PSYCHOPHARMACOLOGY: A COMPREHENSIVE REVIEW

Introduction

Presently, psychoactive substances and their synthetic derivatives are used for a variety of mental disorders ranging from clinical depression to psychosis. At the heart of psychopharmacology lie two important things: psychoactive drugs and mental illness as a clinically diagnosed disorder.

Definitions

Psychopharmacology refers to the study of drugs, *pharmakon*, that influence the human mental state, *psyche*, and behavior. The terms “mental illness”, “mental disorder”, “psychiatric disorder” and “psychiatric illness” are used interchangeably throughout the course. According to the National Alliance on Mental Illness (NAMI), “a mental illness is a medical condition that disrupts a person’s thinking, feeling, mood, ability to relate to others and daily functioning. Just as diabetes is a disorder of the pancreas, mental illnesses are medical conditions that often result in a diminished capacity for coping with the ordinary demands of life”.

The terms “psychopharmacologic drugs”, “psychopharmacologic medications”, “psychopharmacologic treatment”, “psychopharmacologic therapy”, “psychiatric drugs”, “psychiatric
medications”, “psychotropic drugs”, “psychoactive drugs”,
“psychoactive medications”, and “psychotropic medications” are used
interchangeably throughout the course. They are used to refer to the
drugs used to treat mental illness. Additionally, the terms “psychiatric
treatment” and “psychiatric therapy” are used interchangeably
throughout the course. They are defined as the overall interventions,
clinical and nonclinical, used to ameliorate mental illness.

History Of Mental Health

Past cultures attributed mental disorders and migraines to demonic
possessions. Healers used to hammer or drill holes into the skulls with
hard instruments solely made for this purpose: to release the demons
occupying the sufferer’s mind.¹ Others purged this disease with blood-
letting.² These brutal practices lasted for centuries, until Hippocrates
challenged the role of supernatural forces in mental illnesses. Instead,
he proposed the idea of physiological abnormalities manifesting as
psychological disturbances. His idea brought forth a new treatment
approach, albeit not the most scientifically sound one – purging.³
Though this approach didn’t help much more than drilling holes into
skulls did, purging introduced the practice of ingesting a substance to
induce vomiting. The oral administration of substances was an
approach that 100 years later would be used again to administer
psychoactive drugs.

During the Middle Ages in England and right up to the 19th century,
one popular answer to mental illness came in the form of a place, the
Royal Bethlem Hospital, now infamously known as Bedlam. These days, the word bedlam, is synonymous with madness. The mental hospital popularized the institutionalization of the mentally ill. A visitation report made in 1403 recorded the presence of mechanical restraints such as manacles, chains, locks and stocks. However, while inhumane treatment of the severely mentally ill may have occurred in the premises, little else is known of the actual treatment of the mad in Bethlem during this period.

Soon after, propelled by the Industrial Revolution, asylums were constructed everywhere and became an important aspect of managing mental illness. It became the place to be for the “mad men”.

As medicine developed into the 19th century, Sigmund Freud introduced another treatment approach, psychoanalysis, which included hypnosis. It was widely criticized and dismissed, making way for yet another form of treatment, one that dealt with the somatic system. This form of treatment was based on the precept that mental pathology is a result of biochemical imbalance in the body. Its goal was to reestablish this balance in order to restore mental health. Somatic treatment included electroconvulsive therapy, psychosurgery, and psychopharmacology.

The field of psychopharmacology is not a new one. Like many aspects of medicine, its roots date back to ancient times. It has been around for as long as humans have started using psychoactive substances from plant and animal sources. Its beginnings can be traced as far
back as the times when hunters and gatherers picked up magic mushrooms and cannabis flowers for use during ritual ceremonies. The mind-altering properties of these substances evoke divine revelations that many took to heart. If you think about it, it isn’t a far cry to say that tribal wars have been fought because of mushrooms. Many have paid with their lives when hallucinatory visions commanded a human sacrifice. The survivors soon paid a price too, and so did their future generations. Unbeknownst to them, they have paved the way for mankind’s first endeavor into what the average modern man would call a “drug habit”. Ignorance was bliss, for a while at least, before psychological dependence kicked in and ruined the “trip”.

Modern psychopharmacology focuses on the drugs that are clinically relevant to modern psychiatry practice. History has taught medical practitioners the one lesson that their predecessors have paid dearly to learn: control. Intensive research and historical data backed by scientific experiments have lead to the isolation of active compounds from their plant and animal sources, successfully identifying the single chemical entity that makes each psychologically active.

As a result, modern psychopharmacology can boast a wealth of benefits that these active compounds offer to its patients and practitioners alike. Perhaps the most important benefit is the semblance of control that synthetic versions of these drugs give to practitioners and patients. The isolation of active compounds set the foundation for its structural elucidation and ultimately, its synthesis in the laboratory. The association between the two is now known as
structure-activity relationship (SAR) and was pioneered by Bovet and his colleagues in the 1930s using psychoactive drugs related to antihistamines. Synthetic variations of the same active component allowed scientists to experiment with dosages, routes of administration as well as identify therapeutic and side effects. This new knowledge led to tighter restrictions; and, at the same time, the paradoxical freedom and confidence to experiment with its use.

Let’s take the example of Cannabis sativa, a plant commonly known as weed. Weed contains Δ-9-tetrahydrocannabinol (THC), the principal psychoactive component that is responsible for its hallucinogenic properties. These days, cannabis is much more than just a shaman’s drug of choice for evoking the spirits; it has become a popular research molecule in laboratories. There is widespread interest in its use in the treatment of glaucoma, AIDS wasting, neuropathic pain, treatment of spasticity associated with multiple sclerosis, and chemotherapy-induced nausea. Despite this, the U.S. Food and Drug Administration (FDA) has not approved the use of “medical marijuana” in the country, although, it allows and assists in the scientific research of its medical uses. Presently, there are two cannabinoids that received FDA approval, namely Dronabinol and Nabilone. Additionally, the American Marijuana Policy Project released results of clinical trials that show cannabis as a promising treatment for cancer and AIDS patients. Dronabinol is used in anorexia associated with AIDS.
Like many scientific fields, there is always plenty of room for improvement. Perhaps centuries from now, medicine will truly only bring the benefits and eliminate the negative facets altogether. But then again, perhaps not; after all, medicine and menace almost always go hand in hand.

In the context of mental health, little doubt exists that psychopharmacology developed to revolutionize psychotherapy in the 1960s. Aside from those with the severe form of the disease who posed a threat to society, psychopharmacological treatments allowed patients to take an active role in their treatment. The drugs allowed them to go home, hold down jobs and be among their peers; essentially function as normal individuals in polite society. No longer did they carry the stigma of their illness, nor were their peers entitled to even know about it. For the first time in history, mental illness became an acceptable entity in social circles, its dreadful presence controlled and hidden by psychoactive drugs.

This medical advancement came with another price, an ill-concealed one this time. It encouraged the deinstitutionalization of the mentally ill in the U.S. that by the 1980s found many of the mentally ill on the streets, homeless and ill equipped to take care of themselves. Perhaps the greatest mistake here was overestimating the positive effects of psychopharmacological treatment. Patients were treated with drugs instead of locked up in asylums. This was a good thing - to some extent. However, they were still unprepared to handle the demands of being independent and social individuals. Serious repercussions led to the surge of incarceration of the mentally ill during this time. A 1992
survey found that 7.2 percent of the inmate population in the U.S. prisons was “seriously mentally ill” and 25 percent of that population was being detained without charges until the few of the remaining functioning mental hospitals could accommodate them.⁹

**Epidemiology Of Mental Illness**

Mental illness is an important cause for concern in both adults and adolescents. The condition often co-exists with other chronic diseases that amount to even greater morbidity and mortality rates. According to the World Health Organization, disability due to mental disorders is higher than cancer and heart disease in developed countries, such as the U.S. Geographically speaking, the number of depressed individuals is greatest in the Southeastern states with 13.7% in Mississippi and West Virginia vs. 4.3% in North Dakota.¹⁰

**Depression in Adults**

Using continuously gathered data, the two Centers for Disease Control and Prevention (CDC) surveillance systems, NHANES (national estimates) and BRFSS (state estimates), estimate that the occurrence of depression from 2005-2008 (the most current data published) to be 6.8% of the adult population who participated.¹⁰ When it comes to the prevalence of mental disorders among age groups, the aging population living in nursing homes carries the highest number.
Beginning in 2004, mental illness as a primary diagnosis was found in 18.7% of 65-74 years old residents and 23.5% over the age of 85 years old. This is no surprise since the onsets of dementia and Alzheimer disease occur between those age groups. Specifically, mood disorders and dementia were commonly diagnosed among those 65-74 years old and 75-84 years old, respectively. The older the residents are, the higher is their chance of being diagnosed with dementia. For example, 41% of residents over the age of 85 years old were diagnosed with dementia. As of 2004, approximately 67% of nursing home residents had a diagnosis of a mental illness.¹⁰

**Prevalence of Mental Disorders in Adolescents**

According to a National Comorbidity Survey-Adolescent (NCS-A) Supplement published in 2010, the most lifetime prevalent mental disorder in the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) text revision was anxiety (31.9%); followed by behavioral disorders (19.1%), mood disorders (14.3%), and substance use disorders (11.4%).

The overall prevalence of disorders with severe impairment and/or distress was 22.2% (11.2% with mood disorders; 8.3% with anxiety disorders; 9.6% behavior disorders). The median age of onset for disorder classes was earliest for anxiety (6 years), followed by 11 years for behavior, 13 years for mood, and 15 years for substance use disorders.¹¹
The Human Nervous System

The human nervous system is basically composed of the central nervous system (CNS) and the peripheral nervous system (PNS). The brain and spinal cord comprises the central nervous system while the peripheral nervous system is composed of spinal nerves that branch from the spinal cord and the brain.

The Brain

The brain is the most complex organ in the human body. It is divided into three main parts: the cerebrum, cerebellum and brain stem.

Cerebrum

The cerebrum is part of the forebrain, along with thalamus and hypothalamus. It is the largest component of the human brain and is further divided into the right and left hemispheres, which are joined together by a collection of white matter of fibers, termed as corpus callosum. Each of the cerebral hemispheres in the cerebral cortex is further divided into four lobes: the frontal lobe, the parietal lobe, the temporal lobe and the occipital lobe.

One of the brain’s most prominent fissures, the lateral sulcus, partitions the frontal and parietal lobes from the temporal lobe above. Similarly, the central fissure called the central sulcus, partitions the frontal lobe above from the parietal lobe below. An embryonic telencephalon is the equivalent of the cerebral cortex and basal ganglia in the fully developed human brain. The limbic system is a
network of structures from the telencephalon, diencephalon and mesencephalon.

Forebrain:

The cerebral cortex is the outermost layer of the cerebrum, which is composed of gray matter. The gray matter is made up of neuronal cell bodies, unmyelinated axons, and dendrites, which are important nerve structures involved in communicating muscle movements and sensory perception. The cortex has a folded structure called gyrus accompanied by prominent fissures called sulcus.

Below the cortex are cortical fibers that form a connection with the neurons. Axons are covered by myelin sheath that facilitates the fast conduction of nerve impulses. Myelin is what gives the name of white matter to the cortex. The cortical and the subcortical parts together form the limbic system, which is responsible for the formation of memory and emotional responses. A study by Jong H. Hoon of the University of California-Davis in 2013 suggests that the circuit connecting the prefrontal cortex with the basal ganglia is a site of communication disturbance in schizophrenics. The results of the fMRI data found that schizophrenics have a reduced and increased activities in the prefrontal cortex and the basal ganglia, respectively.\(^{191}\)

The limbic system allows the interaction between the cortex, thalamus, hypothalamus, and the brainstem. It borders the thalamus at both
sides, just under the cerebrum, and encompasses the structures hippocampus, amygdala, hypothalamus, and thalamus.

Hippocampus:
The hippocampus is made up of two horn-like structures that originate from the amygdala. It is responsible for making and storing new memories, or short-term memories, into long-term memories. When damaged, the person might recall old memories but unable to make and store new ones. Skills that were learned prior to the damage will still be intact. According to the National Institute of Health (NIH), it may play a role in mood disorders through its control of a major mood circuit called the hypothalamic-pituitary-adrenal (HPA) axis. A study using mouse models, by Schobel, et al. published in 2013, found reduced hippocampal size as a result of glutamate-driven hypermetabolism. The results suggest that the brains of patients with schizophrenia may also exhibit significant atrophy of the hippocampus and hypermetabolic activity.

Amygdala:
Amygdala is made up of two lumps of neurons that are shaped like almonds. When stimulated, the person responds with anger and fear. The so-called fight and flight response is believed to originate from this region. It is also responsible for storing memories that stimulated past fear responses such as falling from a first story window as a child. A full understanding of this structure may be useful in the treatment of phobias, anxiety, and post-traumatic stress disorder (PTSD).
Hypothalamus:

The hypothalamus is the thermostat of the body, located in the brain. Its primary function is homeostasis. It is part of the autonomic nervous system that regulates blood pressure, anger, sexual response, heart rate, digestion, etc. The hypothalamic nuclei are positioned on the walls of the third ventricle.

Thalamus:

Thalamus is largely made up of gray matter and plays an important role in receiving and filtering all sensory information (except olfactory). A Swedish study published in 2010 found that mentally ill patients, such as schizophrenics, share a common brain feature involving the thalamus with creative individuals. These individuals had lesser dopamine receptors (D2) in their thalamus, which indicates less filtration of information.\(^\text{13}\)

*Cerebellum*

The cerebellum occupies the portion of posterior fossa, which is located dorsally to the pons and medulla. It is involved in motor control, posture and balance. The cerebellum encompasses structures like finer folia and fissures similar to gyri and sulci in the cerebrum. The cerebellum is composed of two hemispheres that are connected at the center by the midline structure, vermis.
The cerebellar cortex is made up of three layers: molecular, Purkinje, and granular. Also, there are four deep cerebral nuclei in the cerebellum termed as the fastigial, globose, emboliform, and dentate nuclei. Aside from these three structural layers, there are also other structures in the brain such as the meninges and cerebrospinal fluid that help it fulfill its overall functions. They are discussed individually, in brief below.

Meninges:
There are three layers of meninges that cover the brain and the spinal cord. These are:\[14\]
- Pia mater
- Arachnoid layer
- The dura mater

The innermost of the layers is called the pia mater, which tightly encloses the brain. It is rich in blood vessels. The arachnoid layer is situated outside the pia mater and looks like a thin layer of web. Between these two layers is the arachnoid space, which contains the cerebrospinal fluid.

Cerebrospinal fluid:
The brain is completely immersed in a serum-like liquid called the cerebrospinal fluid. It is produced in the choroid plexus and freely circulates around the ventricles of the brain, spinal cord and the
subarachnoid space. It is both a mechanical and an immunological barrier that helps keep the brain infection-free and void of mechanical injuries.\textsuperscript{14,15}

\textit{Brain Stem}

Under the limbic system is the brain stem. It is made up of the medulla, pons and the midbrain. Each structure is discussed below.

Medulla:

The medulla, also called the medulla oblongata, is situated in the lowest part of the brain. It is connected to the midbrain via the pons and continues posteriorly to the spinal cord. The medulla has both gray and white matter in its structure just like the cerebellum and cerebrum. Its primary function is regulation of breathing and heart rate.

Pons:

The pons lies superior to the medulla. It has a ventral surface, which is characterized by a band of horizontal fibers that enters the area of contralateral middle cerebellar peduncle and finally the cerebellum. It plays a role in sensory analysis and movement. Its connection to the cerebellum also makes it an important organ in maintaining posture.

Midbrain:

The midbrain is the most superior aspect of the brainstem, which lies between the forebrain and hindbrain. It contains a reticular formation,
a part of the tagamentum, which is implicated in the regulation of motor functions. On the ventral side of the midbrain, there are two bundles that diverge to form cerebral peduncles. The third cranial nerve (oculomotor nerve) can be seen between the cerebral peduncles. On the posterior side of the midbrain, there are two pairs of protrusions, which are the superior and inferior colliculi.

Additionally, there are twelve cranial nerves with the function to send the motor signals to and from the head and neck. The nervous system is further discussed in the following section.

**The Nervous System**

There are basically two types of cells in the nervous system; the glial cells and the neurons or nerve cells. Glial cells play a supportive role in the synaptic and electrical interactions, *i.e.*, they support the nerve cells that are primarily responsible for this role.\(^{16}\)

The main functions of glial cells are to:

- Nourish neurons
- Provide a structural support to the neurons
- Help in the removal of waste products from the neurons
- Insulate neurons

Neurons, on the other hand, play a significant role in electrical signaling and synaptic communication in the nervous system and are
regarded as the primary line of communication between its various parts. The neuron is the messenger in the body that receives and processes information before relaying the same information to the brain and other parts of the body. It is made up of three parts: the dendrites, soma and the axons.

**Dendrites**

Dendrites are the branched extensions from a nerve cell body (soma). They are found in more numbers than axons. Anatomically, they look like numerous twigs and branches that project from a tree. These projections increase the surface area of the cell body. Their primary function is to receive nerve signals from other neurons through its terminals called synapse. Basically, dendrites form the postsynaptic terminal of a synapse.

**Soma**

Soma is the nerve cell body. It is the most important part of the neuron as it contains the nucleus and other important cellular organelles such as the mitochondria and Golgi apparatus. The presence of these organelles makes the soma the metabolic center of the neuron. The soma is the part where the signals from the dendrites are received before being passed on further. The cell body and its nucleus maintain the functional role of the overall neuron structure. At
the end of the soma is a structure called axon hillock, which controls the firing of the neuron.

**Axon**

Axons are the single long fibers that extend from the soma. Their primary function is to send information to the muscles, other neurons, the brain and parts of the body. The larger the surface of the axons, the faster is the rate of neuronal transmission between neurons.

At the one end of the axon is the axon terminal, which transmits information across the synapse and into another neuron. The junction between the axon of one neuron and the dendrites of the neighboring neuron is called the synapse.\[^{17}\] The neuron whose axon sends out the information is called the presynaptic neuron and the neuron whose dendrites receive the same information is called the postsynaptic neuron. A fatty substance coats and insulates the axons called the myelin sheath. The Schwann cells manufacture it, and one of its primary functions is to facilitate and speed up neuronal transmission along the axon fiber.

**Resting Potential**

A fluid found intracellularly and extracellularly of a nerve cell serves as a medium to conduct electrochemical signal in and out of cells. It contains positively and negatively charged molecules (ions), though not in equal concentrations. The membrane that separates the two is called the semi-permeable membrane.
The intracellular compartment harbors more negatively charged ions when at rest, making it a slightly more negatively charged environment. At this state, there are more sodium ions (Na+) outside the neuron than inside it and more potassium ions (K+) inside than outside it. A nucleus at its resting potential is inactive, a state wherein there is a charge of about \(-70 \text{ mV}\).

*Action Potential*

When a neuron is stimulated with an electrochemical impulse, its resting potential moves towards 0 mV. It is triggered by the opening of the voltage-gated channels of the neuronal membrane, allowing the inward movement of the sodium ions and increasing the amount of positively charged ions in the neuron. An increased amount of positive charges in the neuron results in its depolarization. When this happens, the channels close and inhibit further inward movement of ions. This short period of time results in a dormant span of about 1-2 milliseconds and is called the absolute refractory period. The neural impulses always follow the All or None Law, which means that neurons only fire an impulse when stimulation reaches a certain threshold. Otherwise, no neural firing happens because a weak stimulus is not strong enough to generate an action potential.

