational drugs like alcohol and cocaine, and some hormones. Some larger molecules that the brain needs, (e.g., glucose) are ferried across the blood-brain barrier by transporter proteins that are located in the walls of the blood vessels in the brain and can pull the desired molecule from the blood into the brain. Many potential drug treatments for brain disorders are rendered ineffective as the molecules of the drug cannot pass the blood-brain barrier.

There are three parts of the brain where the blood-brain barrier is absent: (a) the pineal gland; (b) the pituitary gland; and (c) the area postrema at the base of the brain stem in the medulla. The first two

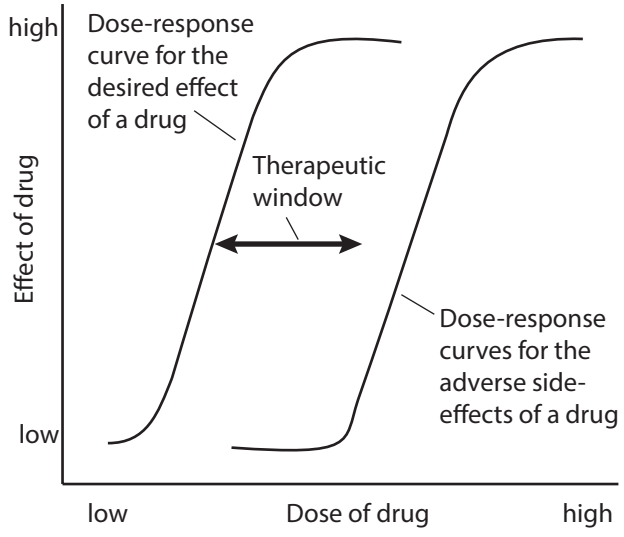
structures are part of the endocrine system and have no barrier to allow the easy passage of hormones. Area postrema allows for toxic substances to trigger a vomiting response.

Drugs do not remain in the body indefinitely. The liver is especially active in breaking down drugs, but the kidneys and intestines also contribute to this task. Drugs are excreted in urine, feces, sweat, and exhaled air.

Dose-Response Curves

The dosage of a drug is typically positively correlated with its effect on behavior up to an asymptote of maximum behavioral effect. Figure 4.1 shows two hypothetical dose-response curves for morphine, one for its analgesic effects and one for the adverse depressive respiratory side effects. The range of dosages over which a drug is effective in altering the target behavior (in this case reducing the perception of pain) is known as the *therapeutic window.* Increasing the dosage beyond the therapeutic window does not have any further analgesic effect on behavior and it is unsafe. The *margin of safety* between the two dose-response curves shows the range of dosages for morphine that can be safely prescribed without the adverse side effect depressing heart rate and respiration possibly leading to fatality. For some drugs (such as lithium that is used in the treatment of bipolar disorder) there is a very small margin of safety between the therapeutic window and dosages that led to toxic effects.

FIGURE 4.1 Hypothetical dose-response curves for the analgesic and respiration depressing side effect of morphine



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Drug Tolerance and Withdrawal Effects

Repeated consumption of a drug over time will often result in a reduction in its behavioral effect. In other words, higher and higher dosages of the drug are needed to produce the same behavioral effect, a phenomenon known as *tolerance*. Tolerance occurs because the brain recognizes that the drug is a foreign substance and produces its own chemicals to try and counteract the effect of the drug (Hyman & Nestler, 1996).

Abruptly stopping psychoactive drugs that cause tolerance often result in *withdrawal effects*. These effects are the opposite of the typical behavioral effects of the drug. For example, heroin has a positive effect on a person's psyche by producing euphoria, whereas withdrawal effects have a negative, dysphoric influence. When a drug is abruptly discontinued the chemicals that the brain was producing to counteract its effect are suddenly acting unopposed.

The Site of Drug Action: The Synapse

Drugs that affect behavior do so by affecting synaptic transmission. Drugs are either: (a) *agonists* that facilitate neurotransmitter effects; or (b) *antagonists* that inhibit neurotransmitter effects. Do not confuse the facilitatory and inhibitory effects of drugs with the excitatory and inhibitory effects of ion movement across the membrane. These occur independently of each other. For example, a drug might act as agonist (facilitator) for a neurotransmitter that has an inhibitory effect on action potential generation (by binding with receptor sites in Cl^- ion channels).

Drugs that act as agonists and antagonists for neurotransmitters do so in different ways depending upon what stage in the life of a neurotransmitter they impact. There are six different stages in the life of a neurotransmitter: (a) synthesis; (b) storage in synaptic vesicles; (c) release into the synapse (sometimes called exocytosis); (d) modulation of amount via autoreceptors; (e) binding with postsynaptic ion channels via direct or indirect mechanisms; and (f) deactivation. Deactivation is an active process whereby the neuron tries to recover unbound neurotransmitter molecules after their release. For acetylcholine, deactivation involves a chemical process whereby the molecules of the neurotransmitter are broken down into acetyl and choline. Deactivation keeps neurotransmitter effects specific. A psychoactive drug can serve as either an agonist or an antagonist at each of these stages with the exception that storage in synaptic vesicles can be inhibited (antagonist) but not facilitated.

Example of drug action: Levodopa

Parkinson disease is associated with low levels of the neurotransmitter dopamine. Levodopa is a drug used, since 1968, to treat Parkinson disease as this chemical can be used by the brain to synthesis dopamine. Levodopa acts at the first (synthesis) stage in the life of a neurotransmitter as an agonist. Although highly effective initially in the relief of the behavioral effects of Parkinson disease that include bilateral tremor, stiff muscles (rigidity), facial masking (blank facial expression), and difficulty initiating movement, patients develop tolerance to levodopa. This means that the overall amount of dopamine in the brain gradually diminishes over time despite the presence of levodopa with a consequent gradual increase in the severity of the brain injury-related behavioral changes.

Example of drug action: Botulin toxin

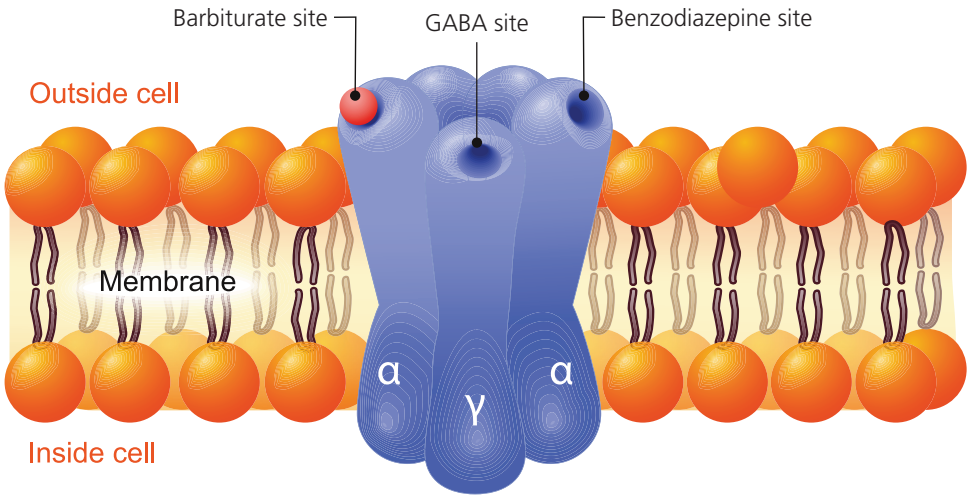
Botulin toxin (botox) is a drug that is widely used in the cosmetic medicine industry to remove facial wrinkles. It works by blocking the release of the neurotransmitter acetylcholine at neuromuscular junctions throughout the body. Botulin toxin works at the third stage, release into the synapse, in the life of a neurotransmitter as an antagonist. Functionally, post-synaptic neurons and eventually muscle fibers receive less input.

Example of drug action: Valium

Valium is a member of the class of drugs known as the benzodiazepines or minor tranquillizers. These were primarily used as anti-anxiety agents, but they also have sedative and anti-seizure effects. Valium molecules are able to activate the same ion channels as $GABA_A$, the primary inhibitory neurotransmitter within the brain. Valium works at the fifth, (binding) stage in the life of a neurotransmitter as an agonist. Figure 4.2 shows a Cl^- ion channel in the cell membrane that is opened when either a molecule of $GABA_A$, benzodiazepine, or barbiturates binds with the receptor.

FIGURE 4.2 Opening of a Cl^- ion channel

A Cl^- ion channel that is normally opened by neurotransmitter GABA binding, can also be opened by certain drugs, like the benzodiazepine valium or barbiturates.



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The Biological Revolution in Psychiatry

The past 60 or so years has seen the biological revolution in psychiatry, whereby mental disorders are viewed as being caused by chemical imbalances within the brain that can be cured, or at least managed, by altering brain chemistry via daily use of psychotropic drugs. Such hypotheses had their infancy as far back as the late 19th century. For example Herbert Page, a surgeon in the employ of a British railroad

company, argued that the nervous condition seen in some survivors of railway accidents known as *railway spine*, was not due to "coarse pathological lesions, which we are wont to see in the post-mortem room, or which are shown us by the microscope … (but) may be a chemical one" (Page, 1891, p. 62).

Exactly what chemical imbalances exist has been hypothesized for just two of the myriad number of mental disorders, namely schizophrenia and major depression. The chemical imbalance associated with schizophrenia is a high level of the neurotransmitter dopamine, while major depression is associated with a low level of the neurotransmitter serotonin. Both chemical imbalances are *hypothesized* to exist as current scientific techniques do not allow measurement of patient levels of any neurotransmitter, including dopamine and serotonin, while the patient is still alive. Barriers to accurate measurement include: (a) the response time of neurotransmitters is extremely fast; (b) concentration levels are low; and (c) many neurotransmitters are molecularly similar (Si & Song, 2018). There is no evidence that measurement of neurotransmitter levels in urine analysis bears any relationship to neurotransmitter levels in the brain (Hinz, Stein, Trachte, & Uncini, 2010). Postmortem studies are difficult to interpret and inconclusive (Harrison, 2000). Chemical imbalances in neurotransmitters became linked with schizophrenia and major depression by happenstance and subsequent evidence supporting the chemical imbalance model of mental disorder is virtually nonexistent.

Seeds of the revolution

The 1975 movie *One Flew over the Cuckoo's Nest* directed by Milos Forman and starring Jack Nicholson as a convicted felon who chose to serve his sentence in a mental institution, provides some insight into the asylum medicine model of inpatient psychiatric care that preceded the biological revolution in psychiatry. The impetus for asylums in the U. S. came from Dorothea Dix (1802–1887) and other humanitarian reformers who decried the then current system whereby individuals with mental disorders who could not be cared for by their families were housed in private homes or "madhouses". These were run by lay persons who received payment for their efforts from local authorities. That system resulted in numerous abuses and atrocities and the mentally disordered were generally housed in deplorable conditions.

FIGURE 4.3 Utica State Hospital that opened in 1843 as the New York State Lunatic Asylum at Utica

Source: "Utica State Hospital Center December 2007," by Doncram, available under a CC BY-SA 4.0 International license

Asylum medicine would dominate the management of mental disorders through to the mid-1950s. Over this entire period available treatments were limited. In Great Britain they were described as: "Few mental hospitals…are able to offer recently admitted patients… much more than custodianship, rug-making, the cinema and a chat every week or two with the doctor" (Bourne, 1953, p. 965). Asylum medicine did employ some specialized physical treatment techniques in addition to psychoanalysis or other forms of psychological (talk) therapy, most commonly: (a) insulin coma therapy whereby large doses of insulin were injected daily over several weeks to produce temporary comas; (b) psychosurgery (see Box 4.1); and (c) electroshock therapy (see Box 4.2).

BOX 4.1 PSYCHOSURGERY

Psychosurgery refers to the use of neurosurgery to produce emotional or behavioral changes in a patient. Modern psychosurgery originated with Portuguese psychiatrist Egas Moniz (1874–1955) after he became aware of research on a chimpanzee that was excitable and belligerent until calmed after the frontal lobes were removed (Jacobsen, Wolfe, & Jackson, 1935). Moniz (1937) pioneered the use of the prefrontal leucotomy (the forerunner of frontal lobotomy) in psychiatric patients, winning the Nobel Prize in physiology or medicine in 1949. The procedure involves disrupting the white matter connections between the frontal lobes and the rest of the brain. It was reported to be widely successful in calming agitated patients and it flourished in the U. S. in the 1940s and 1950s when some 50,000 patients underwent the procedure. Its popularity waned when it was realized that the procedure caused patients to lose the ability to show any emotion at all, becoming apathetic to all activities. They also experienced severe executive impairment and were unable to carry out plans or function adaptively in society. Moniz had noted that some of his patients were "somewhat apathetic" (1937, p. 1379) post-surgery, but attributed this disposition to preinjury personality factors.