There are certain drugs and poisons that alter the axon conduction. One such example is the antiepileptic drug, levetiracetam. Its exact mechanism is unknown; however it is believed that it inhibits the
opening of voltage-gated channels, thereby, blocking the impulse conduction across the synapses. Similarly, valproic acid, which is another anticonvulsant drug, is used to enhance the transmission of the neurotransmitter GABA by inhibiting GABA transaminase, the enzyme responsible for the breakdown of GABA. The drug also blocks the voltage-gated sodium channels.

Several deadly toxins work similarly; they interfere with neural transmission. As mentioned above, the flow of sodium ions in and out of neurons is a vital step in the conduction of the nerve impulse along the axons. The toxin produced by puffer fish, tetrodotoxin, specifically binds tightly with the sodium ion channels of neural cell membranes and prevent the conduction of nerve impulses along its nerve fibers. The result is respiratory paralysis.\textsuperscript{18} Alcohol is another example. It inhibits axonal transmission by blocking the excitatory channels on the postsynaptic neuron. Moreover, it lowers the rate of action potential coming from the presynaptic neuron.

\textit{Synapse}

An understanding of synaptic transmission is important in understanding the basic principle of chemical signaling between neurons. The biochemical interaction between neurons occurs at the end of the axon, in a structure called synapse.
As briefly mentioned above, a synapse is the gap that forms at the junction between the axon of one neuron and the dendrite of another neuron. It is basically the site, though not a physical one, where an axon terminal ends near a receiving dendrite. As neurons form a network, they need to be interconnected for the purpose of transmission of nerve impulse from one neuron to the other but unlike other cells; there is a lack of a cellular continuity between two neurons, a gap between them called synaptic space. Moreover, these synaptic connections are not inert.

Neurons form new synapses or fortify existing synaptic connections in response to new experiences. The constant activity in neuronal connections is the foundation of learning.\(^{19}\) The mechanism of chemical signaling involves the release of a chemical called neurotransmitter from the presynaptic neuron, which binds with receptors at the postsynaptic neuron to generate an impulse that travels across to the axon terminal to elicit a response.

**Neurotransmitters**

Neurotransmitters are endogenous chemicals in the human body that are responsible for the transmission of nerve impulses between neurons and target cells across a synapse. Each neuron has a specialized function, \textit{i.e.}, whether it is a cholinergic, dopaminergic, and glutamatergic. A dopaminergic neuron primarily synthesizes the neurotransmitter dopamine and a glutamatergic neuron synthesizes the amino acid neurotransmitter, glutamate.
For a signal to get transmitted across, an optimum amount of neurotransmitters in the synaptic space must be present. In mentally healthy individuals, there is a balance between the amount of neurotransmitters in the synaptic space and in the presynaptic neuron. It is the disruption of this balance that leads to mental and metabolic disorders affecting sleep, mood, weight, etc. Neurotransmitters can be categorized according to their chemical composition, namely:

1. Small molecule neurotransmitters
2. Neuropeptide or peptide transmitters

Small molecule neurotransmitters are synthesized at the terminal site of the axon. The enzymes needed for the synthesis of these neurotransmitters are synthesized within the cell body of the neuron and then transported to the nerve terminal cytoplasm by means of a process called slow axonal transport. These enzymes then generate a pool of neurotransmitters in the cytoplasm.²⁰

The mechanism involved in the synthesis of neuropeptides is different from that of the small molecule neurotransmitters. It involves protein synthesis. The first step involves gene transcription within the nucleus of the cell; a process involving the construction of the corresponding strand of messenger RNA by using a peptide coding sequence of DNA as a template. The messenger RNA then acts as a code to form a sequence of the amino acids, forming the neuropeptide needed at the nerve terminal.²⁰ After synthesis, the neurotransmitters, both small molecules and neuropeptides, are stored in small vesicles within the axon terminal, awaiting an action potential to arrive and stimulate
their release. Some of the important neurotransmitters implicated in psychopharmacology are acetylcholine, serotonin, dopamine, norepinephrine, epinephrine, glutamate and GABA. Each one is discussed individually briefly below.

Acetylcholine

Acetylcholine is basically synthesized by the combination of two compounds; choline and acetyl-CoA. The reaction is catalyzed by the enzyme choline acetyltransferase. After its synthesis, it is stored in the vesicles to prevent its degradation by the enzyme, acetylcholinesterase. Acetylcholine is released from its vesicles as a response to an action potential that moves along the motor neuron and carries the depolarization wave to the terminal buttons.

Acetylcholine is used to regulate muscle movement. Its cholinergic neurons are found all over the CNS, especially the brain, where it is involved in numerous functions such as pain perception, neuroendocrine regulation, REM regulation and memory and learning formation. Damage to the cholinergic system is an important pathology implicated in Alzheimer’s disease.

The two main receptors upon which acetylcholine act on are muscarinic and nicotinic receptors. When bound to the ligand-gated ion channels, nicotinic receptors, acetylcholine stimulates the influx of sodium ions, resulting in the depolarization of the effector cells. The
succeeding hyperpolarization and slow depolarization are mediated by the binding of acetylcholine with muscarinic receptors, specifically the M₂ and M₁. All muscarinic receptors are G-protein coupled receptors, which are classified as M₁, M₂, M₃, M₄, and M₅.

*Norepinephrine*

Norepinephrine is the neurotransmitter that plays an important role in conditions related to stress. Along with epinephrine, it enables the body to “fight or flight” in emergencies by stimulating the heart rate, blood circulation and respiration to compensate for the increased oxygen requirement of the muscles.

Norepinephrine is the primary neurotransmitter for postganglionic sympathetic adrenergic nerves. It is synthesized within the nerve axon, stored in vesicles and released when an action potential travels downward in a nerve. It is synthesized from another neurotransmitter, dopamine.

The 1ˢᵗ step in its synthesis involves the transport of the amino acid, tyrosine, into the sympathetic nerve axon where tyrosine is converted to DOPA by the enzyme tyrosine hydroxylase. DOPA then gets converted to dopamine, which in turn, is converted into norepinephrine by the enzyme, dopamine beta hydroxylase. Norepinephrine is primarily released into the extracellular space whenever there is an increased intracellular calcium level. Other factors that trigger its
release are cyclic nucleotides, phosphodiesterase inhibitors, beta-adrenoceptor agonists, cholinergic nicotinic agonists, and angiotensin.

Norepinephrine is metabolized by the enzyme catechol-o-methyltransferase (COMT) and its final metabolic product is vanillylmandelic acid. The norepinephrine transporter (NET) is responsible for the reuptake of extracellular norepinephrine. NET is a target of many antidepressant drugs. A decreased number of NET is associated with Attention Deficit Hyperactivity Disorder (ADHD).

**Dopamine**

As mentioned just above, dopamine is synthesized from the amino acid, tyrosine. Tyrosine is converted to dopamine by the action of enzymes, tyrosine hydroxylase and L-amino acid decarboxylase, respectively. Just like the other neurotransmitters mentioned previously, dopamine is stored in the vesicles of the dopaminergic neurons. Like norepinephrine, the exocytosis of dopamine is triggered by an increased influx of calcium ions within the neuron.

Two types of transporters called the dopamine transporter (DAT) and vesicular monoamine transporter (VMAT) are implicated in dopamine reuptake. DAT functions as a means of transport for dopamine from the extracellular space to the intracellular space while VMAT is responsible for reloading dopamine back into the vesicles.
Dopamine reuptake inhibitors help to maintain high levels of dopamine at the postsynaptic space, sustaining and prolonging its effects. The main enzymes involved in its metabolism are MAO and COMT. The latter is the target enzyme of older antidepressants such as tranylcypromine. Deficiency of dopamine in the brain is implicated in the pathology of Parkinson’s disease.

**Serotonin**

The synthesis of serotonin involves the conversion of another amino acid, L-tryptophan, to 5-hydroxytryptophan, by the enzyme L-tryptophan hydroxylase. The final step involves the decarboxylation of 5-hydroxytryptophan by the enzyme L-aromatic amino acid decarboxylase. Serotonin is metabolized by the enzyme monoamine oxidase inhibitor (MAO) to 5-hydroxyindoleacetic acid (5-HIAA).

The main function of serotonin is regulation of mood, appetite, sleep, cognition, and blood coagulation. The most widely prescribed and efficacious antidepressants, selective serotonin reuptake inhibitors (SSRIs), and older antidepressants such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), act on the serotonergic system by inhibiting serotonin reuptake into the presynaptic vesicle.

**Glutamate**
Glutamate is the primary excitatory neurotransmitter in the brain. An injury to a nerve (i.e., brain injury) results in its release and excessive concentration in the extracellular space, leading to excitotoxicity. Unlike the other neurotransmitters, it is an amino acid itself, rather than synthesized from it. Its precursor is glutamine. A study conducted by researchers at Columbia University Medical Center (CUMC) and published in the April 2013 issue of Neuron, found that excessive glutamate levels in the brain is a precursor to psychosis in individuals at high risk for developing schizophrenia. The study suggests using its findings as an early diagnostic tool to identify those individuals and consequently correct the increased glutamate levels in order to slow the progression to full blown schizophrenia later in life.

GABA

The inhibitory neurotransmitter GABA is synthesized from the amino acid, glutamate, by the enzyme glutamate decarboxylase in the GABAergic neurons. The neurotransmitters are then transported into the vesicles with the help of vesicular transporters. Upon release, these neurotransmitters are taken up with the help of the membrane transporters into the neurons where they can be recycled and metabolized by their respective enzymes.

**Basics Of Psychopharmacology**

Psychopharmacology is very complex and extensive division of medicine with roots in the mechanisms of action of psychotropic drugs. Generally speaking, the mechanism of action of drugs is largely due to pharmacodynamic factors.
On the other hand, the onset, duration and magnitude of drug action, are determined by pharmacokinetic factors.

**Overview of Mechanisms of Action**

Psychotropic drugs are amphiphilic in nature, *i.e.*, they possess both hydrophilic and hydrophobic properties. Because of this physical property, psychotropic drugs rapidly reach their sites of action (*i.e.*, cellular membranes, cytoplasm), accounting for the various rapid and short acting anxiolytics and sedatives.

**Pharmacokinetic factors: polarity of psychotropic drugs**

Psychotropic drugs either permeate through plasma membrane (hydrophilic) or build up in the hydrophobic interior of the lipid bilayer of cell membranes. The movement allows cellular interactions with both the membrane macromolecules and with the cytoplasmic molecules. Essentially, the drug’s polarity is a vital factor that allows it to reach the target site or site of action. The concept of polarity as it refers to the elimination of the drug will be discussed later under the “Elimination” section.

Other examples of psychotropic drugs or psychoactive substances that are amphiphilic in nature are:

- Fluoxetine (can be used to treat anorexia nervosa at higher doses)
• Caffeine
• Imipramine

Absorption and distribution

Absorption refers to the movement of drug from the site of administration to the blood circulation. In the case of many psychotropic drugs, the site of drug entry is usually the mouth or the veins. In the case of the latter, no absorption takes place since the drug is injected directly into the blood. The different routes of drug administration will be discussed later in detail in the Section VI of this course.

Oral administration of drugs requires disintegration of the formulation, absorption from the small intestines and distribution into the site of action (brain) in order to exert its pharmacological action. The speed at which the stomach empties (gastric emptying rate) its contents into the small intestines is the most important factor that determines the rate of absorption or orally administered drugs. Physical activities, amount of food and the type of food consumed determine the gastric emptying rate. It is this reason that certain drugs are best administered before meals.26

Another factor that influences drug absorption is its concentration, which is determined by gender, age, body size and comorbidities. Generally, the larger the patient, the greater the dilutions of the drug (due to greater ratio of fat to water) in the fluid volume, which in turn
results in lesser amount of drug reaching the target sites. This is why certain individuals require greater dosage than others. Dosages are based on the average individual size: 68 kg between 18-65 years of age.

Gender also plays a role in this absorption factor. Women tend to have smaller fluid volume (where the drug is concentrated) than men, resulting in greater accumulation of the drug at the target site. Finally, the other two factors that influence absorption are solubility and ionization of the drug. Once absorbed, the drug enters the systemic circulation and distribute into the tissues. Unpredictable differences in protein binding in tissues, regional variations in pH, and differences in the permeability of cellular membranes determine the extent of tissue distribution.²⁷

Generally, the highest concentrations of drugs are found in the heart, brain, kidneys, and liver. The brain is a lipophilic organ, allowing it to receive about 20% of the blood that leaves the heart. Its lipophilicity enables the rapid distribution of lipid-soluble drugs to brain tissues. However, the blood-brain barrier also restricts the movement of ionized molecules from the blood to the brain. The blood brain barrier (BBB) plays a vital function in the distribution of psychoactive substances and their subsequent circulation in the brain. For example, alcohol is a lipophilic substance, which readily crosses the blood brain barrier to cause its mind-altering effects.
Protein binding

The binding of drugs with plasma proteins such as albumin and α-glycoproteins (inactive sites) is known as protein binding. It limits the amount of drug that can be distributed to the target site. Because protein-bound drugs do not cause a pharmacological effect, they are kept in reserve. This type of binding is also referred to as depot binding.28

Protein binding affects the magnitude and duration of drug action. These consequences are listed in the table below:

The effects of protein binding

<table>
<thead>
<tr>
<th>Protein binding features</th>
<th>Effects on drug action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid binding to inactive sites</td>
<td>Late onset; smaller magnitude</td>
</tr>
<tr>
<td>Varying extent of binding</td>
<td>High affinity: less free drug</td>
</tr>
<tr>
<td></td>
<td>Low affinity: more free drug</td>
</tr>
<tr>
<td>Competitive inhibition or inducement</td>
<td>Drug displacement resulting in toxicity</td>
</tr>
<tr>
<td></td>
<td>and greater side effects</td>
</tr>
<tr>
<td>Unmetabolized bound drug</td>
<td>Prolonged duration</td>
</tr>
<tr>
<td>Redistribution</td>
<td>Quick cessation of action</td>
</tr>
</tbody>
</table>
Protein binding can cause significant drug-drug interactions. An example is the displacement of phenytoin from protein binding sites by the NSAID, aspirin and another antiepileptic drug, valproic acid. The implication of the interactions between these two drugs with phenytoin is not clinically significant because of the transitory nature of the interactions. The displaced phenytoin (unbound) is rapidly metabolized, maintaining its steady state plasma concentration and preventing untoward side effects. On the other hand, the interaction poses a challenge to clinicians who are monitoring phenytoin levels in certain patient groups.

Other psychotropic medications such as fluoxetine and diazepam exhibit an extensive affinity to proteins, thus, making them frequently susceptible to drug interactions. Another implication of increased protein binding is a slower rate of drug metabolism. A good example is the detection of delta(9)-tetrahydrocannabinoid (THC) in the urine even after cessation of cannabis intake several days before a sample is taken for testing. THC is the primary psychoactive component of cannabis, which is lipophilic and stored in fat tissues, making its release and metabolism slow. This concept makes pre-employment and student drug testing possible.²⁰⁵

Lastly, protein binding is implicated in rapid termination of drug action. A good example is the drug thiopental, a rapid but short acting, highly lipid soluble barbiturate that is used in the induction of general anesthesia. Its rapid and short duration of action is due to its highly
lipophilic nature that allows it to immediately penetrate the blood-brain barrier, distribute into the brain tissues and exit again. The rapid movement is reflected in its blood level that goes up and falls short quickly.

**Biotransformation**

The metabolism of drugs is essential to its final removal from the body. Drug molecules are biochemically changed by enzymatic reactions in the stomach, kidneys, blood, brain, and the liver, where the majority occurs. The process occurs in two stages.

**Phase 1 (Stage 1):**

At the first stage, the drug molecules are modified via nonsynthetic chemical reactions that render them water-soluble. The most common reaction that takes place is oxidation followed by reduction, or hydrolysis. Prodrugs rely on oxidation for conversion to an active metabolite. A good example is the anticonvulsant, primidone, which is oxidized to phenobarbital and phenylethylmalonamide (PEMA) by the most important microsomal enzyme - cytochrome P450 family of enzymes.

**Phase 2 (Stage 2):**

The second stage involves the conjugation of the drug molecules with glucuronide (glucuronidation), sulfate and methyl functional groups. Most psychoactive drugs are deactivated by glucuronide conjugation.
The resulting metabolic products are almost always biologically inactive and freely water-soluble. However, there are exceptions. Oxazepam, the metabolite of diazepam (prodrug) from glucuronidation, is biologically active and exerts GABA inhibitory effects similar to other benzodiazepines. Oxazepam does not go through hepatic oxidation, which makes it useful in patients with hepatic failure. This is clinically useful in older patients with liver disease because oxazepam is less likely to accumulate and cause adverse reactions. Other examples of psychoactive prodrugs and their metabolites are shown in the table below:

<table>
<thead>
<tr>
<th>Psychoactive drugs and their metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage of metabolism</strong></td>
</tr>
<tr>
<td>Stage 1</td>
</tr>
<tr>
<td>Stage 1</td>
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<tr>
<td>Stage 1</td>
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<tr>
<td>Stage 1</td>
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<td>Stage 1</td>
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<tr>
<td>Stage 2</td>
</tr>
<tr>
<td>Stage 2</td>
</tr>
<tr>
<td>Stage 2</td>
</tr>
</tbody>
</table>
There are numerous factors influencing the rate of biotransformation of psychoactive drugs in the liver, as discussed separately below.

Enzyme induction:

The chronic and heavy use of certain drugs cause a corresponding increased release of cytochrome P450 enzymes in the liver to metabolize them, a phenomenon known as enzyme induction. An example of this is the use of the antiseizure drug, carbamazepine (Tegretol), which induces the family of CYP3A4 enzymes, the same enzyme responsible for the metabolism of estrogen and progesterone hormones. It is for this reason that female patients of reproductive age are not advised to take these two drugs concomitantly since the former decreases the blood levels of the latter and its subsequent contraceptive effects.

Enzyme inhibition:

Much like induction, the activity of enzymes can also be prevented. The phenomenon of metabolic enzyme inhibition is the primary mechanism of action of the drug, disulfiram (Antabuse). Disulfiram is an enzyme inhibitor of aldehyde oxidase. Alcoholics to discourage their own alcohol intake use this drug.

Alcohol is oxidized to its intermediate metabolite, acetaldehyde in the liver, which is in turn further oxidized to the final metabolite, acetic
acid, by aldehyde oxidase enzyme. This action is demonstrated through the equation (below):

\[
\begin{align*}
\text{Alcohol dehydrogenase} & \quad \text{Aldehyde oxidase} \\
\text{alcohol} & \quad \rightarrow \text{acetaldehyde} \quad \rightarrow \text{acetic acid}
\end{align*}
\]

Disulfiram prevents the oxidation of acetaldehyde by blocking aldehyde oxidase. The metabolic inhibition causes the toxic accumulation of acetaldehyde, which is manifested in the form of severe hangover symptoms. These symptoms are often more severe than a “regular” hangover.

Genetic polymorphism:

The genetic make up of individuals (i.e., existence or absence of mutations) influence the metabolism of drugs and substances in the body. For example, Asian men are more susceptible to hangovers than their Caucasian counterpart. The presence of the genetic mutation, ALDH2*2 alleles in Asian genes resulted in their reduced capacity to metabolize the intermediate metabolite of alcohol, acetaldehyde, the substance primarily responsible for the symptoms of hangover.\(^{29}\)

Elimination:

The principal role of metabolism is to prepare drugs for elimination via the liver and kidneys. Other routes of elimination include the breast milk, sweat, hair, feces and breath. The water-soluble metabolites are
trapped by the kidney tubules and subsequently filtered out in the form of urine.

**Pharmacodynamic interactions**

Pharmacodynamic interactions refer to the physiological and biochemical activities of the drug with the body tissues. There are four chief proteins which can bind any drug:

1. Enzymes
2. Membrane carriers
3. Ion channels – pore-forming membrane proteins that act as gate-keepers to the flow of ions across the cell membrane
4. Receptors – surface proteins to which specific signaling molecules may bind

The role of drug-receptor interactions has been discussed briefly in the preceding pages and will be discussed in detail in the succeeding pages of this section. Psychotropic drugs exert their pharmacologic action primarily by agonism or antagonism of neurotransmitter receptors, inhibition of regulatory enzymes or blockade of stimulators of neurotransmitter membrane transporters; the general mechanisms of drug action are outlined in the table below.

**General mechanisms of action of psychoactive drugs**
General mechanism of actions of psychotropic drugs

<table>
<thead>
<tr>
<th>General mechanism of actions of psychotropic drugs</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthesis and storage of neurotransmitters</td>
<td>L-Dopa</td>
</tr>
<tr>
<td>Release of neurotransmitters from presynapse</td>
<td>Zolpidem, benzodiazepine</td>
</tr>
<tr>
<td>Blockade of receptors</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>Breakdown of neurotransmitters</td>
<td>MAO inhibitors, amphetamines</td>
</tr>
<tr>
<td>Reuptake of neurotransmitters</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Transduction of G-proteins</td>
<td>Phenothiazines, butyrophenones</td>
</tr>
<tr>
<td>Effector system</td>
<td>Antidepressants</td>
</tr>
</tbody>
</table>

Drug receptors are large protein molecules in the cell’s plasma membrane, cytoplasm and nucleus that bind with ligands (i.e., drugs, xenobiotics, hormones, neurotransmitters) at the receptor binding (active) sites. The binding of a drug with a receptor results in the formation of drug-receptor complex. A good example of a drug-receptor complex is the binding of GABA receptors with gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system.

GABA receptors are of two types:

1. GABA<sub>A</sub> / ionotropic receptors which form ion-channel pores that allow ions such as Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>, or Cl<sup>-</sup> to pass when GABA binds
with its active site. Benzodiazepines primarily act on \( \text{GABA}_A \) receptors.

2. \( \text{GABA}_B \) / metabotropic receptors are connected with potassium ion channels via G-proteins (transducers). The binding of GABA with these receptors triggers a series of intracellular events that result in the opening of ion channels and activation of secondary messengers.

Common characteristics of drug-receptor complexes that induce physiological and pharmacological effects, include:

- **Specificity:**
  
  Affinity for a receptor is specific, \( i.e. \), the structure of the ligand must conform to the 3D structure of the receptor. High affinity results in high efficacy. Drugs with high affinity and exert pharmacological effects are called agonists. A good example of an agonist is morphine, which mimics endogenous endorphins at opioid receptor binding sites.

- **Receptor occupation:**
  
  Drugs that compete with agonists for the same receptor binding sites but have no efficacy are called competitive antagonists. A good example of a drug that exhibits its pharmacological action through competitive antagonism is memantine. It is a competitive \( N \)-methyl-D-aspartate (NMDA) receptor antagonist that is used in Alzheimer’s disease. It blocks the excitatory effects of the
neurotransmitter, glutamate, in the brain by displacing it from the binding site, essentially preventing neuronal excitotoxicity (a hypothetical pathologic cause of Alzheimer’s disease).

Another type of antagonism via receptor interaction is the binding of a drug with a different receptor that results in the inhibition of drug effect. In this case, the antagonist did not compete for the same receptor hence, the name, non-competitive antagonist. A good example of this antagonistic interaction is the binding of ketamine, another NMDA receptor antagonist with the NMDA receptor channel pore while the endogenous agonist, glutamate, binds to the extracellular surface of the receptor. Activation of two different binding sites results in non-competitive inhibition.

- Longevity of complexes:
  The binding of ligands with receptors is either temporary (reversible) or permanent (irreversible). The drug-receptor complex remains as long as there’s no competition for its binding site. With irreversible antagonists, the drug-receptor complex bond cannot be broken nor overcome simply by increasing the dose of the agonist. On the other hand, some agonists can be displaced from the receptor-binding site by increasing the dose of the antagonist and vice versa.

- Receptor structural change:
The binding of drugs with receptors alters the 3D protein structure of the receptor to cause pharmacological effects.

- **Receptor population:**
  
  The number of receptors available to bind with drugs influences drug response. The up-regulation and down-regulation of receptors is responsible for drug desensitization (tolerance) and tachyphylaxis.

Partial agonists are those drugs that have the affinity for the receptor-binding site but do not exert full efficacy. An example is the anxiolytic, buspirone, which is a partial serotonin 5-HT$_{1A}$ receptor agonist. Psychoactive drugs are almost always used over a long period of time since they are used to control symptoms rather than treat the root cause one time, unlike antibiotics which kill/inactivate offending microorganisms. The chronic use results in changes in the degree of receptor activation and enzyme population. These changes are responsible for some of their most well known adverse effects.

**Up-regulation and Down-regulation:**

*Up-regulation* is an increase in the number of receptors as a compensatory response after continual absence of agonists. *Down-regulation* is a decrease in the number of receptors as a compensatory response after chronic presence of agonists.
Withdrawal syndrome and Rebound effect:

Withdrawal syndrome is a group of symptoms that results from the abrupt discontinuation of receptor activation, following chronic administration of an agonist. The return of symptoms that were previously under control when an agonist is abruptly withdrawn is known as the rebound effect. Examples are rebound depression and insomnia, which happen when benzodiazepines are suddenly discontinued. Because of this, benzodiazepines should be discontinued slowly, with doses tapered off gradually over a period of weeks.

Tolerance (receptor desensitization):

The scale of drug response (i.e., tolerance) is influenced by the concentration of the agonist at the receptor-binding site. Also, the sensitivity of the receptor to the agonist plays a role. Tolerance is basically the body’s adaptation to the constant presence of an agonist. Once the body develops a tolerance for a drug, its sensitivity for it is reduced, thus, requiring a higher dose to produce the original effect.

Tachyphylaxis:

It is a form of drug tolerance that is sudden in onset following successive doses of agonists in short intervals. Heroin causes tachyphylaxis and so do psilocybin and LSD, all well-known illicit drugs. Psychotropic drugs are most often classified according to their effects on the central nervous system functions.
General effects of psychotropic drugs on the CNS

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Effects</th>
<th>Class</th>
<th>Drug examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigilance / Alertness</td>
<td>Positive</td>
<td>Stimulants</td>
<td>Amphetamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Hypnotics</td>
<td>Barbiturates, benzodiazepines</td>
</tr>
<tr>
<td>Affectivity</td>
<td>Positive</td>
<td>Antidepressants</td>
<td>MAOIs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Dysphoric drugs</td>
<td>Reserpine</td>
</tr>
<tr>
<td>Psychic mechanism</td>
<td>Positive</td>
<td>Atypical antipsychotics</td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Hallucinogens</td>
<td>PCP, marijuana</td>
</tr>
<tr>
<td>Memory</td>
<td>Positive</td>
<td>Nootropics</td>
<td>Piracetam</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Amnestic drugs</td>
<td>Anticholinergics</td>
</tr>
</tbody>
</table>

Overview of Goals in Management

Management of mental illness encompasses a broad field of medical practice that includes pharmacology, psychiatry and behavioral science. The management and treatment plans for mental illness depends on its type, severity and individual history and preference. The full discussion is outside the scope of this article, but students may wish to defer to later study to address the cumulative approach to the management of mental illness. Generally, however, the management and treatment plans may include one or more of the following interventions:30
1. Psychopharmacologic treatment

2. Psychotherapy approaches
   • Brain stimulation
   • Institutionalization / rehabilitation programs
   • Psychodynamic therapy
   • Cognitive-behavioral therapy
   • Group therapy
   • Family intervention
   • Social rhythm therapy

3. Self-care

Other interventions and services may include:
   • Employment assistance
   • Housing assistance
   • Reintegration measures into society
   • Psychosocial rehabilitation
   • Assertive community treatment

Additionally, several healthcare personnel may be involved in the execution of the management and treatment plans, such as:
   • Family clinician
• Psychotherapist
• Psychiatrist
• Pharmacist
• Social worker
• Family members
• Guardian

The psychopharmacologic treatment plan used will depend on the type of mental illness and may include any or more of the following:

• Antidepressants
• Antipsychotics
• Nootropics
• Anxiolytics
• Mood stabilizers

An example of how treatment plans often evolve and might be revised based upon organic and other causes is well known in therapies for individuals with a diagnosis of substance abuse and addiction. Recovering drug addicts are often beset with comorbid mental disorders (depression, anorexia nervosa, insomnia) and may require an antidepressant and a sleep aid.
Recovering addicts may receive and require enrolment in the following programs and treatments:

- Psychotherapy
- Psychopharmacologic drugs
- Detoxification
- Support groups
- Partial hospitalization programs

**Psychopharmacologic Treatment Plan**

Psychopharmacologic treatment plans are based on 3 fundamental needs of the mentally ill patient. These are:

- Resolution of acute episodes
- Long term symptom control
- Improvement quality of life

Chronic psychopharmacologic treatment presents a mixture of trepidation and warm anticipation to both clinician and patients. Trepidation because psychoactive drugs are known to cause physical and physiological dependence even at therapeutic doses, and warm anticipation because these drugs are backed by evidence-based studies that prove their effectiveness in improving the quality of life. Needless to say, important in the diagnosis of mentally ill individuals, such as those with schizophrenia, mood and anxiety disorders, is to
distinguish which patients requires short term and long term maintenance medications.

In general, there are three characteristic features of mental disorders that indicate the need for maintenance therapy on psychoactive medications. These are listed as:

- Early onset
- Persistence
- Risk of relapse

The standard approach is to differentiate acute symptom relief from partial remission. If the episode occurred while on maintenance medication, the clinician should consider the probability of recurrence (and its implications) against the consequences of maintenance medication (i.e., adverse effects). A rational strategy in this case is to maintain medications for six months after full remission is achieved. If the symptoms occur more than once (recurrence), the strategy should shift to maintaining medications for more than six months after the initial episode. General goals of short term and long-term treatments are compared below.

**General goals of short term and long-term treatments**

<table>
<thead>
<tr>
<th>Long term</th>
<th>Short term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimization of relapse risk</td>
<td>Reduction of symptoms</td>
</tr>
</tbody>
</table>
Reduction of symptom exacerbation | Alliance with patient and family
Maintenance of effective dose | Patient and family education
Frequent monitoring of side effects | Return to premorbid condition
Maximization of compliance | 
Reduction of the social burdens of mental illness | 

The table below lists the specific mental disorders and the more specific and rational approaches to their long-term and short-term treatments. While they are included in a separate category of personality disorders, Developmentally delayed (DD) and Antisocial Personality Disorder are also worth mentioning here as they also have their own specific set of short or long-term treatment approaches.

**Different mental disorders and their treatment approaches**

<table>
<thead>
<tr>
<th>Mental disorder</th>
<th>Short term treatment</th>
<th>Long term treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>Reduction of severe psychotic symptoms (acute phase); sustenance of therapeutic gains (resolving phase)</td>
<td>Prevention of relapse; rehabilitation; tardive dyskinesia prevention / minimization; cognitive and negative symptoms management; Facilitation of</td>
</tr>
<tr>
<td>Disorder</td>
<td>Goals</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Rapid reduction of affective symptoms; return to premorbid state; frequent monitoring</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Facilitation of mood and functioning recovery; facilitation of indefinite psychopharmacologic treatment with tapering of doses at end and initiation of each drug.</td>
<td></td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>Acute treatment; identification of and removal of exogenous triggers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aggressive treatment of residual subsyndromal symptoms; facilitation of compliance to therapy.</td>
<td></td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>Remission of symptoms; restoration to normal levels of psychosocial function</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prevention of withdrawal symptoms by tapering of doses between drugs; maintenance of psychosocial function, employment and relationships.</td>
<td></td>
</tr>
</tbody>
</table>

**Overview of Newer Versus Older Psychotropic Medications**

The 19th and 20th centuries saw the emergence of psychotropic drugs that were initially used to treat other medical conditions. Bromides were introduced in 1857 as an anticonvulsant, and the oldest group of depressants, barbiturates, in 1912 for insomnia. These two groups of drugs were found to have sedative effects. Other drugs soon emerged such as amphetamines for depression and lithium for agitation in manic states. The first antipsychotic, chlorpromazine, was first studied for its sedative properties in anesthesiology. Tricyclic antidepressants and monoamine oxidase inhibitors became the
standard of treatment for depression in the 1950s. The most widely prescribed anxiolytics today, benzodiazepines, were introduced in the 1960s.\(^32\)

Initial studies on chlorpromazine showed improved behavior and intellectual performance however, subsequent clinical reports employing more thorough scientific methods did not corroborate these findings. Symptoms such as aggression, hyperactivity, anxiety and intellectual function were not improved with chlorpromazine use. The positive therapeutic outcome of chlorpromazine was attributed largely of its sedating properties.

The first report on the adverse effects of antipsychotics emerged in the 1960s. It was reported that the confined mentally ill on psychotropic medications were experiencing serious side effects ranging from sedation, seizures to tardive dyskinesia. Growing concern amid overuse and misuse of psychotropic medications led to several lawsuits in the 1970s and 1980s.

*Chemical restraints*

The 1970s saw the advent of psychotropic drugs as “chemical restraints”. According to the Accreditation Council for Facilities for the Mentally Retarded (ACMR) Standards for Institutions (1971), chemical restraints are:\(^{33}\)

- For staff convenience
• Drugs that restrict patient activities and movement (i.e., benzodiazepines)

Presently, the FDA approves no drugs for these purposes anymore. According to the Federal Nursing Home Reform Act, patients have the right to be free from physical or chemical restraints imposed for purposes of discipline or convenience and not required to treat their medical symptoms. The list below summarizes the consequences of chemical restraints.³⁴

• Agitation
• Gait disturbance
• Memory impairment
• Sedation
• Withdrawal
• Functional decline
• Movement disorders
• Orthostatic hypotension

The last 20 years have seen the emergence of evidence that indicate dual diagnosis of illness. Patients with developmental disabilities (i.e., mental retardation) may also most likely have a comorbid psychiatric disorder. The newfound knowledge has resulted in a multidisciplinary approach in the treatment of both mental illness and retardation. Another example of a dual diagnosis is substance abuse and mental
illness. The presence of both mental illnesses in a patient requires a complex treatment strategy than that of either condition alone. The primary goal of treatment is to prevent life-threatening complications of intoxication.\textsuperscript{35}

In 1987, the Psychotropic Monitoring Checklist for Rule 34 facilities was established to tackle psychotropic drug use in mental institutions and community facilities. The 1990s showed a shift in treatment approach of the mentally ill which was exemplified by the Accreditation Council on Services for People with Disabilities (ACD). The ACD took an outcome-based performance strategy, with the patient’s personal quality of life at the center of it. It primarily centered on patient personal goals, choice, social inclusion, relationships, rights, dignity, respect, health, environment, security, and satisfaction.\textsuperscript{36}

Presently, standard practice requires the thorough assessment of function and behavior, which then forms the basis of psychopharmacologic treatment plans. The assessment includes:

- Eliminating possible medical variables
- Evaluation of environmental triggers
- Assessment of organic causes of illness

**Classification Of Psychotropic Drugs**
In a medical context, psychotropic drugs refer to a class of prescription medications that primarily exert their therapeutic effects on the central nervous system. Whether taken orally or administered intravenously, psychotropic drugs are absorbed by the blood and transported into the brain. They pass through the protective membrane, the blood brain barrier (BBB) and into the brain circulation.

The BBB comprises of capillaries made of tight junctions that do not allow free mixing of substances contained within the blood with the extra cellular fluid. Most drugs cannot filter through the BBB and do not affect brain function. Psychotropic drugs, on the other hand, are formulated especially to cross the BBB and act directly on the brain to alter perception and mood, induce behavioral changes and affect consciousness along with cognition. The basic purpose of these drugs is to bring about the desired changes in mood and behavior to treat and manage psychiatric disorders.

Classifying psychotropic drugs into particular groups that is universally acceptable is difficult and yet it needs to be done. Many of these medications have different primary functions but may eventually exert a wide range of pharmacologic effects on the user. Many strategies have been proposed, however, a definite classification with little or no overlap is yet to be defined.

Psychotropic medications are generally categorized into the following:

- Antipsychotics
- Antidepressants
• Anxiolytics
• Mood stabilizers
• Prescription stimulants
• Sedative-hypnotics
• Miscellaneous drugs (i.e., herbal supplements)

**Antipsychotics**

This subgroup contains a large number of medications that are used to treat psychosis. Psychosis is a generic term that encompasses disorders resulting from abnormal perception of reality accompanied by a defective insight. Psychotic patients primarily experience these two characteristics:

- **Hallucinations:**
  
  Sensory perceptions without an actual stimulus being present

- **Delusions:**

  False beliefs about reality

Psychotic patients also present with social cognition impairments, personality changes and thought disorders. Antipsychotics are used in the treatment of mental illnesses such as schizophrenia, bipolar disorder, delusional disorders, and also wide range of non-psychotic disorders such as Tourette syndrome, autism, and dementia.

Antipsychotics work differently from regular medications in a way that they may not always produce the same effect in different patients
despite the similarities in their psychotic states. They may very well exhibit different efficacies and duration of treatment across different patient groups. Interestingly, some atypicals are prescribed in lower doses in people prone to weight gain and depression and anxiety; they can also be used for pain management and insomnia in some patients. In short, they are unpredictable, just like the disease they have been designed to manage.

Psychosis proceeds in an unpredictable pattern and symptomatic relief of a particular state is by no means a criterion to discontinue an antipsychotic drug. Patients need to be thoroughly assessed by their clinician before any changes to the dosage and timing of the medication can be taken. Additionally, patients need to be educated about the need for these drugs to be tapered down slowly over a period of time to avoid serious drug withdrawal responses associated with their sudden discontinuation. Withdrawal symptoms and manifestations of relapse such as insomnia, agitation and, motor disorders can ensue and seriously undermine the progress made during the duration of treatment.  \(^{38}\)

However, premature discontinuation is a reality and clinicians must then realign their treatment strategies in order to accommodate the patient’s level of comfort regarding the therapy. Individuals with sensitivities relative to their mental illness and medication management are a huge part of the clinical follow up plan. Educating them and persuading them to follow the treatment strategy of
“starting low and going slow”, may be a challenge. Also, some people are attached to their routine drug of choice, i.e., Ativan at bedtime or anti-depressant, and may be resistant to a change in medication and its dosing schedule. In these individuals, resistance and self-sabotage to a newly improved drug therapy often turns into a negotiation between the therapist and client.

Patients on antipsychotics need to be mindful of their diet and over the counter (OTC) medications or nutrient product use (including “health” products) since they are notoriously known to interact with many drugs including vitamins. The clinician’s opinion should be sought prior to commencing OTC medications or products if the patient is already on antipsychotics.