While the era of frontal lobotomy has run its course, the practice of other forms of psychosurgery persists to this day. For example, cingulotomy, involving bilateral lesions in anterior cingulate cortex that forms part of the limbic system, originated in Great Britain (Ward, 1948) after research on monkeys showed that bilateral anterior cingulate cortex lesions resulted in increased tameness and reduction of aggressiveness (Glees, Cole, Whitty, & Cairns, 1950). It has subsequently been used to treat a variety of treatment resistant psychiatric conditions including: obsessive-compulsive disorder (Dougherty et al., 2002); emotional concomitants of chronic pain (Foltz & White, 1962); depression (Ballantine, Bouckoms, Thomas, & Giriunas, 1987); and substance abuse (Balasubramaniam, Kanaka, & Ramanujam, 1973). Success rates range from 30–80% with much of the variability due to differing definitions of "success".

Other attempts by neurosurgeons to alleviate various conditions by severing connections within the brain have produced some unique medical cases. For example, so-called "split-brain" neurosurgery that involves severing the pathways of the corpus callosum that connect the two cerebral hemispheres was performed on patients with treatment resistant seizure disorders in the 1940s and 1960s. This surgery prevents the seizures from spreading throughout the brain with resultant loss of consciousness. Extensive research conducted on split-brain patients showed the post-surgical exchange of information between the two hemispheres was profoundly limited and furthered an understanding of the differential role of the two hemispheres in information processing. For example, a split-brain patient can no longer verbally describe stimuli presented to the right hemisphere, as the disconnected left hemisphere is specialized for language processing (Gazzaniga, 2005).

The use of insulin coma therapy dated from 1928 following the observation that morphine addicts going through withdrawal, who also happened to be diabetic, appeared much calmer when their physician

accidently administered insulin overdoses, sending them into a temporary coma (Sakel, 1937). There was never any evidence that this therapy ever worked, even though it became a popular treatment for patients with schizophrenia (Bourne, 1953). It is no longer used at all. Electroshock therapy and psychosurgery cause structural brain injury, but both have extremely restricted indications in the treatment of psychiatric patients to this day. As these treatments were of limited effectiveness in promoting functional change, asylums soon became over-crowded with chronic cases and the indigent. The warehousing nature of the system led to underfunding, appalling conditions, and abuse of patients that was frequently a source of embarrassment to local authorities. The aging of mental asylums and the need for costly repairs added further fuel to the need for social change.

BOX 4.2 ELECTROSHOCK THERAPY

The use of shocks to treat various illnesses dates from the time of the Roman Empire. The use of electroshock therapy to treat psychiatric conditions was developed in Italy in 1938 by Ugo Cerletti (1877–1963) and his collaborators (Endler, 1988). It involves applying an electrical current to the brain to cause a seizure. It is quite effective in the short term relief of major depression but usually repeat treatments are necessary over time. Unfortunately as with naturally occurring seizure disorders, electroshock seizures result in injury to the hippocampus bilaterally, with consequent memory impairment. Despite this adverse side effect, electroshock therapy is still indicated in cases of treatment resistant major depression where the patient is at risk of committing suicide. In these cases it is felt that the positive effects of the electroshock treatment in reducing the risk of suicide outweighs the risk of memory impairment.

By the middle of the 20th century, the stage was set for social reform of the asylum system. Concurrently psychiatry, that had long been afforded second class status in relation to other medical disciplines, was ready to become more like the rest of medicine by treating mental disorders as diseases with "real" medical treatments. The preferred treatment approach that could align psychiatry with mainstream medicine was drug therapy.

The break-down of the asylum medicine system combined with the idea that mental disorders were diseases caused by chemical imbalances in the brain that could be treated with drugs would usher in a radical new approach to the treatment of mental disorders, known as *deinstitutionalization*. This involved a shift from long-term stays in the state- and county-run mental asylums to short-term stays in private hospital or other community settings. There were about 525,000 psychiatric beds in 1970 in the U. S., with 80% being located in state- and county-run asylums, compared with about 212,000 psychiatric beds in 2002 of which 27% were in state- and county-run asylums (Sharfstein & Dickerson, 2009). It was expected that drug therapy would enable patients, who had previously required chronic long-term inpatient care, to survive in community settings.

The societal push for deinstitutionalization and the idea that mental disorders were caused by chemical imbalances within the brain that could be corrected by drugs formed a perfect partnership to usher in the biological revolution in psychiatry. The pharmaceutical industry was only too willing to jump on board. The first mental disorder to be associated with a chemical imbalance in the brain was schizophrenia. Patients with this diagnosis had frequently become permanently institutionalized under asylum medicine.

Schizophrenia

Schizophrenia is a severe mental disorder that is included within the larger category of the psychoses. It affects 1% of the world's population. It is difficult to diagnose as there is no objective test and its associated behaviors are highly varied (see Box 4.3), overlap with those of other mental disorders, and frequently change as the disorder progresses. Behavioral changes characteristic of schizophrenia tend to first present in late adolescence or early adulthood. These distinctive features (see Table 4.1) are divided into positive (i.e., present) and negative (i.e., absence of normal behavior) types. Positive behaviors are: (a) thought disorder: disorganized, irrational thinking; (b) delusions: beliefs contrary to fact; and (c) hallucinations: usually auditory, such as hearing voices that issue various commands. Negative behavioral indicators of schizophrenia include: (a) flattered emotional response; (b) poverty of speech; (c) lack of initiation; (d) perseveration (repeatedly making the same mistake); (e) difficulty experiencing pleasure; and (f) social withdrawal. These negative behaviors are not specific to schizophrenia, but occur in other neurological conditions that involve compromise to the frontal lobes. Patients with schizophrenia also demonstrate neurocognitive impairment across all domains with memory skills being affected the most and somatosensory/motor skills least (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009).