Antipsychotics are broadly classified into two subcategories, i.e., typical and atypical (first generation and second generation). The major difference between the two groups lies in their mechanisms of action. In general, psychosis is believed to be a product of excessive dopamine activation and although all antipsychotics mainly block the pathway leading to this, the atypical antipsychotics also act on the serotonin receptors. The dual action results in fewer side effects.

Clozapine
The first atypical antipsychotic that gained FDA approval was clozapine in 1989.³⁹ It became the drug of choice for the treatment of treatment-resistant schizophrenia and recurrent suicidal behavior in
schizophrenia. Not too long after its widespread acceptance and use, its most debilitating side effect, agranulocytosis, began to surface. When clozapine fell out of favor, other drugs of the same class emerged, namely risperidone and olanzapine. Expert consensus agrees that atypical antipsychotics exhibit lower incidence of extrapyramidal effects and prolonged elevated prolactin levels. It blocks D4 at the mesolimbic pathway, accounting for its efficacy in managing psychiatric symptoms minus the extrapyramidal symptoms (EPS).

Clozapine is a tricyclic benzodiapine with of 8-Chloro-11-(4-methylpiperazin-1-yl)-5H-dibenzo[b,e]1,4-diazepine. Clozapine blocks weakly D2-receptor and D1-receptor. It primarily acts on the D4-receptors, a specificity that accounts for its lower incidence of EPS. It also exhibits of anticholinergic, antiserotonergic, and antihistaminic activity. The latter is responsible for the adverse effects it has on sleep patterns. It has a 50-60% bioavailability following oral administration, reaching a peak plasma concentration of 102-771 ng/mL within 1.5 - 2.5 hours. It is excreted both in the urine and feces.

*Risperidone*

Risperidone is another example of atypical antipsychotic drug. Its exact mechanism of action is not completely understood but studies show that it is also a serotonin and dopamine receptor antagonist. Its antidopaminergic and antiserotonergic activities stem from its blockade of the D2 and 5-HT2 receptors in the brain, respectively. Dopamine receptor blockade rarely results in neuroleptic malignant
syndrome, a fatal neurological disorder characterized by muscle rigidity, fever and autonomic instability. Neuroleptic malignant syndrome is most commonly associated with the typical (older) antipsychotics.

Risperidone has also been found to possess antiadrenergic and antihistaminergic properties. Aside from schizophrenia, it is prescribed as an adjunct to lithium in patients with acute manic episodes associated with bipolar disorder,40,41 and treatment of irritability and behavioral problems associated with autistic disorders.42

The chemical formula of Risperidone is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is C23H27FN4O2.

Most drugs when passing the liver via the blood stream undergo the first pass effect or hepatic metabolism. Risperidone, when given orally, is almost completely absorbed. One-third of the drug undergoes hepatic metabolism, with its primary metabolite, paliperidone, exhibiting as much efficacy as its parent drug. This is the reason why the bioavailability of risperidone is close to 100%. Its mean half-life is between 19-23 hours; the diverse number is attributed to the variability in the CYP26D group of enzymes that metabolize it. It reaches steady state concentration within 5-6 days from the start of therapy. It is primarily excreted in the urine.
Initially, risperidone is given to adults in a dose of 2 mg/day (either once or twice daily tablet). The dosage can be increased to up to 4 mg on the second day with further increments as required. Severe side effects are expected with higher doses of the drug. Generally, doses above 10 mg/day have not been proven to be more efficacious than lower doses and since they are associated with serious side effects, they should only be administered when the clinicians deem its benefits to outweigh its risks.

Risperidone is the first antipsychotic approved by the FDA for the treatment of schizophrenia in adolescents aged 13-17. When used in the elderly, the starting dose should not be more than 1 mg/day. It carries a FDA black box warning because of its propensity to cause death in patients with dementia-related psychosis. Additionally, risperidone is best avoided in patients with renal and hepatic impairments. More than 900 medications are believed to interact with this drug and 46 of those have serious consequences. A detailed medication history should be taken to check for possible interactions prior to start of therapy.

**Quetiapine**

Another novel atypical antipsychotic is quetiapine. Quetiapine is also indicated in the treatment of psychotic disorders. Anecdotal evidence points to its effectiveness in manic disorders as well, although, no multicenter control trials have been found to support it. It is considered a first line drug for bipolar disorders.43
Quetiapine is a diabenzothiazepine derivative that also possesses dopamine antagonistic effects responsible for its antimanic properties. Its antiserotonergic and antiadrenergic properties give this drug its antidepressant effects. Its molecular formula is C21H25N3O2S.

The drug is rapidly absorbed following oral administration and takes about 1.5 hours to reach peak plasma levels. Compared to risperidone, quetiapine reaches steady state concentration faster, i.e., approximately 2 days. The liver metabolizes quetiapine extensively to produce inactive metabolites. Its average half-life is 2-3 hours.

Quetiapine is given as a daily dose of 25 mg once or twice daily, which can be increased up to a maximum of 400 mg per day. However, some clinical trials showed that doses above 300 mg/day did not exhibit superior efficacy to lower doses. Dosage adjustment is indicated in patients with hepatic impairment. Age, gender, ethnicity and smoking do not affect its pharmacokinetics.

Like risperidone, quetiapine has also been linked to early death in elderly patients with dementia and likewise carries a black box warning on its label. The black box warnings against the use of risperidone and quetiapine (Seroquel) in dementia-related psychosis in geriatric patients are due to their fatal adverse effects on the cardiovascular and respiratory systems. Patients have reportedly died suddenly because of heart failure and pneumonia.
In 2009, quetiapine joined risperidone as an FDA-approved monotherapy for the treatment of schizophrenia in adolescents aged 13 to 17 years and as an adjunct to both lithium and valproic acid for acute manic episodes in children and adolescents aged 10 to 17 years with bipolar disorder.

The older (typical) antipsychotics first emerged in the 1950’s, some 40 plus years before clozapine came into the picture. These drugs act on the dopamine receptors (D2) of the CNS, essentially blocking the endogenous dopamine from binding with them and exerting their normal physiological effects. The older antipsychotics initially fell out of favor because of their propensity to cause extrapyramidal symptoms (EPS). This adverse effect stems from the drug’s antidopaminergic action on the basal ganglia. EPS includes the following movement dysfunctions:

- Akinesia
- Akathisia

Additionally, typical antipsychotics also exhibit other adverse effects such as:

- Parkinsonism (tremors, rigidity)
- Bradykinesia
- Erectile dysfunction
**Haldoperidol**

Haloperidol was developed in 1958 and approved for antipsychotic use by the FDA in 1967. It is also indicated for the treatment of schizophrenia and has been found to be effective in treating the vocal utterances in Tourette’s syndrome. It belongs to the butyrophenone class of drugs that include droperidol, a neuroleptanalgesic anesthesia and sedative and, domperidone, an antiemetic.

Haloperidol is available in oral and injectable forms. The IM formulation contains the active drug haloperidol along with lactic acid, an excipients, used to stabilize the pH of the formulation. It is also given intravenously. As expected, its onset of action and response is very rapid with a bioavailability of 100%. When administered as an infusion, its pharmacological effects are sustained over a long period of time.

Haloperidol is believed to cause QT prolongation and should be given with extreme caution to patients suffering from conditions that cause prolonged QT intervals, patients who are receiving drugs that cause electrolyte imbalances, and critically ill patients.\(^4^5\) Coadministration with carbamazepine decreases its plasma concentration, thus, requiring dose adjustment in such cases.\(^4^6\) Haloperidol is absolutely contraindicated in patients with stroke, cardiac conditions, known hypersensitivity to the drug, and severely intoxicated with alcohol and other central nervous system depressants. Just like the atypical
Antipsychotics, haloperidol carries the risk of early death in elderly patients with dementia-related psychosis.

**Antidepressants**

Antidepressants comprise a wide variety of drugs that are basically indicated to treat the various symptoms of depressive disorders. However, many off-label indications for using antidepressants also exist and conditions such as anxiety, sleep disorders, obsessive compulsive disorders, eating disorders, neuropathic pain, ADHD, migraines and substance abuse benefit from its use. Antidepressants are subdivided into the following classes, and are further discussed in the section below.

1. Selective serotonin reuptake inhibitors (SSRIs)
2. Norepinephrine reuptake inhibitors (NERIs)
3. Noradrenergic and specific serotonergic antidepressants (NaSSA)
4. Serotonin–norepinephrine reuptake inhibitors (SNRIs)
5. Serotonin antagonist and reuptake inhibitors (SARIs)
6. Norepinephrine-dopamine reuptake inhibitors (NDRIs)
7. Selective serotonin reuptake enhancers (SSREs)
8. Norepinephrine-dopamine disinhibitors (NDDIs)
9. Tricyclic antidepressants (TCAs)
10. Monoamine oxidase inhibitors (MAOIs)

**Selective Serotonin Reuptake Inhibitors (SSRIs)**
The exact mechanism of action of SSRIs remains unclear to date; however, it is believed that these drugs inhibit the reuptake of serotonin from the synaptic cleft at the neuronal junctions, thus, maintaining high serotonin levels for binding with the postsynaptic 5-HT receptors. SSRIs are widely prescribed worldwide and its most famous member is fluoxetine.

Fluoxetine or (±)-N-methyl-3-phenyl-3-[(alpha),(alpha),(alpha)-trifluoro-p-tolyl)oxy]propylamine hydrochloride has the empirical formula of C17H18F3NO·HCl.

Fluoxetine is a white crystalline substance available as a tablet. Sustained release formulations are also available to facilitate easy administration of the drug and encourage patient compliance. Fluoxetine is indicated in the following conditions:

- Major depressive disorder (MDD)
- Obsessive compulsive disorder (OCD)
- Bulimia nervosa
- Panic disorder (PD)
- Premenstrual dysphoric disorder (PDD)

It is also used off label in the following conditions:

- Fibromyalgia
- Migraine
- Hot flashes
- Reynaud’s phenomenon
For MDD, OCD, PD and PDD, an initial 20 mg is usually the preferred dose. Depending on patient needs, the dose can be gradually increased but should not exceed 80 mg/day. Peak plasma levels are achieved within 6-8 hours of administration. It undergoes extensive hepatic first pass metabolism, which produces one active metabolite, norfluoxetine, and multiple unidentified inactive metabolites. It is renally excreted.

Variations in metabolism are seen in patient populations with reduced cytochrome P450 enzyme concentrations. However, the net pharmacodynamics in these patients was also observed to be the same, making it an efficacious drug of choice despite the said metabolic variations. Fluoxetine has a special formulation called Prozac Weekly, a delayed-release capsule that sustains the required plasma drug levels without the inconvenience of daily administration.

Patients with liver diseases may show impaired elimination of the drug and should be given it cautiously, and under close clinician supervision. A lower and less frequent dosing schedule should be followed in these patients. Similarly, since the metabolites may accumulate in patients with renal impairment, a similar dosing regimen is best adopted.

The efficacy of a 20 mg dose of fluoxetine has been established in both adult and pediatric patients suffering from major depressive disorders.
In both cases, the drug was found to be significantly more potent than placebo in eliminating symptoms of the disease. Multiple clinical trials have demonstrated the efficacy of the drug in treating panic disorders, bulimia nervosa and obsessive-compulsive disorders especially in combination with cognitive behavioral therapy in children as well as in adults.

**Norepinephrine Reuptake Inhibitors (NERIs)**

This class of antidepressants exclusively blocks the presynaptic membrane protein, norepinephrine transporter (NET). NERI’s are indicated in anxiety disorders, panic disorders, narcolepsy, ADHD and major depressive disorder.

Atomoxetine belongs to this class of drugs and received FDA approval in 2004 for the treatment of ADHD. Currently, it is the only drug approved for the treatment of ADHD in adults and the only non-stimulant drug approved for children and adults for the same indication. Although it was initially designed as an antidepressant, its clinical efficacy in depressed patients could not be established significantly. Following the results of such studies, it was proposed that atomoxetine exhibited a therapeutic potential in the treatment of ADHD patients.

Children under 6 years however should not be given the drug since no guarantee of safety exists below this age group. The main reason for its popularity in ADHD treatment is that it is not a stimulant and therefore, do not have the abuse potential of the older stimulant
medications. The drug is expected to take at least a week to show any therapeutic benefits and some studies suggest that the true potential of the drug can only be felt in about 6-8 weeks after which discontinuation should be proposed if no improvements are shown.

Stimulant drugs (i.e., methylphenidate) are no longer recommended in ADHD patients with nervous disorders (i.e., spasms and tics). Atomoxetine becomes the drug of choice for these patients.\textsuperscript{48} Its chemical name is (-)-N-methyl-3-phenyl-3-(o-tolyloxy)-propylamine hydrochloride. Atomoxetine is a white solid and usually marketed as a capsule formulation for oral administration. It is rapidly absorbed after oral administration. Its bioavailability is not significantly altered by food.

Serious drug interactions may occur when Atomoxetine is taken with a MAOI within 2 weeks of its discontinuation. The interaction can be fatal and caution should be taken in this regard. Patients with pheochromocytoma also need to be monitored closely when prescribed with it.

Noradrenergic and specific serotonergic antidepressants (NaSSA)

NaSSA exhibit its antidepressant effects by blocking a\textsubscript{2}-adrenergic receptors and certain subset of serotonin receptors, thereby enhancing noradrenergic and serotonergic neurotransmission. Because of the drug’s selective serotonin action, many of the unwanted serotonergic
side effects associated with other antidepressants (i.e., TCAs and SSRIs) are prevented.

*Mirtazapine* is a prototype of the noradrenergic and specific serotonergic receptor antidepressants (NaSSA) that was initially marketed in the U.S. in the 1990’s. It is currently the only tetracyclic antidepressant to have received FDA approval for the treatment of depression. It belongs to the piperazinoazepine class. Its designated chemical name is \(1,2,3,4,10,14b\)-hexahydro-2-methylpyrazino \([2,1-a]\) pyrido \([2,3-c]\) benzazepine and its empirical formula is \(C_{17}H_{19}N_{3}\).

Worldwide studies have shown mirtazapine to be superior to placebo in treating moderate to severe depression and having potentially less side effects than other antidepressants. It is often preferred as a first line treatment in these disorders. Mirtazapine is used off label for the treatment of post-traumatic stress disorder (PTSD).

Mirtazapine is also extensively metabolized in the liver by demethylation and hydroxylation into four metabolites, which then undergo glucuronide conjugation. These metabolites are less potent than the parent compound.

*Serotonin norepinephrine reuptake inhibitors (SNRI)*

SNRI’s are a class of antidepressants that have a dual action; they block the reuptake of the two neurotransmitters that have the most
significant effect on moods – serotonin and norepinephrine, thereby increasing their levels in the postsynaptic junction. They are prescribed to patients who have not responded to SSRIs. Other approved uses of SNRIs are:

- Neuropathic pain
- Fibromyalgia
- Appetite suppression

Venlafaxine was the first SNRI to gain FDA approval for depression. It is one of the most commonly prescribed SNRI and used in the treatment of major depressive disorder, and generalized anxiety disorder. It is also used in the treatment of panic disorders, social phobias and vasomotor symptoms. It is structurally unrelated to other antidepressants.

Venlafaxine is absorbed well and extensively metabolized in the liver to form its active metabolite, O-desmethylvenlafaxine (ODV) and two other inactive metabolites, N-desmethylvenlafaxine and N,O-didesmethylvenlafaxine. At least 92% of a single dose of venlafaxine is absorbed after 24 hours of administration and 87% of it is recovered in various forms in the urine.

At low doses, i.e., less than 150 mg/day, venlafaxine acts only on the serotonergic neurotransmission. However, at slightly higher doses, i.e., more than 150 mg/day, it affects both serotonergic and
noradrenergic transmission. At doses above 300 mg/day, it also affects the dopaminergic transmission.

In patients with hepatic dysfunction, there is a significant reduction in the half-life elimination of venlafaxine that may require up to 50% dose adjustment. Patients with renal impairment are recommended to reduce their total daily dose as much as 25%. Similar to other antidepressants, its discontinuation requires a gradual tapering of the dose to avoid withdrawal symptoms.

Other serotonin norepinephrine reuptake inhibitors (SNRIs) approved in the U.S. are Duloxetine and Milnacipran. The latter was approved in 2009 for the sole indication of fibromyalgia, not depression. SNRIs carry the black box warning that cautions patients about its propensity to precipitate suicidal thoughts.

*Serotonin antagonist reuptake inhibitors (SARIs)*

SARIs are antidepressants that stimulate 5-HT1A receptors by binding with 5-HT2A receptors and essentially block the 5-HT reuptake in the brain. *Trazodone* is a phenylpiperazine compound that belongs to the SARI class of antidepressants. It is structurally unrelated to other antidepressants such as the serotonin reuptake inhibitors and monoamine oxidase inhibitors. Its structural formula is 2-[3-[4-(m-Chlorophenyl)-1-piperazinyl]propyl]-s-triazolo[4,3-a]pyridin-3(2H)-one monohydrochloride.
It does not affect norepinephrine and dopamine reuptake in the CNS. Its sedative activity stems from its blockade of alpha-adrenergic and histamine receptors. It is approved for the treatment of depression. It is also used off label for the following conditions:

- Aggressive behavior
- Alcohol withdrawal
- Insomnia
- Migraine prophylaxis

For major depressive disorder, the usual dose of trazodone is 150 mg/day given once daily. An increment of 75 mg can be made 3 days after the start of therapy with a maximum dose not exceeding 375 mg/day. Trazodone is well absorbed after oral administration and extensively metabolized in the liver to form its major active metabolite, m-chlorophenylpiperazine (m-CPP). It is predominantly renally excreted, and after 72 hours up to 75% of the drug is found in the urine; the remaining 25% is found in the feces.

Safety of trazodone has not been established in pediatric populations and should not be used. Additionally, short-term studies report an increase in suicidal thoughts associated with its use.

*Norepinephrine dopamine reuptake inhibitors (NDRIs)*

NDRIs block the dopamine and norepinephrine transporters, essentially inhibiting the reuptake of their neurotransmitters. The
blockade increases the extracellular concentration of dopamine and norepinephrine, which results in an increase in their neurotransmission and mood elevation.

*Bupropion* is a drug that falls under the NDRI category of antidepressants. Structurally, it is an aminoketone that is chemically unrelated to other groups of antidepressants. As such, it is a weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine. Moreover, bupropion does not inhibit monoamine oxidase.

In major depressive disorder, 100 mg twice daily is the initial starting dose. By day 4, the dose can be increased to 100 mg three times daily, and increased up to 150 mg three times daily if no improvements are seen in the former regimen. Bupropion tablets taste bitter and produce local anesthetic effects in the oral mucosa.

After oral administration, it takes about 5 hours for the drug to reach its peak plasma levels. Sustained release formulations usually reach peak plasma levels within 3 hours. Bupropion is extensively metabolized in the liver to form hydroxybupropion, its major metabolite that possesses 50% of its potency. The kidneys mainly excrete it and less than 0.5% of it remains unchanged in the urine.

The drug is contraindicated in seizure disorders and under no circumstances can be taken concomitantly with monoamine oxidase inhibitors.
Selective Serotonin Reuptake Enhancers (SSREs)

SSREs are structurally related to the TCAs but have an entirely different mechanism of action that is currently unclear to this date. Studies that have attempted to investigate their mechanisms of action suggest allosteric modulation of the serotonin transporter and modification of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor activity as possibilities.

Tianeptine is an SSRE approved in France for major depressive disorders. It is not approved for such an indication in either the U.S. or United Kingdom. It has strong anxiolytic and antidepressant properties but lacks the usual sedative affects associated with other antidepressants, making it an ideal drug for patients with a dual diagnosis of alcohol abuse and depression.51

Norepinephrine dopamine disinhibitors (NDDIs)

NDDIs inhibit the 5-HT2c receptors in the frontal cortex region of the brain that releases dopamine and norepinephrine. Agomelatine is a relatively new compound that belongs to this category of antidepressants. In addition to its serotonergic actions, it is also a melatonergic agonist that resynchronizes circadian rhythm (proven in animal model studies). It is currently not available in the United States.
Structurally speaking, agomelatine, as the name suggests, is similar to the sleep-regulating hormone, melatonin. Its chemical structure is shown here. In Australia, it is used for the treatment of major depressive disorder in adults. One of its advantages over other antidepressants is that it has minimal sexual adverse effects. The starting dose is 25-50 mg/day at bedtime.

Three of the six placebo controlled trials performed on agomelatine showed superior efficacy to placebo in the treatment of major depressive disorder.\(^5^2\) The efficacy was observed as early as the first week of treatment. The studies also show no abuse potential. Its efficacy in children has not been proven and is not recommended for patients below the age of 18.

**Tricyclic antidepressants (TCAs)**

Tricyclic antidepressants were introduced in the early 1950s and were the drugs of choice in the treatment of depressive disorders until SSRIs came into the picture with better side effect profile. The first TCA developed was chlorpromazine, followed by its derivatives, imipramine, desipramine and clomipramine.

Currently, tetracyclic antidepressants are only indicated when treatment with newer antidepressants failed to yield favorable results. Similar to SNRIs, TCAs block the serotonin and norepinephrine transporters to increase available serotonin and norepinephrine in the synapse. *Amitriptyline* was the second TCA marketed in the US after
chlorpromazine. It is a dibenzocycloheptene-derivative tricyclic antidepressant (TCA) with an empirical formula of C20H23N·HCl.

Therapeutic effects can take up to one month to show up. Due to its strong anticholinergic activity, pediatric and geriatric patients may need to lower their doses. Oral administration results in only a 30-60% bioavailability due to the extensive hepatic metabolism. Its major active metabolite is nortriptyline. Peak plasma levels are achieved within 2-12 hours after oral and intramuscular administration. Studies show that 1/2 to 1/3 of the drug is excreted 24 hours after administration. Amitriptyline is used off label for:

- post-herpetic neuralgia
- fibromyalgia
- vulvodynia
- ADHD
- Migraine prophylaxis
- Eating disorders

**Monoamine oxidase inhibitors (MAOIs)**

This is a class of antidepressants that inhibits the monoamine oxidase enzyme family. They are used in the treatment of depression but fell out of favor because of the strict dietary restrictions and severe interactions that accompany their use. They are often used as the last line of treatment, when all other treatments have failed.
Monoamine oxidase inhibitors are subdivided into classes according to the isoform of the enzyme they act on.

- **MAOI-A** (*i.e.*, tranylcypromine, isocarboxazid, phenelzine)
- **MAOI-B** (*i.e.*, selegiline)

Traditionally, only the MAOI-A are used for antidepressant treatment since they selectively deaminate the neurotransmitters primarily involved in mood and depression such as serotonin, dopamine and norepinephrine. Drugs that act on MAO-B are used in Parkinson’s disease as they selectively deaminate dopamine, the neurotransmitter implicated in the symptoms of Parkinson’s disease. Additionally, MAOIs have shown usefulness in the treatment of panic disorder, agoraphobia, sociophobia, anxiety, bulimia, post-traumatic stress disorder, borderline personality disorder and narcolepsy.\(^5^3\)

MAOIs function by inhibiting the enzyme that breaks down monoamine oxide, thereby increasing its availability in the synapse. Drugs that act on MAO-A irreversibly inhibit the enzyme permanently by degrading it. The body takes about 2 weeks to regenerate the enzyme, accounting for the long gap period required when starting on another class of antidepressant.

The drug that acts selectively on MAO-B, selegiline is used in Parkinson’s disease as an adjunct to levodopa. It prevents the
degradation of levodopa by the MAO-B enzyme, thereby, prolonging and enhancing its effects on the brain.

The FDA approved the use of the transdermal patch containing the active ingredient, selegiline in 2006. It is indicated for the treatment of major depression.

The patch contains approximately 1 mg per cm\(^2\) of selegiline and delivers approximately 0.3 mg of selegiline per cm\(^2\). Different sizes of the patch deliver different doses. The patch is applied on dry intact skin on the upper torso, thigh or arm once in 24 hours. The usual indicated dose is 6 mg/day. After application and adhesion of dermal to intact skin, approximately 25-30\% of the drug is delivered systemically over a period of 24 hours. The absorbed drug does not undergo first pass metabolism and exhibits 100\% bioavailability. Patients with renal impairment do not require any dose adjustment.

It is very important that tyramine rich foods and beverages are avoided once patients initiate therapy with MAOIs. The same restriction applies to the patch at doses higher than 9 mg/day.

**Anxiolytics**

Anxiolytics, as the name suggests, are medications that are used to curb anxiety. Anxiolytics basically include many of the drugs mentioned above and many other drugs that are not primarily
indicated for anxiety but exhibit anxiolytic properties. Tricyclic antidepressants and monoamine oxidase inhibitors also relieve anxiety but are rarely prescribed because of their extensive side effect profile.

Barbiturates and benzodiazepines exhibit dose-dependent effects on the CNS, i.e., the higher the dose, the deeper the sedation-anxiolysis-anesthesia on the CNS. Benzodiazepines are primarily used for panic disorders and generalized anxiety disorder.54

Benzodiazepines

Benzodiazepines are a class of psychoactive drugs used as anxiolytics, depressants, sedatives, anticonvulsants, and muscle relaxants. Their muscle relaxant and anxiolytic properties are useful in medical and dental procedures to relieve nervousness and dental phobia.55 Due to their high abuse potential, most of the benzodiazepines are controlled medications and are not the first line drug for panic and anxiety disorders.

The chemical structure of benzodiazepines shows a characteristic fusion of the benzene rings and diazepine rings. Benzodiazepines exert their pharmacological action by enhancing the activity of the inhibitory neurotransmitter, gamma amino butyric acid (GABA). They are divided into categories according to their duration and onset of action:

- Short acting benzodiazepines
- Intermediate acting benzodiazepines
- Long acting benzodiazepines
Each category is used differently. The short and intermediate acting benzodiazepines are used in patients with insomnia before bedtime. Additionally, due to their short onset of action, short-acting benzodiazepines are used to provide symptomatic relief during panic episodes.

Diazepam is one of the earliest benzodiazepines marketed and is used as an antiseizure, anxiolytic, sedative and muscle relaxant. Its empirical formula is C16H13ClN2O and its structural formula is shown here.

Diazepam is well absorbed in the gut and achieves peak plasma concentration within 1-1.5 hours following oral administration. The absorption may be hampered if taken with a moderately fat meal. The drug is extensively metabolized in the liver to yield active metabolites such as desmethyldiazepam, temazepam and oxazepam. These metabolites cross the blood brain barrier and the placental barrier. Their excretion is mainly through the kidneys.

Another benzodiazepine that is commonly prescribed is alprazolam. Its short onset and duration of action afford patients with generalized anxiety and panic disorders quick symptomatic relief. Its chemical structure is shown here. It undergoes hepatic metabolism to form α-hydroxyalprazolam, which is also active.
**Beta-blockers**

The non-selective beta-blockers such as propranolol, although not primarily indicated for anxiety, controls anxiety symptoms such as palpitations prior to surgery.\(^5\)\(^6\) It is contraindicated in asthma patients.

**Mood Stabilizers**

Mood stabilizers are a group of antipsychotic medications that are primarily used to treat the symptoms associated with mood shifts in bipolar disorder, schizoaffective disorders, and sometimes even borderline personality disorders. The main purpose of the drug is to stabilize the intense mood shifts between depressive and manic episodes.

The classic drug in this category is lithium carbonate. Its effectiveness in manic states is unclear but may be attributed to the following mechanisms:

- Inhibition of glycogen synthase kinase 3 and inositol phosphatases
- Modulation of glutamate receptors

Lithium has a strong side effect and toxicity profile, which is directly related to its plasma drug concentrations. It has a narrow therapeutic window, with the therapeutic dose overlapping with the toxicity dose in
certain patient populations. Lithium should not be co-administered with diuretics because the renal sodium loss induced by the drug may lead to increased lithium levels in the body and consequently, toxicity. Similar effects may be seen when lithium is given with metronidazole.

Although monotherapy has been the ideal practice, it is often inadequate in meeting the realistic needs of many bipolar patients. Bipolar disorder requires psychopharmacologic management combined with evidence-based practice principles in order to reach optimal remission. The favorable side effect profiles and efficacy of atypical antipsychotics have made them ideal candidates to augment lithium in the management of manic disorders. Studies in the recent years have found them to be more effective than placebo in acute manic disorder and maintenance of bipolar disorder, and even more effective when combined with lithium or valproate. There are off-label uses for Lithium. For example, it is used for migraine and cluster headache prophylaxis.

Other mood stabilizers are the anticonvulsants carbamazepine and valproic acid. Carbamazepine is used in refractory bipolar disorder. It may cause lupus reactions in women thereby, requiring close monitoring while on therapy.

**Stimulants**
Stimulants are psychoactive drugs that elevate mood and improve physical and mental functioning for a temporary period of time. They are used worldwide as prescription drugs and also have been widely abused as recreational substances. Essentially, stimulants increase brain activity within the central nervous system and peripheral nervous system. They are used to treat lethargy, obesity, excessive appetite, narcolepsy, and improve concentration in ADHD patients.

There are many types of stimulants, *i.e.*, amfakines, amphetamine-related substances, eugeroics, norepinephrine reuptake inhibitors (NERIs), norepinephrine dopamine reuptake inhibitors (NDRIs), xanthine and caffeine-related drugs. Each type has a unique mechanism of action.

In this category of drugs, amphetamine derivatives are the most commonly prescribed psychostimulants for the management of ADHD and narcolepsy. They mimic NDRI’s mode of action by increasing the levels of norepinephrine and dopamine via reuptake inhibition. They are contraindicated in patients who are on MAOIs because of the risk of hypertensive crisis.

Another psychostimulant is methylphenidate. It is similar to cocaine though with less potency and longer duration of action. It inhibits the reuptake of dopamine from the synapse. The main deterrent in the use of stimulants is their high risk for abuse.\(^{57}\)
**Sedatives or Hypnotics**

Sedatives or tranquilizers are a group of drugs that induces sleep by decreasing the excitatory mechanisms of the brain. Many of the drugs mentioned above have sedative effects, namely benzodiazepines. Barbiturates and antihistamines can all act as sedatives.

Sedatives, when used prior to medical surgeries, are called sedative-hypnotics because their effects on the CNS are dose-dependent, *i.e.*, at lower doses; they may act as anxiolytics but at higher doses, can induce unconsciousness. They are used to induce sleep and are adjuncts to general anesthesia.

**Barbiturates**

Just like benzodiazepines, barbiturates potentiate the inhibitory effects of GABA at its receptor. Additionally, they also block the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, a type of glutamate receptor, to effectively lower glutamate levels in the CNS.

Barbiturates were commonly used for their anxiolytic properties but have been largely replaced by benzodiazepines and nonbenzodiazepines for their better safety profile (lower risk of overdose). At lower doses, they exert anxiolytic effects and at higher doses, they exert total anesthesia. The ultra-short acting barbiturate, *thiopental*, is used as a general anesthetic. Sedatives should not be
used in combination with alcohol. Since both substances have a depressant effect on the central nervous system, their additive effects are fatal.

These drugs also cause anterograde amnesia and are often implicated in criminal activities (i.e., date rape) by combining them with alcohol or other drugs.\textsuperscript{58}

**Herbal and Over The Counter Drugs**

In the last 10 years, herbal formulations have been gaining popularity in the U.S. for the treatment of psychiatric disorders. These supplements are widely purported by their manufacturers to exhibit fewer and lighter side effects compared to their counterparts that require prescription. The herbal supplement, St. John’s Wort, is one such example. It is obtained from the flowers and leaves of the herb, *Hypericum perforatum*. It is known by a number of other names including Tipton's weed, rosin rose, Amber, Amber Touch-and-Heal, goatweed, and Klamath weed.

Several studies propose the significant role of St. John’s Wort in the treatment of mild to moderate depression.\textsuperscript{59} Some users have also reported experiencing therapeutic benefits in the treatment of anxiety and related disorders. A study conducted in France showed that preparations of St. John’s Wort were superior to placebo in treating clinical depression. A total of 375 patients were enrolled in the study with the outcome measured by improvement in Hamilton scores.\textsuperscript{60}
Studies performed in Germany have also led to a similar conclusion, leading many experts in the field to postulate its effectiveness to be so superior that it may just become the first line treatment for depression in some countries. On the other hand, there are also many studies that contradict this assumption, showing a failed superiority over placebo in treating depression. Large-scale studies are needed to establish the efficacy of this herbal supplement and its therapeutic value in the treatment of psychiatric disorders.

The exact mechanism of action of St. Johns Wort is not completely understood. Initial studies reported that the active components of the extracts exhibited weak inhibitory effects on the monoamine oxidase enzyme family. It has also been reported to inhibit the synaptosomal uptake of serotonin, dopamine and noradrenaline. Studies done on rat models have seen the drug cause a down regulation of the beta-adrenergic receptors and an up regulation of the serotonin receptors.

St. John’s Wort is notorious for its interaction with various medications. When it is administered with fexofenadine, it causes an initial rise on the latter’s plasma levels. Continued co-administration leads to increased renal clearance of fexofenadine and a marked decrease in the peak plasma levels of the drug. When administered with amitriptyline, the herb decreases the plasma concentration of the antidepressant. The efficacy of the immunosuppressive agents, cyclosporine and tacrolimus, can be severely impaired when
administered with St. John’s Wort. The interaction is reversible and cessation of herbal therapy generally results in restored efficacy of the drugs.

Additionally, St. John’s Wort significantly alters the pharmacodynamics of benzodiazepines, antihypertensive drugs, selective sinus node channel inhibitors and anticancer drugs such as imatinib mesylate. Most of these interactions occur via the P-glycoprotein and cytochrome P450 pathways.

*Valerian* is another herbal supplement with psychoactive properties. It is obtained from the perennial flowering herb, *Valeriana officinalis*, and used for its hypnotic and sedative properties in the treatment of insomnia, anxiety, depression, and migraines. It is known by a variety of other names such as All-Heal, Amantilla, Baldrian, Fragrant Valerian and Garden Heliotrope, just to name a few.

Studies have shown valerian to exert sedative effects by acting on the GABA receptors, the same receptors targeted by benzodiazepines. Small-scale placebo-controlled trials have reported this drug to be beneficial when given to elderly patients with sleep disturbance issues. Just like St. John’s Wort, there is an enormous amount of contradictory data on the effectiveness of Valerian as a sleep aid. When it comes to safety, valerian is known to interact with a number of drugs, alcohol, and vitamin supplements and cause serious adverse effects.
The active ingredients in valerian cause severe secondary effects when given with benzodiazepines as they enhance its inhibitory activity, thereby, producing an additive sedative effect. Published case reports showed an increased side effect profile when patients on lorazepam had self-medicated with over the counter preparations of valerian.

The widespread availability of herbal supplements makes them easy methods which allow dangerous interactions to take place when patients already on medications self-medicate with them. Because they are easily obtained, the general consensus is that they are safe, regardless of any food and medication that’s being taken with them. Reports have implicated this false sense of security in many emergency department visits over the years, some with fatal consequences.

**Adverse Effects Of Psychotropic Medications**

Adverse drug events (ADEs) or adverse drug reactions (ADRs) are a burden to everyone involved; to the patient, to the families, to the clinicians and to the entire healthcare system. According to the American Society of Hospital Pharmacists (ASHP), ASHP defines a significant ADR as any unexpected, unintended, undesired, or excessive response to a drug that:

- Requires discontinuing the drug (therapeutic or diagnostic)
- Requires changing the drug therapy
• Requires modifying the dose (except for minor dosage adjustments)
• Necessitates admission to a hospital
• Prolongs stay in a health care facility
• Necessitates supportive treatment
• Significantly complicates diagnosis
• Negatively affects prognosis
• Results in temporary or permanent harm, disability, or death

Adverse drug events include manifestations of side effects and toxic effects. From the patient’s perspective as well as its impacts upon the health system, adverse events (ADEs) are discussed in greater depth in the following section.

**Patients on Psychotropic Medications**

It is not unusual for patients on psychotropic medications to experience serious adverse effects. In fact, their notorious serious adverse effect profiles are known to undermine patient compliance. These untoward reactions may manifest in any of the following signs and symptoms:

• Allergic reaction
• Change in level of alertness
• Change in eating patterns
• GIT disturbances
• Cardiac disturbances
• Fainting or dizziness
• Abnormal gait
• Jaundice
• Unusual bruising

Additionally, the mentally ill patient may not always be able to verbalize the side effects they’re experiencing, making them all the more vulnerable. It is the clinicians’ and guardians’ responsibility to observe their patients closely and watch out for the early signs of these side effects before they worsen and cause fatalities. Moreover, an awareness of the medications with black box warning is important. A black box warning is an FDA notice to the public and appears on the package inserts of drugs that have serious adverse effects. Below is a list of drugs with a “black box warning” on their labels.⁶³

Table 7: Commonly prescribed psychotropic drugs with black box warnings

<table>
<thead>
<tr>
<th>Bupropion</th>
<th>Desipramine</th>
<th>Amoxapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Amitriptyline</td>
<td>Trimipramine</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Trazodone</td>
<td>Imipramine</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Citalopram</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Venlafaxine</td>
<td>Mirtazapine</td>
</tr>
</tbody>
</table>
Clinicians and the Healthcare System

Adverse drug events do not only affect the patient and families. They affect the hospital and the entire healthcare system. They cost a lot of money. It is estimated that close to 770,000 people suffer from ADEs of one kind or another in a year and the cost of legal fees to each hospital can be as high as $5.6 million\textsuperscript{64,65} yearly. This figure is exclusive of the litigation and malpractice costs and does not include the cost of admissions.

Cost

One of the common most and basic ADE is the patient injury associated with it. The consequence in these cases may range from a simple allergic reaction to sudden death. Studies have shown that up to 9.7% of ADE’s lead to a permanent form of disability. In the U.S., institutionalized patients who experienced ADE’s during their confinement are covered by the hospital. The prolonged hospital stays is a costly sequel to ADEs, with thousands of dollars consumed in the process, from hospitalization costs to insurance employment benefits.

The length of hospital stay also depends on the type of adverse event that caused the hospitalization. A U.S. study found that patients who

<table>
<thead>
<tr>
<th>Escitalopram</th>
<th>Maprotyline</th>
<th>Protriptyline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isocarboxazid</td>
<td>Nortryptiline</td>
<td>Phenelzine</td>
</tr>
</tbody>
</table>
experience serious ADEs such as arrhythmias, seizures, bleeding disorders, and CNS suppression could be confined up to 20 days in the hospital. On the other hand, patients who experienced milder ADEs can be confined for up to 13 days. When these numbers are compared to those who encountered no ADEs at all during their hospital stay, the average length of admission was only 5 days.\textsuperscript{66} Outpatients are most likely covered by their insurance companies in the event of ADEs.