BOX 4.3 INFAMOUS AND FAMOUS CASES OF SCHIZOPHRENIA

Some infamous mass murders and assassination attempts can be attributed to psychotic thinking, including:

1. Connecticut postman David Berkowitz was nicknamed the Son of Sam killer after terrorizing New York City by committing random serial killings from the summer of 1976 through August, 1977. He killed six and wounded seven. In May 1978 he pleaded guilty (refusing to consider an insanity defense) and was sentenced to 25 ye ars to life. He attributed the reason for his murderous spree to his neighbor's dog called Sam who would bark at night commanding Berkowitz to go out and kill. The 1999 movie *Summer of Sam* directed and produced by Spike Lee is a story that described the effect of these random murders on residents of New York City.
2. Mark David Chapman shot and killed ex-Beetle John Lennon in New York City on December 8, 1980. Chapman was a born-again Christian who had become incensed over a statement by Lennon that the Beetles were "more popular than Jesus". His legal defense team wanted to mount an insanity defense, but Chapman insisted on pleading guilty.
3. John Hinckley shot and wounded President Ronald Reagan and his Press Secretary James Brady in an assassination attempt on March 30, 1981. He was later found guilty by reason of insanity. The motivation for the crime was apparently his love for then child actress Jodie Foster, whom he had witnessed playing the role of a 12 year old prostitute in the 1976 movie *Taxi Driver* directed by Martin Scorsese. In the movie, the lead character, Travis Bickle (portrayed by Robert De Niro) unsuccessfully attempted to assassinate a U. S. presidential candidate.
4. Jared Lee Loughner shot six persons and wounded 13 others including U. S. Representative Gabrielle Giffords (his original target) on January 8, 2011, in Tucson, Arizona. He became incensed with Giffords after she failed to answer his question: "What is government if words have no meaning?", posed at a prior campaign event. After the shooting he was diagnosed with paranoid schizophrenia and initially found incompetent to stand trial. The latter was eventually over-turned and in November 2012 he was sentenced to life plus 140 years after pleading guilty.
5. James Holmes was convicted of the July 20, 2012 movie theater mass shooting in Aurora, Colorado that left 12 dead and 70 injured. Just prior to the shooting he had withdrawn from the University of Colorado doctoral neuroscience program. A court-appointed psychiatrist diagnosed him with schizotypal personality disorder but

found him competent to stand trial. On August 26, 2014, he was sentenced to 12 consecutive life sentences plus 3,318 years. When asked why he targeted a movie theater he stated that he initially thought about an airport but changed his mind as he did not want the message to be terrorism-related. "My message is: there is no message" he was quoted as saying.

This is not meant to give the impression that all individuals with schizophrenia are prone to violence. The vast majority are not. Recall that John Nash the Princeton mathematics professor who won the Nobel Prize in economic sciences in 1994 and was the subject of the 2001 movie *A Beautiful Mind*, directed by Ron Howard, was diagnosed with schizophrenia. The movie portrayal shows that the extent of his psychotic thinking extends to imaginary friends and a fantasy role within the Central Intelligence Agency.

TABLE 4.1 Behavioral indicators of schizophrenia.

Positive indicators

Positive behavioral indicators are present and are thought to result from high levels of dopamine:

- thought disorder: disorganized, irrational thinking;
- delusions: beliefs contrary to fact; and
- hallucinations: usually auditory, such as hearing voices that issue various commands.

Negative indicators

Negative behavioral indicators are absent and are associated with frontal lobe dysfunction:

- flattered emotional response;
- poverty of speech;
- lack of initiation;
- perseveration (repetition of the same mistake);
- difficulty experiencing pleasure; and
- social withdrawal.

The etiology of schizophrenia is poorly understood, but is thought to involve multiple factors, both genetic and environmental. Genetic factors are implicated in schizophrenia as the concordance rate for identical twins is 45% compared to 10% for fraternal twins (Holzman & Matthyse, 1990). It has been suggested that an individual will inherit a susceptibility to develop schizophrenia, but the disorder itself will be triggered by other environmental factors.

The only environmental factor that has consistently been associated with an increased risk of developing schizophrenia is immigration (Gasquoine, 2014b). It is normal for immigrants to experience *culture shock,* or as it is now known *acculturative stress,* in the immediate post-immigration period due to loss of family support, extensive new cultural learning, changes in diet, and so forth. Despite this stress, the vast majority of immigrants adjust and successfully transition to the new culture. Higher rates of mental disorders among voluntary (refugees have higher rates of mental disorders like depression and post-traumatic stress disorder) immigrant groups have not been found with the sole exception of schizophrenia. First and second generation immigrants (i.e., immigrants and their children) have higher rates of schizophrenia than the native born population of their country of origin or the host country (Cantor-Graae & Selten, 2005; Fearon et al.,

2006). For example, African Caribbean immigrants to the United Kingdom who hail from the West Indies, especially the English-speaking islands of Jamaica, Trinidad, and Barbados are diagnosed with schizophrenia seven times more frequently than British native-born individuals. Rates of schizophrenia among the African population of the Caribbean, who are the descendants of former slaves, are not markedly raised. The reason why immigration increases the risk for schizophrenia is unknown.

Neuroleptics and the dopamine hypothesis of schizophrenia

The chemical imbalance in schizophrenia is hypothesized to be an oversupply of dopamine within the brain. This hypothesis was derived from the discovery of drugs that relieved the positive behavioral indicators of schizophrenia. They were unearthed by accident when a French pharmaceutical company, Rhone Pôulenc Laboratories began the search for new anti-histamine drugs in the 1930s. In 1950 they produced chlorpromazine (later marketed in the U. S. as thorazine) that in addition to its anti-histamine effects was successfully used by a French surgeon as a type of anesthetic boost to calm surgical patients pre- and post-surgery. It was soon tried on psychiatric patients with good success in relieving the positive behavioral indicators of schizophrenia, but was ineffective in cases of depression (López-Muñoz et al., 2005). In 1953 it was licensed to SmithKline and French (now GlaxoSmithKline) in the U. S..

The mechanism of action of chlorpromazine was initially unknown but animal studies would show it was a dopamine antagonist and worked by blocking dopamine receptors in post-synaptic ion channels (Carlsson & Lindqvist, 1963). Chlorpromazine is an antagonist at the fifth (binding) stage in the life of the neurotransmitter dopamine. The dopamine hypothesis of schizophrenia whereby the positive behavioral indicators of schizophrenia were linked with high levels of dopamine in the brain was developed from this finding, in combination with the observation that amphetamine abuse produced a psychosis similar to schizophrenia (Snyder, Banerjee, Yamamura, & Greenberg, 1974). Amphetamine is a dopamine agonist that worked at the sixth (deactivation) stage in the life of a neurotransmitter. It also serves as an agonist for norepinephrine.

Chlorpromazine is a member of the class of drugs known as *neuroleptics*. Nowadays, so-called second generation neuroleptics, such as risperdal, are used as they are believed to produce less severe side effects than the first generation drugs. The most common side effects of neuroleptic drugs are motor impairments like tardive dyskinesia that are known collectively as extrapyramidal effects (see Chapter 9). Side effects associated with the long-term usage of neuroleptic drugs contribute to patient non-compliance with drug regimens but another reason patients with schizophrenia avoid taking neuroleptics is that they do not feel they need them. Patients with schizophrenia often feel they are the sane ones and that it is the rest of society that is crazy. Not all patients with schizophrenia require continuous neuroleptic drug regimens (Harrow, Jobe, & Faull, 2012), but patients may not be the best judge of who should, and who should not, be taking neuroleptics.