\textit{Causes}

Most adverse drug events are preventable. This is why patients need to be vigilant while on therapy and clinicians and other healthcare professionals be thorough in their work and proceed with caution. One cause of ADEs is attributed to errors that occurred during a pharmacy visit. This could be anywhere from wrong prescription, wrong transcription and medication dispensing. Clinicians do make mistakes too. They may prescribe the wrong dose or miss an allergic history, \textit{etc.}

A study on typical errors that lead to ADEs reported that missed doses accounted for 7\% of the errors whereas wrong technique and illegibility errors accounted for 6\% of ADEs. Duplicate therapy accounted for another 5\%, which was almost similar to the ADEs caused by drug–drug interactions. Additionally, equipment issues, lack of proper monitoring and preparation errors each accounted for about 1 \% of the total adverse events that occurred.\textsuperscript{67,68,69,70}
Prevention

Studies have proven a centralized and computerized monitoring system to be an effective method of preventing ADEs. The data entered into the computers was able to notify all healthcare workers involved of any allergic reaction, drug-drug interaction, and drug-food interaction. The system enabled pharmacists to check for any errors that could occur because of excessive or inappropriate doses. Moreover, allergic reactions to drugs were identified earlier through this process, preventing the reaction to escalate to a serious event. Physicians were then notified and able to modify their prescriptions.

Computerized physician order entry (CPOE) was also shown to reduce the errors caused by illegible orders, inappropriate doses, and improper routes and frequency of administration. Essentially, ADEs have greater chances of being caught in time because of the sophisticated technological advances in healthcare computer systems. In fact, almost all hospitals in the country have invested in state of the art monitoring systems to protect their patients and themselves, preferring that than risk facing the consequences of ADEs.⁶⁶

Drug-Drug Interactions (DDIs)

Drug-drug interactions are preventable in many cases. This is especially true for those that are mediated by the cytochrome P-450 enzyme family. Correct and sufficient knowledge of a drug’s pharmacokinetic and pharmacodynamics profiles will enable clinicians to educate their patients and families on their use. Drug interactions
result from the concomitant administration of multiple drugs, alcohol, substance and food. In this section, most of the section will focus on drug-drug interactions of psychotropic drugs with other drugs. As mentioned previously, coadministration practices such as polypharmacy, and multiple comorbid conditions predispose individuals to drug-drug interactions.

Drug-drug interactions exhibit varying degrees of the severity of their consequences. DDIs may make drugs less effective, cause unexpected side effects, or increase/decrease the action of another drug. Some drug interactions can even lead to fatal consequences. There are cases too where drug interactions cause nothing more than inconvenient side effects. One of the reasons why drug interactions are particularly common with psychotropic drugs is because they are usually prescribed over a long period of time. Mentally ill patients may need to use other drugs for other conditions during this period such as antibiotics, pain and hypertensive drugs. Doctors, nurses and pharmacists who see such patients should be made aware of their psychotropic medication regimens and prescribe, administer, and dispense accordingly.

As mentioned above, there are two mechanisms upon which drug-drug interactions occur. Firstly, they may occur via pharmacodynamics interactions, i.e., the physiological effect of the drug may either be enhanced or weakened or secondly, it may occur through the alteration of the pharmacokinetics of the drug i.e. its availability,
absorption, bioavailability, distribution, metabolism, and excretion may be changed.

*Pharmacokinetic interactions*

Drug-drug interactions that affect the pharmacokinetics of drugs are due to the cytochrome P450 group of microsomal enzymes in the liver. The cytochrome P450 enzyme family is responsible for the metabolism of the majority of drugs, eleven of which have been identified as major players. Not all individuals exhibit the same degree of CYP isozyme activity; genetic variations divide the human population into three types of metabolizers, as outlined below.

- **Poor metabolizers:**
  They have dysfunctional or inactive CYP isozymes and are more prone to suffer from drug toxicity as a result of reduced drug metabolism and elimination processes. Since some drugs are formulated as prodrugs, poor metabolizers may respond poorly or not at all to such treatments.

- **Extensive metabolizers:**
  They are considered to have normal CYP isozyme activity, the majority of individuals fall under this category.

- **Ultra rapid metabolizers:**
  They have overactive CYP isozymes. Drugs are rapidly metabolized by these enzymes; leading to sub-therapeutic
plasma levels of the drug. These individuals may receive little or no therapeutic benefit. When prodrugs are administered, toxicity is a very real possibility—with very high levels of active metabolites circulating in such a short period of time.

In drug-drug interactions involving the CYP isozymes, drugs either induce or inhibit their activity, resulting in a change in the substrate metabolism and subsequent clearance of the drug. Two of the most common isozymes involved in these interactions are the CYP2D6 and CYP3A4.

Carbamazepine, phenobarbital, phenytoin, rifampicin and St John’s Wort are all inducers of the CYP3A4 enzyme. An example of a DDI mediated by the induction of CYP3A4 is the reduced metabolism and efficacy of haloperidol when coadministered with carbamazepine. The latter is an inducer of the same CYP isozyme. Another example is the reported severe myotoxic effects (i.e., rhabdomyolysis) associated with the use of the antidepressant, nefazodone, with simvastatin, a cholesterol-lowering drug. These toxic effects are the direct result of the nefazodone-induced inhibition of the CYP3A4 isozyme pathway, wherein simvastatin is also a substrate. Alcohol is also a substrate and an inducer of the CYP2E1 isozyme. When alcohol is given in combination with venlafaxine, a substrate of the CYP2E1 isozyme, it induces its metabolism, resulting in faster clearance and diminished antidepressant effects.
The absorption of amphetamines is decreased when given with gastrointestinal acidifying agents and reduced when given with alkalinizing agents. Monoamine oxidase inhibitors slow down the metabolism of amphetamine, which results in deleterious effects. Hypertensive crisis and hyperpyrexia may ensue, fatal consequences of the drug-drug interaction. Amphetamines also interact with haloperidol, lithium carbonate, ethosuxamide, meperidine, phenobarbital, norepinephrine, phenytoin and a number of other drugs. Another mode of DDI is through enzyme inhibition via competitive enzyme binding. Enzyme inhibition is directly proportional to the plasma levels of the drug. Amiodarone, cimetidine, fluoxetine are enzyme inhibitors. The table below has the detailed list of enzymes and their competing substrates.

## Psychotropic drugs and their competing substrates

<table>
<thead>
<tr>
<th>CYP enzymes</th>
<th>Substrate</th>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1A2</strong></td>
<td>Amitriptyline, clozapine, duloxetine, fluvoxamine</td>
<td>Phenobarbital, inhaled smoke, insulin</td>
<td>Paroxetine, fluvoxamine</td>
</tr>
<tr>
<td><strong>2E1</strong></td>
<td>Venlafaxine</td>
<td>Disulfiram, alcohol</td>
<td>Isoniazid</td>
</tr>
<tr>
<td><strong>3A4/5/7</strong></td>
<td>Alprazolam, amitriptyline, aripiprazole, benzodiazepines, clozapine, citalopram, caffeine, propranolol</td>
<td>Barbiturates, carbamazepine, phenytoin, phenobarbital, St John’s Wort.</td>
<td>Cimetidine, chloramphenicol, diltiazem.</td>
</tr>
</tbody>
</table>
Amitriptyline, fluoxetine, Fluoxetine, fluvoxamine
Phenobarbital

Diazepam, citalopram, Diazepam, citalopram, Carbamazepine
amitriptyline amitriptyline

Carbamazepine
Cimetidine

Amitriptyline
Amitriptyline
Dexamethasone, Dexamethasone, Diazepam, citalopram, Carbamazepine, Carbamazepine, Atomoxetine, Atomoxetine, rifampicin rifampicin

Duloxetine, Fluoxetine Duloxetine, Fluoxetine
Fluvoxamine
Fluvoxamine

Similarly, the plasma concentration of lithium is increased when co-administered with diuretics that promote sodium loss, leading to toxicity. Calcium channel blockers and methyldopa can also increase the toxicity of lithium carbonate and should not be given in combination. Tinnitus, diarrhea, nausea, vomiting and even ataxia occur with concomitant use of lithium and calcium channel blockers.

Likewise, simultaneous use of lithium with antihypertensives such as ACE inhibitors (i.e., captopril) and angiotensin-2 receptor antagonists (i.e., losartan), and NSAIDS also lead to dangerously high plasma lithium levels.

Metronidazole, when combined with lithium, decreases the renal clearance of lithium, also resulting in increased plasma levels of the drug. These two drugs should be very carefully monitored if ever administered concomitantly. A well-known interaction mediated by the CYP2D6 isozyme is the one between tamoxifen and antidepressants.
The following table summarizes the severity of the interaction among different antidepressants with tamoxifen and the clinical advice associated with their concomitant use.\textsuperscript{72}

### Drug interaction of antidepressants with tamoxifen

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Severity of effect on CYP2D6</th>
<th>Clinical advice on the safety of coadministration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>Minimal</td>
<td>Safest to concomitantly administer with tamoxifen</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>No studies</td>
<td>N/A</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Mild</td>
<td>Secondary choice if venlafaxine or mirtazapine are not available</td>
</tr>
<tr>
<td>Nefazodone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Moderate</td>
<td>Weigh benefits against risks</td>
</tr>
<tr>
<td>Sertraline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Strong</td>
<td>Avoid concomitant administration</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pharmacodynamic interactions**
The cytochrome P450 enzymes also influence the effects of antipsychotic drugs on the body, i.e., its pharmacodynamic effects. The coadministration of psychotropic drugs can result in the potentiation or addition of the effect of another.

The risk of agranulocytosis, the very serious blood dyscrasia side effect associated with Clozapine monotherapy is amplified when combined with carbamazepine, imipramine and mirtazapine which have also been reported to exhibit the same side effect. The additive effects can be devastating on the immune system of patients.

Even common food and vegetables like broccoli, Brussels sprout, and charred grill meat affect the CYP isozymes activity. Grapefruit juice is a well-known inhibitor of the CYP3A4/5/7 isozymes and interacts with their substrates. The smoke inhaled from the environment and tobaccos are also known to affect CYP isozymes.

Selective serotonin reuptake inhibitors (SSRIs), when given with B-blockers, may cause additive depressant effects on the heart that manifests as bradycardia. In this case, SSRIs increased the concentration of the beta-blocker by inhibiting the CYP isozymes responsible for its metabolism.

Tetracyclic antidepressants, when given with type 1A anti-arrhythmic, can cause conduction abnormalities in the heart that may lead to
arrhythmias. Also, when combined with sublingual nitrates, they may not be orally absorbed well due to their anticholinergic effects manifesting as reduced oral secretions and dry mouth. When antipsychotics are combined with alcohol, TCAs, benzodiazepines and antihistamine, the result is additive sedation. Furthermore, risperidone, chlorpromazine, clozapine and pimozide when combined with antihypertensives and TCAs have greater potential of causing orthostatic hypotension. Tricyclic antidepressants potentiate the stimulation exerted by amphetamines that may lead to cardiac effects being enhanced.

Serotonin syndrome is another potentially lethal drug interaction that occurs with use of many psychotropic drugs. It has been discussed in detail in the previous sections. Patients taking MAOIs need up to wait 2 weeks before other antidepressants or any other drugs are safe to administer.

Norepinephrine reuptake inhibitors should be cautiously administered with beta-2 agonists like albuterol as the cardiovascular affects of the latter are potentiated and an increase in heart rate and blood pressure may be experienced. Also, coadministration of SNRIs and SSRIs cause alterations of the activity of anticoagulants which can result in increased bleeding times. Therefore, patients on warfarin should be closely monitored when given these medications.

Side effects
Side effects are expected adverse drug events related to the pharmacological effects of the medication. They are often the “menace” that accompanies the therapeutic benefits. However, some side effects are used to the patient’s advantage. For example, the mild antidepressant, trazodone, may be prescribed in patients who require its sedative effects to help them sleep at night.

The following side effects are common in many psychotropic drugs and are discussed briefly followed by its in-depth discussion as it relates to each group of psychotropic drugs.

**Orthostatic hypotension**

A sudden drop in blood pressure (>20 mmHg for systolic or 10 mmHg for diastolic) when a patient stands up and accompanied by a dizzy spell has occurred in patients on a combination of antidepressants. Some SSRIs and TCAs, and almost all MAOIs (except moclobemide) cause significant hypotension. Isolated cases have been published reporting alarmingly low blood pressures when SSRI’s were given in combination with small doses of TCAs in 2 elderly patients. Similarly, a study in Germany concluded that a strong correlation was found between the decrease in blood pressure levels and serum drug concentrations of SSRIs and TCAs. Not only this, but the newer generation antipsychotics are also believed to have significant orthostatic effects even though they are appear to have more benign side effect profiles. Antipsychotics that cause orthostatic hypotension are clozapine, olanzapine, risperidone, aripiprazole, and quetiapine.
Sexual dysfunction and hyperprolactinemia

Sexual dysfunction is a common side effect of most psychotropic medications, particularly antipsychotics. In some cases libido, sexual drive and function seem to improve after discontinuation of these drugs. The dysfunction occurs as a result of the dopamine antagonism at its receptor and transporter sites, and also partly due to increased prolactin levels which is mediated by dopamine.

Typical antipsychotics cause sexual dysfunction more than the newer atypical agents. Olanzapine, quetiapine and clozapine show none to moderate prolactin elevation when compared to risperidone. Long-term benzodiazepine use is also associated with sexual dysfunction. Lithium, when given alone to treat bipolar disorder, seem to have less effect on sexual functioning when compared to its co-administration with a benzodiazepines.\textsuperscript{75} Medications like phenothiazines, butyrophenones, metoclopramide, and risperidone block the action of dopamine on the pituitary gland.\textsuperscript{76} A rise in prolactin levels is associated with a host of sexual problems such as galactorrhoea, gynecomastia, amenorrhea, infertility, loss of libido, and erectile dysfunction.

Selective serotonin reuptake inhibitors were once wrongly believed to cause excessive elevation of serum prolactin levels. No long-term large-scale studies proved its hypothesis. On the contrary, SSRIs actually cause very little increase in prolactin levels. Out of all the available SSRIs, only patients treated with paroxetine were seen with
clinically significant elevated prolactin levels. Fluoxetine also elevates prolactin levels but only with post-menopausal women.\textsuperscript{77}

\textit{Liver or kidney dysfunction}

Clozapine also causes liver damage in some patients. The damage is similar to the cholestasis that occurs in with phenothiazine use. Only a benign rise in ALT was seen in these patients, however, serious liver damage has also been reported in other cases. Similarly, TCAs and MAOIs are believed to have the highest hepatotoxic potential amongst antidepressants especially in comparison to the newer drugs like selective serotonin reuptake inhibitors.\textsuperscript{78} Amineptine, although not prescribed in the U.S., causes cholestatic liver disease and some reports have shown it to also cause necrosis. Imipramine also has the potential to cause cholestatic jaundice.

Amphetamines have been reported to cause acute liver damage, particularly with intravenous use and over the safe and recommended doses, though the elevation of serum AST and ALT levels has not been clearly established. The exact mechanism of liver injury is unknown, however, since amphetamines undergo extensive metabolism in the liver, the formation of a hepatotoxic metabolite is a strong possibility. The typical clinical picture of amphetamine-induced hepatitis is fatigue, weakness and jaundice, which may be clinically apparent 3-14 days after ingestion of the drug. AST, ALT and LDH values may show a
marked increase. Acute liver failure in such cases may also be accompanied by other organ damage.

Renal toxicity is not frequently observed with psychotropic medication but since many of these drugs are eliminated by the kidneys, it is important to recognize the effects of pre-existing kidney disease on renal excretion so that dose adjustments may be made accordingly.

*Syndrome of inappropriate antidiuretic hormone secretion (SIADH)*

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the abnormal release of antidiuretic hormone (ADH) from the posterior pituitary gland that results in decreased diuresis and consequently, fluid overload in the body. The syndrome manifests as a slowly progressive hyponatremia with chronic pain. The patient history may hint at drug use, CNS injury and tumors. SIADH is associated with hyponatremia without edema. A severe form of hyponatremia and unresolved volume status can result in patients experiencing lethargy, delirium, headache, confusion, nervousness, apathy, irritability, and in very severe cases, convulsions, and coma.

Deaths have resulted from untreated SIADH. Many of the psychotropics drugs that cause SIADH have the propensity to affect the elderly patients, especially those above 65 years of age. Although tricyclic antidepressants are associated with SIADH, they have not been consistently observed. Selective serotonin reuptake inhibitors, haloperidol, phenothiazines, monoamine oxidase inhibitors and
Barbiturates are all associated with SIADH. Sometimes the symptoms of depression may be hard to distinguish from that of SIADH, making the diagnosis a difficult one. Laboratory values are needed to correlate clinical symptoms and affirm or rule out the diagnosis.

**Bone mineral density (BMD)**

Many psychotropic drugs also cause a decrease in bone mineral density. The side effect is attributed to the dopamine inhibition that leads to hyperprolactinemia that may in turn lead to secondary hypogonadism. Prolactin interferes with the pulsatile release of Gonadotropin-releasing hormone (GnRH) and inhibits follicle stimulating hormone (FSH) and luteinizing hormone (LH) production. Schizophrenic patients who are on long term antipsychotic medications are especially susceptible to this particular side effect. In general, vitamin deficiencies can occur with many psychotropic drugs, such as B6, calcium, and magnesium deficiencies, among others.

A study conducted by the Massachusetts General Hospital in Boston reported that significant morbidity is associated with low bone density prompting clinicians to consider its diagnosis as an integral part of patient management on long-term antipsychotic medications. On the other hand, tricyclic antidepressants are known to possess protective effects against osteoporosis and can be used when severe bone mineral density loss is suspected.

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[79] On the

[80] On the
The “menacing” side effects mentioned above of antipsychotics, antidepressants, benzodiazepines and other anxiolytics, sedative-hypnotics, stimulants and mood stabilizers are discussed in more detail in the succeeding sections.

**Antipsychotics**

As mentioned in the last section, antipsychotics have a broad side effect profile. They cause extrapyramidal symptoms, weight gain, thyroid dysfunction, and metabolic disturbances, hyperprolactinemia, agranulocytosis and sexual dysfunction.

*Extrapyramidal symptoms (EPS)*

Extrapyramidal symptoms are drug-induced side effects, a consequence of dopamine blockade. All medications that block dopamine or interfere with its function, synthesis, release and reuptake will exhibit extrapyramidal symptoms as side effects. Antipsychotics interfere with normal functioning of dopamine. Extrapyramidal symptoms include dystonia, akathisia, tremors and rigidity (parkinsonian symptoms) tachycardia, hypotension, nightmares, sexual disturbances, and seizures. Their appearance and severity vary individually and overlap, making it the more difficult to diagnose them.

Patients with severe EPS may need treatment options. Dose titration or a switch to another antipsychotic (with lesser EPS risk) may be
needed if the patient cannot tolerate the EPS. Discontinuation should be done gradually to prevent relapse and withdrawal symptoms. Medications that help manage EPS are anticholinergic medications such as benztropine and diphenhydramine. Beta-blockers (i.e., propranolol) and benzodiazepines (i.e., lorazepam) are also used to control restless motor movements. EPS screening measures should be used in patients taking antipsychotics. The 12-item Abnormal Involuntary Movement Scale (AIMS) is commonly used to assess motor movements and the severity of symptoms.