It is widely accepted that neuroleptics have a profound effect on the brain and reduce the positive behavioral indicators of schizophrenia in many cases. For example, meta-analysis of second generation neuroleptic drugs concluded that 41% of patients responded to the drug compared to 24% who received placebo (Leucht, Arbter, Engel, Kissling, & Davis, 2009). What is not so clear is that this therapeutic effect derives from a selective reduction of the neurotransmitter dopamine and/or that high levels of dopamine cause schizophrenia. The dopamine hypothesis of schizophrenia derives from the apparent effectiveness of neuroleptics in reducing the behavioral indicators of schizophrenia yet: (a) many patients with schizophrenia show no benefit from neuroleptic drug usage; (b) neuroleptics are rarely prescribed

in isolation but are usually combined with other psychoactive drugs; (c) drugs like benzodiazepines are also successful in treating the positive behavioral indicators of schizophrenia; (d) neuroleptics have no therapeutic effect on the negative behavioral indicators of schizophrenia; and (e) the outcome for schizophrenia is worse in industrialized than in developing countries even though neuroleptic drug usage is higher in the former (Moncrieff, 2009). Such findings support an alternative interpretation of the action of neuroleptics whereby these drugs have a generalized behavioral effect, reducing all spontaneous thought and action and not just the positive behavioral indicators of schizophrenia.

It has also been argued that the negative behavioral indicators of schizophrenia are the side-effects of neuroleptic drug usage. Neuroimaging of patients with schizophrenia shows they lose brain volume throughout their lives, especially grey matter from the frontal lobes, as evidenced by enlarged ventricles. Initially, it was thought that this loss of grey matter was a result of the natural progression of schizophrenia, but more recently it has been associated with the long-term use of neuroleptics (Ho, Andreasen, Ziebell, Pierson, & Magnotta, 2011; Moncrieff & Leo, 2010).

Long-term use of neuroleptics is thought to contribute to a lower life expectancy of 10–25 years for persons with schizophrenia (Laursen, Munk-Olsen, & Vestergaad, 2012), although other factors like an unhealthy lifestyle and suicide are also involved. Persons with schizophrenia have much higher rates of cardiovascular disease and cancer than in the general population (Crump, Winkleby, Sundquist, & Sundquist, 2013).

Major Depression and Anti-depressants

Depression is a normal human emotion, especially as a reaction to negative life events, and it is only the severity of the symptoms that makes it a mental disorder. Major depression is characterized by sadness, hopelessness, suicidal ideation, difficulty concentrating, sleep disturbance (insomnia or hypersomnia), appetite disturbance (too much or too little), and loss of interest in previously enjoyed activities. *DSM*-5 (American Psychiatric Association, 2013) diagnostic criteria require these behaviors to be present for a period of at least two weeks. The National Institute of Mental Health (www.nimh.nih.gov) estimates that 16.5% of the U. S. population will experience an episode of major depression within their lifetime, but only about half will seek any form of treatment for the condition. Inpatient hospitalization is indicated if there is a risk of suicide.

The etiology of major depression is poorly understood. It affects women twice or three times as often as men. There is a genetic component as the concordance rate for identical twins is 69%, whereas for fraternal twins it is 13% (Gershon, Bunney, Leckman, van Eerdewegh, & DeBauche, 1976). It is estimated that about 35–40% of major depression is explained by heritability factors (Kendler, Gatz, Gardner, & Pedersen, 2006).

There are many psychological theories of major depression. For example, *cognitive behavioral therapy* (CBT: Beck, Rush, Shaw, & Emery, 1979) is a widely used treatment approach that was based upon observations that depressed patients have unrealistically negative cognitions about the self, the future, and the world. It is unclear if such statements cause or result from the depression. Another theoretical conception of depression is *analytical rumination theory* (Andrews & Thomson, 2009) that views major depression as an adaptive evolutionary response that allows rumination to solve complex life problems. No psychological theory of major depression has received consensus acceptance.

Anti-depressants and the serotonin hypothesis of major depression

Like the neuroleptics, the therapeutic effect of anti-depressants on major depression was discovered by accident. The first anti-depressant was iproniazid that was originally developed to treat tuberculosis. Tuberculosis is a highly contagious, bacterial, airborne disease. Tuberculosis and mental disorders especially major depression frequently co-exist as the two conditions share similar risk factors, like homelessness and substance abuse (Doherty et al., 2013). When iproniazid was first used it was observed that many tuberculosis patients experienced "gain in weight, return of appetite… and a sharp return in sense of well-being" (Robitzek & Selikoff, 1952, p. 426). This mood elevation occurred independently of any change in lung pathology and the drug was subsequently tried on tuberculosis patients formally diagnosed by a psychiatrist with concurrent major depression with good success in reducing depressive behavioral indicators (Crane, 1957). Iproniazid belongs to a class of drugs known as MAO (monoamine oxidase) inhibitors that animal research later showed are agonists for the monoamine neurotransmitters dopamine, norepinephrine, and serotonin.

The second generation of anti-depressants was the class of drugs now known as tricyclics (the term comes from their chemical structure). The first variant, imipramine was used with patients who had mental disorders in the 1950s in Switzerland. The chemical formula for imipramine was very similar to that of chlorpromazine so it was initially used to treat schizophrenia, but it made them manic, so it was subsequently tried on patients with major depression with better success (Kuhn, 1958). Animal research later showed that tricyclics are serotonin and norepinephrine reuptake inhibitors. They act as an agonist for these neurotransmitters at the sixth (deactivation) stage in the life of the neurotransmitter.

The third generation of anti-depressants originated in 1988 with the release of prozac. Prozac and most current anti-depressants (there are some atypical varieties, such as wellbutrin [generic name bupropion] that works more on dopamine) are selective serotonin reuptake inhibitors. They act as agonists for serotonin at the sixth (deactivation) stage in the life of the neurotransmitter by blocking reuptake of the drug. Examples have trade names like celexa, paxil, and zoloft. They are all characterized by slow onset of clinical effect (often several weeks), a phenomena that has yet to receive adequate explanation. The perceived initial success of the anti-depressants in treating major depression led to the *monoamine hypothesis of depression* (Schildkraut, 1965) that was narrowed to the *serotonin hypothesis of depression* with the advent of the third generation of anti-depressants.