Long-term use of typical antipsychotics increases the likelihood of tardive dyskinesia, which is described as involuntary, purposeless, repetitive movements occurring in various parts of the body. The newer drugs, atypical antipsychotics (i.e., clozapine) are less likely to cause tardive dyskinesia. 81

Another very common side effect of antipsychotics is the effect on overall thyroid function associated with their use. 82 In 2007, researchers in Johns Hopkins suggest that the weight gain is caused by an increase of the enzyme adenosine monophosphate-activated protein kinase (AMPK) in the brain that is normally triggered by the biochemical histamine. What’s interesting is that the study showed that histamine and clozapine act on the same histamine receptor to elevate AMPK levels, making the connection between appetite stimulation and antipsychotics. 83
A study by Khalil, et al., found that patients who took phenothiazines and TCAs should be closely monitored for the development of thyroid function abnormalities. Phenothiazines and atypical antipsychotics change iodine uptake and decrease thyroid-stimulating hormone's (TSH's) sensitivity to thyroid-releasing hormone (TRH) stimulation. Only patients at risk for developing thyroid dysfunctions need to be monitored when they receive typical and/or atypical antipsychotic drugs. Currently, there are no specific recommendations proposed for the thyroid function monitoring in patients receiving any other psychopharmacologic drug.²⁰⁷

Antipsychotics are also known to elevate blood glucose in diabetic geriatric patients. A study published in 2009, *Archives of Internal Medicine*, one of the JAMA Archives journals, reported acute elevation of blood glucose levels after the start of therapy. Moreover, a document released by the American Diabetes Association, warn that mentally ill patients who are not diabetic at the start of antipsychotic therapy may be at an increased risk of developing an impaired glucose intolerance or pre-diabetes.⁸⁴

Clozapine, as discussed in the previous section, causes a severe decrease in white blood cells (neutropenia) during the first few months of therapy. Unresolved neutropenia (PMP <500 cells/µl) results in agranulocytosis, a marked near-absence of circulating white blood cells.⁸⁵ The side effect was widely known prior to its FDA approval. However, because of its demonstrated efficacy in treatment-resistant
schizophrenia and less liability to cause EPS, it was approved with strict orders to maintain bi-weekly hematologic monitoring for the entire duration of therapy. Moreover, at the first signs of neutropenia, patients should be monitored very closely for the onset of fever and other signs of infections.

As mentioned previously, prolactin levels may rise in patients taking atypical antipsychotics (i.e., risperidone). This is due to the drug’s blockade of the dopamine in the brain. Aside from mood regulation, dopamine also inhibits the release of prolactin from the pituitary glands. The manifestations of hyperprolactinemia are seen in the breast enlargement and secretion of milk of patients, regardless of gender. Risperidone has a high affinity for D2 receptors. It produces a rapid, dose dependent rise in the prolactin levels that is quite similar to that of haloperidol; however, it must be noted that studies did not prove this rise to be directly related to the clinically related adverse effects associated with elevated prolactin levels at usual doses. A study showed that 90% of patients taking the drug had an increase in serum prolactin levels whereas only half of the patients taking olanzapine had experienced the same.86

Clozapine has a lesser affinity for the dopamine receptors and cause lesser degree dopamine inhibition. Quetiapine has shown comparable prolactin level effects to placebo in some studies. A study that compared haloperidol with placebo found that the drug significantly raised serum prolactin levels, up to a nine-fold increase after only a
single injection. The weeks after the start of treatment showed an expected persistent rise of prolactin levels. Phenothiazines also cause elevated serum prolactin levels that range between two to tenfold when compared to baseline. An initial steep rise is seen in the first three days of treatment followed by a lesser but sustained rise in the following weeks.

Heterocyclic antidepressants have also been thought to cause mild elevation of serum prolactin levels, however, further studies are needed to validate the hypothesis. A study showed that patients treated with the two tricyclic antidepressants, clomipramine and amitriptyline, showed a temporary rise in prolactin levels at the start of therapy. After sustained administration of the drugs for 28 days, confusing results were seen; the patients treated with clomipramine and amitriptyline showed a significant increase and decrease in prolactin levels, respectively.

Another side effect of antipsychotics is sexual dysfunction such as impotence, decreased sexual interest and ejaculation problems. However, these side effects disappear as soon as the drug is discontinued. Importantly, pooled FDA studies point to the most fatal adverse effects of older and new antipsychotics – sudden death in geriatric patients with dementia-related psychosis. The black box warnings on the labels of the drugs listed above are actually about this life-threatening risk. Although the exact causes of the deaths were not identified, a series of possible effects may play a role such
disturbances in cardiovascular conductance, EPS, and anticholinergic effects.\textsuperscript{88}

**Antidepressants**

Antidepressants exert their pharmacological actions differently to treat depressive symptoms. Likewise, the side effects also vary according to the neurotransmitter or receptor system being targeted by the drug, and may overlap as well. Generally speaking, their side effects improve with time. The most common of these are:

- Erectile dysfunction
- Dry mouth
- Drowsiness
- Restlessness
- Weight gain
- Constipation
- Nausea
- Headaches

*Tricyclic antidepressants (TCAs)*

The unpredictable and much more pronounced side effects of TCAs have made it unpopular with prescribers and patients alike in the last decade. TCAs cause blurred vision, drowsiness, dysuria, sweating, and
constipation. Some of these side effects may decrease after 7-10 days of therapy.

**Monoamine oxidase inhibitors (MAOIs)**

Monoamine oxidase inhibitors also cause serious adverse effects. They are usually avoided as first line treatment for this very same reason and relegated to being a secondary treatment option when:

- The patient did not respond to the first line antidepressants (usually SSRIs)
- The patient has low tolerance for the side effects of the other class of antidepressants
- The patient is experiencing weight gain and unusual sleeping patterns

Nausea, shaking and trembling, insomnia, and blurred vision are commonly associated with MAOI use. These drugs also have the potential to cause sudden elevation of blood pressure (hypertensive reactions) with patients experiencing severe headache, stiff neck, chest pain and/or palpitations. The emergence of such symptoms should prompt a medical emergency.

Monoamine oxidase inhibitors cause orthostatic hypotension in most patients being treated with traditional monoamine oxidase inhibitors. The MAOI-A, selegiline, is particularly intentionally co-administered with levodopa to augment the latter’s dopaminergic effects on the
Parkinsonian brain. The concomitant use, however, also produces orthostatic hypotension. Phenelzine, a MAOI-B inhibitor, also causes significant hypotension.

Generally, the cardiovascular symptoms appear after 2-3 weeks after the initiation of therapy, and their severity is directly proportional to the peak plasma levels of the drugs. It is postulated that changes in dosing intervals might still not be enough to have a significant impact on avoiding orthostatic hypotension and interventions that increase intravascular volume might just prove to be more helpful.

Monoamine oxidase inhibitors come with severe dietary restrictions. When combined with tyramine-containing foods such as wine, chocolate and cheese, they cause a hypertensive crisis, a medical emergency.195

**Selective serotonin reuptake inhibitors (SSRIs)**

Selective serotonin reuptake inhibitors (SSRIs) especially fluoxetine have many reported side effects on all body systems. On the cardiovascular system, it causes palpitations and rarely, arrhythmias and hypotension. On the nervous system, it causes emotional liability, akathisia, and other movement dysfunctions relating to balance. Bruxism and depersonalization issues along with euphoria have also been reported, although rarely, with the use of fluoxetine Prozac. Additionally, there have been rare reports of patients suffering from hypertonia, an increase in libido and myoclonus. Paranoid reactions
and gynecological disturbances have also been reported with fluoxetine use.

The SSRIs have a black box warning cautioning patients and clinicians about the increased risk of suicidal thoughts in children and adults with this class of antidepressants. The risk was first reported in 1990, shortly after the drugs were introduced.

Antidepressants acting on the serotonin system can precipitate serotonin syndrome. Serotonin syndrome is a potentially life-threatening toxic state brought on by excess serotonin within the CNS. Excessive serotonin activity can lead to cognitive, autonomic and somatic disturbances. The usual clinical picture comprises of increased sweating, palpitations, dilated pupils, myoclonus, and hyperreflexia. The body temperature can rise up to 106 (degree Fahrenheit). Metabolic acidosis, seizures and even renal failure can occur if no immediate treatment is given. These drugs are therefore best avoided in patients diagnosed with serotonin secreting tumors (neuroendocrine tumors).

Serotonin syndrome usually occurs after a dose increase or overdose of a serotonergic agent or the addition of a second agent. The psychototropic agents implicated in serotonin syndrome are:

- SSRIs
- TCAs
- MAOI-A
• Buspirone
• Amphetamines
• Lithium
• St. John’s Wort
• LSD

Long-term use of SSRIs and TCAs is also linked to type 2 diabetes. Patients taking these medications for a prolonged period of time are believed to be more at risk of developing diabetes than others. Worsening of diabetes and loss of glycemic control can also occur while on these medications.

Selective serotonin reuptake inhibitors have a dose dependent effect on sexual dysfunction. Drugs like fluoxetine, fluvoxamine, paroxetine and sertraline show significant effects on the sexual functioning of the users. Significant differences were observed with each drug individually; paroxetine causes delayed ejaculation and orgasm, and impotence compared to the rest of the medications mentioned. Priapism, on the other hand, has been reported with use of all selective serotonin reuptake inhibitors.

Fluoxetine is so far only associated with decreased libido. Some women have reported experiencing orgasmic dysfunction such as anorgasmia.
Norepinephrine reuptake inhibitors (NERIs)

Similarly, norepinephrine reuptake inhibitors like atomoxetine also have profound effects on almost all parts of the human body. It affects the gastrointestinal system and may cause dry mouth, nausea, constipation, and heartburn. Fatigue, chills and jittery feelings may also be experienced in response to atomoxetine use. Effects on the CNS include excessive somnolence, tremors, headaches, paresthesias and also dizzy spells.

Atomoxetine, like other antidepressants acting on the serotonin system, may cause erectile dysfunction and decreased in libido.\textsuperscript{91} Ejaculation disorders and menstrual irregularities have also been reported with NERIs.

Benzodiazepines

Patients on benzodiazepines commonly experience dizziness, drowsiness, orthostatic hypotension, difficulty concentrating and diminished level of alertness. Benzodiazepines cause orthostatic hypotension by decreasing left ventricular contractility and reducing cardiac output. Temazepam is one of the most significant drugs to cause orthostatic hypotension when compared to placebo.

Benzodiazepines also have muscle relaxant properties that can result in impaired coordination. Studies show that elderly patients are more
prone to experience falls after the use of these drugs. The combined effects of diminished alertness and impaired muscle coordination are known to cause road traffic accidents when driving under their influence. Sexual dysfunction is also a fairly common side effect of benzodiazepines.

Paradoxical adverse reactions are also known to occur with benzodiazepine use in patients on high dose regimens, populations who have been taking the drug for prolonged periods of time, children, and recreational users. Patients may experience more frequent seizure activity, violence and aggression. Some reports have seen an increased risk of suicidal tendencies. Some patients on long-term therapy may also experience cognitive impairment. Diazepam is associated with drowsiness, fatigue, muscle weakness, ataxia, depression, dysarthria, slurred speech, headaches, tremor, diplopia, and hypotension. Acute hyper-excited states, anxiety, irritability, rage, psychoses, sleep disturbances and inappropriate responses have also been seen with its use.

**Anxiolytics**

Buspirone is used to treat symptoms of anxiety, such as fear, tension, irritability and dizziness. It can cause fast and irregular heartbeat, nausea, dizziness, impaired coordination, depressed moods, restlessness, diarrhea, and insomnia. Propranolol is a beta-blocker often prescribed to treat anxiety. Its side effects include hypoglycemia,
hypotension, decreased heart rate and increased airway resistance (contraindicated in asthmatics).

Gabapentin is another off label anxiolytic that is prescribed fairly commonly. It causes fever, chills, tremors, increased susceptibility to bruises and body aches, and swelling of extremities.

Sedative-hypnotics

One of the main problems associated with sedative use are their addictive properties and abuse potential. Just like benzodiazepines and other anxiolytics. Commonly associated side effects with sedative-hypnotics are the marked increase in depression, suicidal tendencies and thoughts. Anxiety, aggression and restlessness are seen to improve but at the same time may be paradoxically caused. With prolonged use and at inappropriately high doses, hallucinations may occur with sedative usage.

When taken over a prolonged period of time, sedatives are known to cause physiological and psychological dependence. Withdrawal symptoms are experienced when patients take themselves off these medications suddenly. Symptoms of drug withdrawal range from restlessness and insomnia to severe reactions such as convulsions, and in rare instances, even death. Similarly, fatal events can occur if sedatives are combined with other central nervous system depressants like alcohol. Patients on barbiturates who suddenly cease therapy exhibit strong withdrawal and rebound symptoms, and rapid eye
movement (REM) sleep. Doses need to be calculated accurately because fatalities are known to occur even with a relatively small overdose.

**Mood Stabilizers**

Lithium requires close monitoring to avoid toxicity. Its toxicity is due to the fact that with certain populations, its therapeutic dose overlaps with its toxicity dose, leaving a very narrow window of safety. Signs and symptoms of lithium toxicity are enumerated on the table below.

**Stages of lithium toxicity and associated signs and symptoms**

<table>
<thead>
<tr>
<th>Early stages</th>
<th>Late stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperactive DTR</td>
<td>Nausea</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Vertigo</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Weakness</td>
<td>Twitching</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Lethargy</td>
</tr>
</tbody>
</table>
Commonly observed side effects of lithium at the start of therapy are hand tremors, excessive urination, and excessive thirst. The CNS effects of the drug include hyper-tonicity, ataxia, extra pyramidal signs, vertigo, nystagmus, incontinence, impaired memory, and coma. It affects the cardiovascular system causing hypotension, bradycardia, and even cardiac arrhythmias.

Lithium also affects the endocrine system, causing adverse effects such as hypothyroidism or hyperparathyroidism. Diabetes insipidus is also associated with lithium use. On the gastrointestinal tract, it interferes with digestion to cause anorexia, gastritis, bloating, and even weight gain. Dermatological signs can also be seen with lithium use; these can include pruritus, alopecia and other signs.

**Stimulants**

Stimulants are commonly associated with elevated blood pressure levels, headaches, insomnia, weight loss, and decreased appetite. Amphetamine use can lead to vasoconstriction, blood shot eyes, dilated pupils, restlessness or agitation, dizziness, numbness, aphasia, twitching, acne, pallor, bradycardia, tachycardia, hypotension, and hypertension. It is known to cause erectile dysfunction, aggression, irritability, paranoia, and obsessive behavior.

With prolonged use amphetamine psychosis can also occur. At excessively high doses, death may also occur.
The side effects of methylphenidate are generally well tolerated by patients. Like amphetamines, it also carries an abuse potential. When administered intranasally in doses as high as 200 mg, the stimulation is comparable to amphetamines and crack cocaine. Intravenous use has found doses varying from 40 mg to as high as 1000 mg. Acute toxicity for both amphetamine and methylphenidate produce similar signs and symptoms.

**FAERS database**

In order to improve the clinical safety of drugs approved by the FDA, it has introduced a database that allows individuals to report adverse events. The database, called FDA Adverse Event Reporting System (FAERS), is basically designed to enhance and support the post marketing safety surveillance of drugs that have already been approved by the FDA. The database is in strict compliance with the rules and regulations stated in the International Conference on Harmonization (ICH).

The FDA Adverse Event Reporting System is especially useful in identifying new safety concerns that arise after a drug has been released into the market and also to evaluate if the manufacturers are compliant with reporting all due issues. Any concerns that are entered into the database are reviewed and assessed by the review committee so that appropriate actions can be taken to protect the public. Depending on the decision of the committee, the FDA may choose to
either restrict use of the drug (i.e., issue conditions on the use of the drug), remove it from the market completely (drug recall) or at times only require the manufacturer to relay new safety or warning information (i.e., black box warning) to the public consumers.\textsuperscript{94}

Consumers may voluntarily report any encountered adverse effects to the FDA using the Medwatch website. It is mandatory for the manufacturer to report health and safety issues to the FDA voluntarily. Either way, the reports received are added into the FAERS database. The database is publicly accessible to promote consumer awareness; for example, consumers can review the reports that have been received regarding a particular adverse effect or drug.

\textbf{Classification Of Mental Health Disorders}

Classifying mental health disorders is a universally challenging task. Since the majority of the disorders have overlapping symptoms, it is hard to classify them based on those symptoms alone.

There are currently two main sets of criteria used for classifying mental health disorders worldwide. The World Health Organization’s International Statistical Classification of Diseases and Related Health Problems (ICD) introduced the first criterion. Its latest revision, ICD-10, is an official tool used for diagnosing health conditions, including mental disorders, in the U.S. and in Europe. Its focus and purpose is
providing guidelines in the clinical evaluation of morbid conditions. It is not rigid about definitions.

A second criterion is also recognized universally and was proposed by the American Psychiatric Association (APA). Known as the Diagnostic and Statistical Manual of Mental Disorders or simply DSM, it covers all mental disorders for pediatric, adolescents and adults. The DSM was first developed using data from the United States Army manual and psychiatric hospital statistics in 1952. It was revised in 1980 wherein a number of mental disorders were added. The current version in use is the DSM-5-TR (fifth edition-text revision). The DSM-5 includes extensive details of each mental disorder and adheres to their operational definitions. It is widely used, not just in the U.S., in clinical practice and research settings worldwide.

Although reliable and comprehensive, some experts believe that the DSM-5 manual created a very large pool of diagnostic criteria including unnecessary psychopathologies that are associated with normal psychological responses, such as grief and withdrawal after a stressful and traumatic event. The manual has made diagnoses reliable and consistent but its overall validity remains obscure at best. The prior DSM-IV divided the mental health disorders into 5 axes or dimensions:

- Axis I:
  All diagnostic categories except mental retardation and personality disorder
• Axis II:
  Personality disorders and mental retardation

• Axis III:
  General medical condition; acute medical conditions and physical disorders

• Axis IV:
  Psychosocial and environmental factors contributing to the disorder

• Axis V:
  Global Assessment of Functioning or Children's Global Assessment Scale for children and teens under the age of 18 (the Avis V may be removed in the new DSM V TR version).

Some of the main classifications of mental disorders in the DSM-IV were listed as follows.

1. Developmental disorders:
   Conditions that were diagnosed very early in life such as ADHD and mental retardation
2. Delirium, dementia, amnesia and other cognitive Disorders:
   Alzheimer’s disease
3. Mental disorders due to another disease/disorder:
   AIDS-related psychosis
4. Substance related disorders:
   Alcohol abuse, cocaine addiction
5. Schizophrenia and other psychotic disorders:
   Delusional disorder
6. Mood disorders:
   Major depressive disorder and bipolar disorder
7. Anxiety disorders:
   General anxiety disorders and society anxiety disorder
8. Somatoform disorders:
   Somatization disorder
9. Factitious disorders:
   Munchausen syndrome
10. Dissociative disorders:
    Dissociative identity disorder
11. Sexual and gender identity disorders:
    Gender identity disorder
12. Eating disorders:
    Bulimia nervosa and anorexia nervosa
13. Sleep disorders:
    Insomnia
14. Impulse control disorders:
    Kleptomania
15. Adjustment Disorders
16. Personality disorders:
    Narcissistic personality disorder
17. Other disorders:
    Tardive dyskinesia and child abuse
In the DSM-5 the 5-axial diagnostic system has been replaced with a non-axial documentation of diagnosis; the former axes I, II, and III are combined in separate categories aligned with the medical model of documenting psychosocial, physical and other disabilities. Additionally, in the new DSM-5 clinicians may rate disorders according to severity, and the prior category of "not otherwise specified (NOS)" conditions have been removed in favor of the term "not elsewhere defined" (NED).