Recent evidence has challenged the effectiveness of the anti-depressants in relieving the behaviors associated with major depression. A large-scale national study found that anti-depressants work in only a limited percentage of cases, around 37% (Rush et al., 2006b). Except for cases of very severe major depression this is the same percentage as achieved by placebo treatments (i.e., pills with no chemically active ingredient) in relieving depressive behaviors (Kirsch et al., 2008). The typical clinical response of psychiatrists when treating patients for whom a serotonin reuptake inhibitor anti-depressant does not work is to switch to another type of anti-depressant. This approach rarely works (Rush et al., 2006a). Recent meta-analysis of 131 randomized, placebo-controlled, trials of anti-depressants concluded that the clinical significance of any reduction in depressive behavioral indicators was "questionable" (Jakobsen et al., 2017, p. 2).

If anti-depressants are no more effective than placebos in reducing depressive behavioral indicators, it suggests that any effect they produce is psychological and not due to any chemical change within the brain. They also can have negative side-effects, the most common being sexual dysfunction, including delayed

ejaculation, difficulty achieving orgasm, and decreased libido, that occurs in about 60% of patients. Other common side effects include constipation and dry-mouth (Khawam, Laurencic, & Malone, 2006).

Psychoactive drugs, aside from the neuroleptics and anti-depressants, have been developed for use without any clear indication of the chemical imbalance they are supposed to correct. As with the neuroleptics and anti-depressants, their successful use in treating psychiatric behavioral indicators was discovered by accident. Three examples follow: (a) anti-anxiety drugs, like xanax, in the treatment of anxiety; (b) mood stabilizers, like lithium, in the treatment of bipolar disorder; and (c) amphetamines, like ritalin, in the treatment of attention deficit/hyperactivity disorder (ADHD).

Anti-anxiety Drugs

In the 1940s Frank Berger (1913–2008) a Czech physician was working in England trying to discover a preservative for penicillin. Instead he developed a compound known as mephenesin that produced muscular relaxation in mice without sedation or respiratory arrest (Berger, 1947). He relocated to the U. S., took a position with the New Jersey pharmaceutical company Wallace Laboratories, and developed a similar compound called meprobamate that in 1955 was launched as a treatment for anxiety under the brand name miltown (after a New Jersey borough). Sales exploded and within months it had become the best-selling drug ever marketed in the U. S. It soon became evident that miltown was addictive, with withdrawal effects characterized by increased anxiety and the potential for abuse (Lemere, 1956). Sales declined, especially when it was linked to neurocognitive impairment (memory loss) and found prone to overdose, but the era of mass marketing prescription psychoactive drugs to the general population (not just psychiatric patients) had begun.

The second generation of anti-anxiety drugs were the benzodiazepines, first formulated in 1955 by Leo Sternback (1908–2005), a chemist who worked for the New Jersey based Hoffman-La Roche pharmaceutical company. As the story goes he was trying to manufacture a tranquilizing drug but had been unsuccessful and management terminated the program. Two years later a co-worker was cleaning up the laboratory when she found a compound that Sternback had developed but left untested for some 20 years. When then tested on animals it was found to have prominent anti-seizure, muscle relaxant, and sedative effects (Wick, 2013). It subsequently became the first benzodiazepine, launched in 1960 as librium, followed in 1963 by diazepam (brand name valium). It was eventually discovered in animal studies that valium was an agonist for GABA at the fifth (binding) stage in the life of a neurotransmitter (Haefely et al., 1975: see Figure 4.2). Popularity skyrocketed and valium became the highest selling drug in the U. S. between 1968 and 1982, peaking in 1978 and 1979. Its popularity waned when it was found to be subject to abuse and had become a street drug (Woody, O'Brien, & Greenstein, 1975).

To this day the medical community has ambivalence toward benzodiazepine use. Benzodiazepines were excluded from the Medicare Prescription Drug, Improvement and Modernization Act (2003) among concerns they should not be prescribed to older persons. Then the Patient Protection and Affordable Care Act (2010: known as Obamacare) reversed that decision. From the early 2000s through 2016, when it was replaced by the anti-depressant Zoloft, the benzodiazepine xanax (launched in 1981) was the most widely prescribed psychoactive drug (Grohol, 2017). Xanax remains a popular street drug.

Mania and Mood Stabilizers

Some years before thorazine became indicated for patients with schizophrenia in the U. S., it was discovered in Australia that lithium could be successfully used in the treatment of mania (Cade, 1949). Lithium had previously been used for many years in medicine as a treatment for conditions like gout, arthritis, and rheumatism. When administered to guinea pigs, they became sedated and consequently it was tried on manic patients with some success. It is still used in the treatment of what is now known as bipolar disorder, a mental disorder characterized by alternating periods of mania (at least one episode) and depression. The depressive episodes tend to run much longer than the manic episodes. Bipolar disorder occurs with about equal frequency among men and women.

Although lithium is one of the drugs that seeded the biological revolution in psychiatric medicine (López-Muñoz et al., 2005), the chemical imbalance it is supposed to correct has never been identified. The therapeutic window in lithium is very small, meaning that there is little difference between dosages that produce therapeutic effects and dosages that produce toxic effects (nausea, vomiting, diarrhea, drowsiness, and tremor). It has been argued that the therapeutic effects of lithium on manic patients are actually due to mild toxicity (Moncrieff, 2009).

The dangers of lithium toxicity led to the search for other drugs to treat mania. Drugs used in the treatment of seizure disorder were tried, on the basis that mania and seizures were both recurrent events within the brain (Ballenger & Post, 1980). A process known as "kindling" was hypothesized to take place in both disorders, whereby each seizure or manic episode would make another more likely. Anti-seizure drugs, like tegretol and depakote, are still used in the treatment of mania to this day although why or how they work remains a mystery. These same drugs are also used in the treatment of anxiety disorders

Amphetamines and Attention-Deficit/Hyperactivity Disorder (ADHD)

Like lithium, the chemical imbalance amphetamines like ritalin and adderall are supposed to correct in the treatment of attention-deficit/hyperactivity disorder is unknown. Amphetamines had been widely used in medicine since the 1930s for the treatment of everything from asthma to narcolepsy. It was noted at that time to have a calming effect on children. In the 1960s amphetamines were used in the treatment of major depression and as an appetite suppressant, but both effects were subject to rapid tolerance by patients. Widespread abuse in the 1960s led to its classification as a Schedule II drug under the Comprehensive Drug Abuse Prevention and Control Act (1970). Nowadays, children with attention-deficit/hyperactivity disorder receive low doses of amphetamines that can increase concentration and promote a feeling of calm. Adult amphetamine addicts take much higher doses that increase activity levels and reduce the need for sleep.

Consequences of the Biological Revolution in Psychiatry

In 1955, the number of patients in state and county-run asylums reached its peak of 560,000. In recent times, that number had been reduced to 45,000 (Torrey, Fuller, Geller, Jacobs, & Rogasta, 2012). This

reduction is not due to a decrease in need from the widespread use of psychoactive drugs. In fact, there is evidence that the rate of serious mental disorder increased six fold over that period. In 1955, the rate of inpatient psychiatric hospitalization was 3.38 per 1,000 population. In 2003, 19.69 per 1,000 population were receiving disability payments from Social Security Disability Insurance or Supplemental Security Income programs for psychiatric conditions (Whitaker, 2005).

Where then have all these patients gone? Persons experiencing a mental health crisis are now more likely to encounter the police than medical personnel. American jails and prisons have become the nation's largest mental health care facilities by default (Sisti, Segal, & Emanuel, 2015). Half of all incarcerated inmates have a mental or substance abuse disorder with 15% of state inmates diagnosed with a psychotic disorder (James & Glaze, 2006). In all categories of mental disorder, the incidence among prisoners is far higher than that within the general population. Relatedly, the mentally disordered are over-represented among the homeless population. A national survey of jail inmates showed 15% had a history of homelessness compared with about 1–2% of the general U. S. population (Greenberg & Rosenhack, 2008). Thus, in modern times, asylums have given way to homelessness and incarceration for those with a serious mental disorder.

From a theoretical stand-point, the function of psychoactive drugs is generalized and not disease-specific. There is no convincing evidence that they work by correcting specific chemical imbalances. In some patients they do provide relief from psychological distress, but their actions are likely generic and their mechanism of action within the brain poorly defined. The effectiveness of psychoactive drugs has typically been discovered by accident, rather than by some carefully reasoned scientific process. This lack of a sound scientific theory to guide their manufacture and use has opened the door for unscrupulous business practices and fraud in the psychopharmacological industry (see Box 4.4).

Bizarrely, while street users abuse (i.e., use for nonmedical purposes) certain prescription psychoactive drugs, pharmacological manufacturers are taking their cue from street users in attempts to develop new, more effective psychoactive prescription drugs. As illustration, the party drug ketamine (street name *special-k*) is being studied as an anti-depressant (Kirby, 2015; Serafini, Howland, Rovedi, Girardi, & Amore, 2014) and early trials suggest it is effective in reducing suicidal ideation when used intravenously (Bartoli et al., 2017). In February 2019, a nasal version of the drug known as esketamine was recommended as a new treatment for depression by an advisory panel to the Food and Drug Administration (FDA). The chemical changes ketamine produces in the brain are not well understood, but they are associated with the neurotransmitter glutamate.

Similarly, marijuana has now been legally approved as a treatment for post-traumatic stress disorder in 27 states (Serrano, 2018, January 4). Cannabis (as it was then known) was used medicinally before the possession and transport of marijuana was banned by the Federal government in the Marihuana Tax Act (1937). The ban stemmed from its association with Mexican immigrants. Medical usage was still allowed until the passing of the Comprehensive Drug Abuse Prevention and Control Act (1970). This act classified marijuana on Schedule I (i.e., an illegal drug with no recognized medical use and a high potential for abuse). It is still banned at the federal level, meaning that government agencies have historically done little to fund investigations into its medicinal effectiveness, thus its pharmacological properties are little known. The benefits/harms of long-term marijuana use continue to be debated (Hasin, 2018). One side effect of the federal ban is that pharmaceutical companies have been unable to control its production and distribution, resulting in numerous small start-up companies seizing an opportunity.

The biological revolution in psychiatric care hastened the end of asylum medicine, but the explanation of schizophrenia and major depression in terms of simple chemical imbalances has not survived

scientific scrutiny. The etiology of these and many other mental disorders remains poorly understood, but it is becoming increasingly clear that psychological factors are just as important as the biological, if not more so. It is unlikely that the asylum medicine era will ever return given that it would result in the re-imposition of the financial burden for the care of the seriously mentally disordered upon states and counties. Nevertheless, it is time to recognize the limitations of the biological model and move towards a better understanding of the multifactorial causes of mental disorders.

BOX 4.4 PROFITS BEFORE PATIENT CARE IN THE PSYCHOACTIVE DRUG INDUSTRY

The use of benzodiazepines ushered in an era of mass marketing of psychoactive drugs to the general population, but in the 1980s benzodiazepines were the subject of the largest ever class action lawsuit against drug manufacturers ever filed in the United Kingdom. The lawsuit involved over 14,000 patients and 1,800 law firms alleging that the drug manufacturers were aware of the addictive nature of benzodiazepines, but intentionally withheld this information from physicians. Concurrently, patients sued physicians and hospital boards to recover damages for suffering and loss caused by benzodiazepine dependence and withdrawal. The suit dragged on for years but was never settled (Wick, 2013).

In more recent times in the U. S., Johnson and Johnson were assessed $2.2 billion in criminal and civil fines in 2013 under the False Claims Act (1986) for off-label promotion and payment of kickbacks to physicians. One off-label promotion was the use of risperdal (a neuroleptic) in elderly dementia patients to control behavioral problems like confusion and agitation (U. S. Department of Justice, 2012, November 4). GlaxoSmithKline settled for $3 billion in 2012 for marketing the anti-depressant paxil, approved for the treatment of depression in adults, to the treatment of depression in children and for other unapproved medical conditions (e.g., weight loss). As part of the marketing campaign they also provided illegal kickbacks to physicians, distributed misleading journal articles, and improperly billed Medicaid plans (Thomas & Schmidt, 2012, July 2).

The most prominent current lawsuits involving pharmaceutical companies relate to the *opioid crisis*. Twenty-seven states, Puerto Rico, and numerous counties and cities have filed lawsuits against the privately held Purdue Pharma, the manufacturer of oxycontin (an opioid pain reliever), for downplaying the risk of addiction and deceptive marketing practices (Stempel, 2018, August 14). Oxycontin came on the market in 1996 with an extremely aggressive marketing campaign (van Zee, 2009). With increased sales came an increase in the number of individuals addicted to opioids. This opioid crisis has led to a marked increase in: overdose deaths (42,000 in 2016); emergency room visits for prescription opioid misuse or abuse; babies born to addicted mothers; and heroin use. Heroin is pharmacologically similar to prescription opiods. Prior to being illegalized by the Anti-Heroin Act (1924), heroin had been marketed as a cough suppressant by the German pharmaceutical manufacturer Bayer. Surveys have found that as many as 80% of heroin users report that their opioid use began with the non-medical use of prescription opioids (Compton, Jones, & Baldwin, 2016). Prescription opioid pills that are crushed, dissolved, and snorted or injected, are much more expensive to buy on the street than heroin.

Purdue Pharma has already settled several previous lawsuits related to the sale and manufacture of oxycontin. For example, the company and three executives, the president, top lawyer, and chief medical officer, pled guilty to misbranding oxycontin and agreed to pay $634.5 million to resolve a 2007 U. S. Department of Justice investigation.

Pharmaceutical companies require psychiatrists and other scientists to be complicit in any deceptive marketing practices and such individuals are well compensated for doing so. For example, from 1996–2002 Purdue Pharma provided financial support to the American Pain Society (a professional, multidisciplinary organization) and the American Academy of Pain Medicine (a medical specialty organization) who both endorsed prescription opioid use for the treatment of chronic, non-cancer pain, even though no clinical trials had been conducted. Purdue Pharma physician spokespersons were claiming the risk of addiction from oxycontin was < 1% (Kolodny et al., 2015; van Zee, 2009).

Summary

Psychopharmacology is the study of the effects of drugs on the nervous system and behavior. Psychoactive drugs alter the transmission of messages between cells by affecting chemical signaling within the brain. Differing routes of drug ingestion include: (a) intravenous; (b) inhalation; and (c) oral. To pass from the blood stream to the synapses of the brain and influence behavior a drug must pass through the blood-brain barrier, a mechanism whereby the release of chemicals into brain tissue from blood vessels is restricted. The blood-brain barrier is formed by blood vessels in the brain having much smaller tighter junctions between cells than in the rest of the body.

Repeated consumption of a drug over time will often result in a reduction in its behavioral effect, a phenomenon known as tolerance. Tolerance occurs because the brain recognizes that the drug is a foreign substance and produces its own chemicals to try and counteract the effect of the drug. Abruptly stopping drugs that cause tolerance often result in withdrawal effects that are the opposite of the typical behavioral effects of the drug.

Drugs that affect behavior do so by affecting synaptic transmission as either: (a) agonists that facilitate neurotransmitter effects; or (b) antagonists that inhibit neurotransmitter effects. Drugs can act as an agonist or antagonist at any of the six stages in the life of a neurotransmitter: (a) synthesis; (b) storage in synaptic vesicles (antagonist only); (c) release into the synapse; (d) modulation via autoreceptors; (e) binding with postsynaptic ion channels; and (f) deactivation.

The biological revolution in psychiatric medicine that views mental disorders as chemical imbalances within the brain that can be managed via daily use of psychoactive drugs began in the 1950s. Exactly what the chemical imbalances are has been hypothesized only for schizophrenia (high levels of the neurotransmitter dopamine) and major depression (low levels of serotonin). The biological revolution contributed to the end of the asylum medicine era of inpatient psychiatric care and ushered in deinstitutionalization, involving a shift from long-term stays in state- and county-run mental asylums to short-term stays in private hospital and other community settings.

The theoretical basis of the chemical imbalance started with the neuroleptic drug chlorpromazine (thorazine in the U. S.) that was originally developed as an anti-histamine. It was found to relieve the positive behavioral indicators of schizophrenia. Schizophrenia is a serious mental disorder affecting 1% of the population that usually first manifests in late adolescence or early adulthood. Positive (meaning present) behavioral indicators of schizophrenia are thought disorder, delusions, and hallucinations. Negative (meaning absent) behavioral indicators of schizophrenia include flattered emotional response, poverty of speech, lack of initiation, perseveration, difficulty experiencing pleasure, and social withdrawal. The etiology of schizophrenia is poorly understood, but is thought to involve multiple factors, both genetic and environmental. The only environmental factor that has consistently been associated with an increased risk of developing schizophrenia is immigration.

Animal studies showed chlorpromazine was a dopamine antagonist that worked at the fifth (binding) stage in the life of a neurotransmitter. Amphetamines, that are dopamine agonists, produce behaviors similar to those of schizophrenia in drug addicts. These findings led to the dopamine hypothesis of schizophrenia, whereby high levels are thought to cause schizophrenia. Findings that have contradicted this hypothesis and suggested that neuroleptic drugs have a generalized sedating effect on the brain include: (a) many patients with schizophrenia show no benefit from neuroleptic drug usage; (b) neuroleptics are

rarely prescribed in isolation but are usually combined with other psychoactive drugs; (c) drugs like benzodiazepines are also useful in treating schizophrenia; (d) neuroleptics have no effect on the negative behavioral indicators of schizophrenia; and (e) the outcome for schizophrenia is worse in industrialized than in developing countries even though neuroleptic usage is higher in the former. The negative behavioral indicators of schizophrenia are thought to result from decreased metabolic activity of the frontal lobes, possibly a side-effect of the use of neuroleptic drugs.

Anti-depressants were also discovered by accident with the first, iproniazid, being developed to treat tuberculosis. The second-generation of anti-depressants were the tricyclics (e.g., imipramine), and the third-generation are serotonin reuptake inhibitors (e.g., prozac). The last are widely used to treat major depression, a common mental disorder characterized by sadness, hopelessness, suicidal ideation, difficulty concentrating, sleep disturbance (insomnia or hypersomnia), appetite disturbance (too much or too little), and loss of interest in previously enjoyed activities. Serotonin reuptake inhibitors work as serotonin agonists at the sixth (deactivation) stage in the life of a neurotransmitter. This has led to the serotonin hypothesis of major depression whereby low levels of the neurotransmitter are thought to cause major depression. Recent evidence suggests that anti-depressants work in only a limited percentage of cases, around 37%, a rate little better than placebo. This suggests that depression is not caused by a chemical imbalance in the amount of serotonin within the brain.

Other commonly used prescription psychoactive drugs have never been theoretically associated with chemical imbalances. Anti-anxiety drugs, the most popular of which are the drug class known as the benzodiazepines (includes valium and xanax), were also discovered by accident. Anti-anxiety drugs were marketed to the general population (not just psychiatric patients) in the 1960s and 1970s, skyrocketing sales. Popularity declined when it was found they were addictive. They are still abused by street addicts for non-medical purposes to this day. Lithium and some anti-seizure drugs (tegretol; depakote), known as mood stabilizers, are used to treat bipolar disorder, a mental disorder characterized by alternating periods of mania and depression. The mechanism of action of lithium is unknown. Similarly, amphetamines like ritalin and adderall are used to treat attention-deficit/hyperactivity disorder, but the mechanism of action is unknown.

No psychoactive drug that treats mental disorders by specifically correcting a chemical imbalance currently exists.