**Psychotic Disorders**

Psychotic disorders are those in which a person has difficulty staying in touch with reality. They are serious illnesses affecting the mind and the overall quality of life of patients. Generally, psychotic patients lose their ability to think rationally, communicate effectively, and understand, respond or behave in an appropriate manner. Moreover, in severe psychosis, patients may develop symptoms like delusions and hallucinations.

The good news is that modern treatment approaches to psychotic disorders has improved dramatically in the last few years. Even the most severe form of psychosis can be managed well on a combination of psychopharmacologic and psychiatric therapies. There are different types of psychotic disorders, some of which are described in detail below:

- *Schizophrenia*
Schizophrenia is the most common type of psychotic disorder. It is a mental condition that is identified by “a breakdown of thought processes and a deficit of typical emotional responses”. In the U.S., the span of time between the first onset of symptoms and its diagnosis is about 2 years.

Patients with schizophrenia, or schizophrenics, experience a variety of symptoms that include paranoid delusions, hallucinations (usually auditory), social dysfunction, confused speech and disordered thought processing. Pediatric and adolescent patients generally perform poorly at schoolwork accompanied by a steep decline in their social functioning (i.e., isolation, loss of friends). For the diagnosis of schizophrenia to be valid, these symptoms should be present for a period of at least 6 months. Also, no single laboratory test is diagnostic of schizophrenia, and its diagnosis is largely based on the patient’s history or behavior as observed by others as well as the patient’s own narrative and reported experiences.

Schizophrenia can be caused by a number of factors. Genetics, environmental triggers, psychological and social processes, and substance abuse are considered to be important contributing factors. The mainstay of treatment for schizophrenia is antipsychotics with the atypical antipsychotics being the preferred class for their minimal adverse effects.
Schizophrenics are often required to be on these medications throughout their lifetime since the possibility of symptom relapse is very likely if they are discontinued. Other useful treatment approaches are hospitalization and psychosocial interventions.

• *Schizoaffective disorder*

Schizoaffective disorder is characterized by abnormal mood changes accompanied by psychosis. Patients usually have a combination of symptoms of schizophrenia and a mood disorder (*i.e.*, depression or bipolar disorder). According to the DSM-V criteria of diagnosing schizoaffective disorder, it is very important that there is a period of at least 2 weeks of psychosis without an element of mood disorder with symptoms that are not the result of drugs being taken, substance abuse or any concomitant medical illness.95

The symptoms of schizoaffective disorder are usually first experienced during early adulthood. Significant social and occupational dysfunctions accompanied by incoherent thoughts, hallucinations and delusions are often seen. Cognition and emotions are the most frequently disturbed aspects of the patient’s personality. Specifically, these symptoms are observed as appetite changes, changes in energy levels, lack of hygiene, illogical speech, concentration difficulties, sleeping issues, hallucinations and social isolation.
The identifiable risk factors are similar to those of schizophrenia and its mainstay treatment is the combination of antipsychotic drugs and mood stabilizers or antidepressants, depending on the patient’s individual needs.

- **Schizophreniform disorder**

Schizophreniform disorder is characterized by symptoms of schizophrenia that are present for majority of the time in a one-month period; however, they are not present for a full six-month period, a required criterion for a valid diagnosis of schizophrenia. The onset of symptoms in individuals with this disorder is quite rapid compared to the gradual occurrence of schizophrenic symptoms. However, the nature of the symptoms is similar in both cases.

Patients with schizophreniform disorder may experience delusions, hallucinations, social withdrawal and speech disturbances, and impaired thought processing but their level of social functioning may not decline significantly. Schizophreniform disorder is also treated with atypical antipsychotics combined with occupational therapy or individual psychotherapy. The prognosis in these cases largely depends on the nature of the disease, its severity, and duration of symptoms.
It is quite common for schizophreniform disorder to develop into schizophrenia later in life. In fact, up to two-thirds of individuals diagnosed with schizophreniform disorder develop schizophrenia later on in their lives.

• Brief psychotic disorder

Brief psychotic disorders are conditions in which patients experience short-lived episodes of psychosis following a stressful life event. The recovery in such cases is quick and no residual disease usually lingers.

• Delusional disorder

Delusional disorder is a relatively uncommon psychiatric disorder wherein patients experience delusions that could potentially occur in reality (i.e., being poisoned or chased). Patients with delusional disorder do not have prominent hallucinations, thought or mood disorders and may appear to function quite normally. They also have normal social interactions and even their behavior might not be considered bizarre by an observer.

In order to make a valid diagnosis, it is important to note that no prominent auditory or visual hallucinations are experienced by the patient; however, tactile and olfactory hallucinations pertaining to the delusion may be a noticeable symptom.
Moreover, the DSM criteria stresses the importance of taking into consideration the patient’s cultural, religious and moral beliefs when considering this diagnosis because many cultures have widely accepted beliefs that may be considered delusions in other parts of the world.\textsuperscript{95}

It is also worth mentioning that the delusions in this case can be of any type. Patients may experience grandiose delusions in which the patient considers him/herself to be a very important public figure and possessing exceptional worth, power, knowledge, and, wealth. Erotomanic delusions may also be experienced which is characterized by the patient believing himself to be loved by another person, often a celebrity.\textsuperscript{97}

Another type of delusional disorder is called persecutory delusions. It is the most common of its type in which patients believe they are being malevolently treated in some way. Similarly, patients may also experience jealousy delusions and question the loyalty or faithfulness of their partners. This can be a dangerous delusion that the clinician needs to observe closely in terms of the safety of the “disloyal” spouse. There is a legal obligation called the Tarasoff for the clinician to contact and warn the “suspected spouse” to a possible danger.\textsuperscript{208}

- \textit{Shared psychotic disorder}
Shared psychotic disorder is a rare and complex disorder in which a normal healthy person shares the delusion of a patient who has established delusions such as a patient suffering from schizophrenia. There are no known causative factors that contribute to its development, however; stress and social isolation may play some role. The disorder is often short-lived and can be treated with antipsychotics combined with family therapy and psychotherapy. Additionally, tranquilizers and anxiolytic medications may also be prescribed to treat the intense symptoms of restlessness and insomnia associated with it.

- **Substance-induced psychotic disorder**

Substance-induced psychotic disorder is caused by either excessive use or withdrawal of certain psychoactive substances such as cocaine, amphetamines, caffeine, opioids, sedatives, hallucinogens, and alcohol. Patients may experience symptoms of hallucinations, delusions, and confused speech and thought processing. These symptoms are caused directly by exposure to the toxic substances and not due to an underlying medical condition.

According to the DSM-5-TR, substance-induced disorders include several new changes to the diagnosis.

- Recurrent legal problems criterion has been deleted;
- The criterion has been added of craving to use a
- Substance use disorder diagnosis is set at two or more criteria (rather than just one or more as with DSM-IV);
- Cannabis withdrawal has been added;
- Caffeine withdrawal has been added;
- Criteria for tobacco use disorder are the same as other substance use disorders;
- Severity of substance use disorders are based on the number of criteria endorsed: 2–3 criteria = mild disorder, 4–5 criteria = moderate disorder, 6 or more = severe disorder;
- Removed the diagnosis for “polysubstance dependence”;  
- “Early remission” is based on at least 3 months but less than 12 months without substance use disorder criteria;
- Sustained re-mission is based on at least 12 months without substance use disorder criteria;
- New specifiers include “in a controlled environment” and “on maintenance therapy as the situation warrants.”

Patients recovering from alcohol dependency may experience protracted withdrawal symptoms a few days after the last alcohol intake. Withdrawal symptoms may mimic major depression and anxiety, making diagnosis challenging. One helpful method of differentiating it from the other two is by checking the patient’s history if the same symptoms happened before. Substance delirium caused by alcohol usually occurs...
after drinking copious amounts. Its symptoms include irregular mental status and disorientation. Sedative toxicity and withdrawal symptoms are similar to alcohol accompanied by physical symptoms such as tinnitus, muscle twitching, and paresthesias. Hallucinogen-induced psychosis is a debatable medical entity.

The diagnosis of substance-induced psychosis is based on the history, onset, course and other factors. Moreover, physical examination and laboratory tests usually uncover the patient’s drug dependence, abuse, and withdrawal. The diagnoses may sometimes need to be re-evaluated repeatedly to completely rule out other conditions. Treatment includes discontinuation of the offending substance along with rehabilitation and psychiatric support.

• **Psychotic disorder due to a medical condition**

The essential features of this psychiatric illness are hallucinations, delusions and/or other psychiatric symptoms that are caused directly by the underlying medical condition. The patient’s history, physical examination results, and laboratory findings must also corroborate the signs and symptoms. According to the DSM-5 TR criteria, it is also essential to rule out medical disturbances. For example, an infection or uncontrolled diabetes may cause psychosis and can respond to medical
treatment. Clinicians must rule out such underlying conditions as metabolic, infectious or neurologic diseases in cases of psychosis.

Other neurological conditions that may cause psychotic symptoms include brain tumors, cerebrovascular diseases, Huntington’s disease, multiple sclerosis, migraines, CNS infections, and systemic lupus erythematosus with CNS involvement. Additionally, electrolyte imbalance, severely impaired blood glucose levels, and decreased blood gases such as carbon and oxygen may also cause psychotic symptoms. Although it is important to treat the underlying condition, this may not always result in remission of the psychotic symptoms. In most cases, the symptoms may persist for a very long time even after the underlying disease has been treated or brought under control.

**Personality Disorders**

A personality disorder is a psychiatric condition in which the patient has perception difficulties and exhibit deviant behavior from the norms expected of the surrounding culture and social environment. Patients with this condition often have staunch beliefs and an unhealthy way of thinking and behaving regardless of the circumstances. If left untreated, it can very well lead to significant problems related to work, social interactions and school performances. Patients with a personality disorder experience a number of symptoms including
frequent mood swings, unhealthy relationships, isolated behaviors, anger management issues and, distrust in others.

Personality disorders are broadly grouped into three main categories, depending on the degree of similarity between the symptoms. Each category is discussed below.

Cluster A personality disorders

This is a group of personality disorders characterized by odd, eccentric thinking and behavior which include paranoid personality disorder, schizoid personality disorder and schizotypal personality disorder, all of which are discussed in detail below.99

Patients with paranoid personality disorder have difficulty trusting others, are suspicious of the people around them, and under the impression that they are trying to harm them. They exhibit hostility towards others and are most likely emotionally detached. They tend to hold grudges and are unforgiving. However, they are often extremely sensitive and may not be able to take any form of criticism. These patients often find themselves to be under condemnation or disapproval by other people and may take benign conversations as attacks on their personality and react violently.

Patients with schizoid personality disorder show a general lack of interest in social relationships and also exhibit a lack of emotional
expression, appearing dull or indifferent to the people around them. It is not as debilitating as schizophrenia and the patient does not completely lose touch with reality. Hallucinations and delirium in such patients is a rare or almost nonexistent finding.

Patients with schizotypal personality disorder exhibit strange beliefs and superstitions, attire, thinking patterns and behavior. They are uncomfortable with personal relationships. They are emotionally detached and may appear as indifferent to the people and happenings around them. Another characteristic feature of this disorder is the concept of ‘magical thinking’; these patients believe they have the ability to influence other people by their thoughts alone and vice versa. For example, while listening to a public speech, they may believe that a hidden message is being conveyed to them and exhibit fixation at uncovering it. 99

Cluster B personality disorders

Cluster B category of the personality disorders are characterized by overt expression of emotions and dramatic behavior and thinking patterns. The common disorders included in this category are antisocial personality disorder, borderline personality disorder, histrionic personality disorder and also narcissistic personality disorder.
Antisocial personality disorder is characterized by aggressive behavior patterns, recurrent violations of law and order, disrespect for other people, an indifference towards the safety of other people, along with persistent lying and stealing habits.\(^\text{100}\)

On the other hand, patients with borderline personality disorders have unstable moods with grim fears of being left alone. These patients tend to have intense relationships that are unstable and involve a continuous change in the feelings experienced towards the other people. They may also exhibit unpredictable impulsive behavior such as excessive spending, gambling, and promiscuity. Additionally, they have suicidal tendencies and exhibit risky behavior. In severe cases, patients may also experience episodes of psychosis and its symptoms such as hallucinations. Also, major depressive episodes can occur in such patients, which can markedly increase the risk of suicide.

Patients with histrionic personality disorder show extreme emotional liability and attention seeking behavior. They may also show excessive concern with physical appearances. They experience feelings of discomfort when they do not receive adequate attention in a social arena and may sometimes dress provocatively or act flirtatiously in order to fulfill their attention-seeking needs. They stand out from the crowd easily with overtly dramatic actions. Furthermore, they take criticism poorly and require constant approval from their peers.\(^\text{100}\)
Lastly, patients with narcissistic personality disorder experience extreme self-admiration and are focused mainly on their own self. They believe in their own superiority to others and seek constant praise for their efforts and actions. They also tend to fantasize excessively about their success and attractiveness. They may also fail to acknowledge others people’s feelings and focus only in seeking the attention of others. They also believe they are special and cannot be understood by the general people. Generally, they demonstrate aggressiveness and arrogance, considering others to be envious of them.\textsuperscript{101}

Cluster C personality disorders

Cluster C personality disorders are characterized by anxious and fearful thinking patterns. Included in this classification are obsessive-compulsive personality disorder, dependent personality disorder and avoidant personality disorder.\textsuperscript{102}

Patients with avoidant personality disorder have timid personalities, are socially isolated and demonstrate extreme shyness in social gatherings. They are overly sensitive towards criticism as well.

Similarly, those with dependent personality disorders exhibit extreme dependence on other people. They have submissive personalities and are unable to take any form of abuse. They also tend to jump into relationships right after the previous one has ended in order to fulfill their need to be taken care of by other people.
Obsessive-compulsive personality disorders differ from obsessive-compulsive disorder (OCD), which is a type of anxiety disorder and not a personality disorder. Patients with obsessive-compulsive personality disorders have inflexible personalities and they feel an intense need to maintain law and order. They tend to be preoccupied with rules and regulations and cannot tolerate indiscipline. They need to take charge of and control situations, and expect perfection in most aspects of life. These patients also see themselves to be more reliable, productive and proficient than others.\textsuperscript{102}

**Emotional or Behavioral Disorders**

Emotional and behavioral disorders fall under the category of “emotional disturbances” and are characterized by improper behavior, learning difficulties, prolonged unhappiness or depressive moods, difficulty in maintaining personal healthy relationships and a tendency to develop physical symptoms or fears that are associated with school or other personal factors. In children with emotional or behavioral disorders, these symptoms are present for long periods of time and influence a child’s educational performance in the long run.

There are many factors that contribute towards children developing behavioral disorders. These factors can be biological, \textit{i.e.}, malnutrition, brain damage, physical illness and inborn behavioral characteristics. Sometimes these behavioral disorders develop when children are raised in strained circumstances at home; for example, when they see their parents going through a divorce, suffer from abuse and neglect,
or observe inappropriate parental behavior such as usage of bad language, and a frivolous attitude towards education and school performances.\textsuperscript{103}

There are different screening modalities that help identify children with behavioral disorders at an early age. The screening methods include use of intelligence and achievement tests, behavior ratings when compared to other children of the same age group, intrapersonal assessments tools and also direct behavior observation.

There are several different types of behavioral disorders; each one is briefly described below.\textsuperscript{103}

- \textit{Conduct disorder}

  Conduct disorder is more frequently seen among boys than girls. Children with conduct disorders are excessively aggressive and may be unnecessarily inclined towards lying and stealing. They also have difficulty managing confrontational situations diplomatically and exhibit defiance. Moreover, they are antisocial, destructive, violent and impertinent. They also show resistance to discipline methods normally used by parents and teachers.

- \textit{Oppositional defiant disorder}

  Oppositional defiant disorder is a condition in which children continuously defy and challenge authority figures. They show
resentment and throw tantrums accompanied by physical displays of aggression.

- **Aggression**

Another behavior disorder commonly found among school age children is aggression. It is usually learnt from parents, friends, siblings and even television. It can become permanent if not dealt with early.

- **Socialized aggression disorder**

Socialized aggression disorder is similar to the one described above. Children and young adults with socialized aggression disorder are hostile, defiant, disobedient and both physically and verbally aggressive. They are usually active participants or members of delinquent gangs and may have juvenile criminal records.

- **Anxiety and withdrawal disorder**

Anxiety and withdrawal disorder is characterized by fears related to a future event. Patients with this disorder may also exhibit extreme irrational fears (phobias).

Children with anxiety disorders often exhibit physical symptoms of nausea, pains and aches, crying episodes, sleep disorders and
nightmares. They usually have low self-esteem and are shy and fearful in social gatherings. If left unchecked and untreated, children may develop obsessive-compulsive behaviors in an attempt to overcome the anxiety.

**Mood Disorders**

Mood disorders are characterized by mood disturbances triggered by underlying causes. These disorders are often also called affective disorders. They are classified into the following categories:

*Depressive disorders*

This category includes major depressive disorder (MDD), also known as clinical depression and unipolar depression (in the absence of mania). Major depressive disorders are characterized by at least a 2-week period of lack of interest in social activities, continuous low moods, irritable and depressed state of mind, altered eating and sleeping habits and suicidal tendency. Due to the latter, these patients need prompt medical attention and treatment. MDD has several subcategories under it; namely, atypical depression, melancholic depression, psychotic major depression, catatonic depression, postpartum depression and seasonal affective disorders. Excessive weight gain, increased appetite, and also impaired social relations characterize atypical depression. Melancholic depression is characterized by the loss of pleasure in all activities, excessive weight
loss, early morning wakening, and psychomotor retardation. Patients with psychotic major depression experience depressive episodes accompanied by psychotic symptoms such as delusions and/or hallucinations.

Catatonic depression is rare and characterized by severe depression accompanied by bizarre, purposeless movements or other motor symptoms. Patients are often mute and immobile. It can result from neuroleptic malignant syndrome. Postpartum depression and seasonal affective disorders are also forms of depression that occur after the birth of a baby and depressive episodes that are related to seasons (commonly winter), respectively.

**Bipolar disorders**

Bipolar disorder is characterized by periods of depression alternating with mania (persistently high moods). Bipolar I disorder is predominantly manic or mixed episodes without significant depression. Bipolar II disorder, on the other hand, consists of alternating recurrent episodes of mania and depression. Cyclothymia is another form of bipolar disorder in which patients have hypomanic episodes alternating with dysthymic episodes (with no full blown depressive episode).

**Dysthymic disorder**

Dysthymic disorder is a chronic form of depression, lasting for 2 years and more. There is no 2-month period in which the following
symptoms are not observed; overeating or loss of appetite, excessive sleep or insomnia, fatigue and lack of energy, difficulty concentrating and also constant feelings of hopelessness.

For a diagnosis of dysthymic disorder to be valid, it is important to rule out substance abuse, other underlying medical condition or any other identifiable cause. Furthermore, it is important for patients diagnosed with dysthymia to have not had an episode of major depressive disorder within this 2-year period, and no episodes of mania, hypomania or mixed episode.

*Substance-induced mood disorder*

Substance-induced mood disorder is defined as manic, hypomaniac or depressive symptoms caused by either usage or withdrawal of a specific substance or drug. The DSM-5 TR diagnoses substance abuse disorder on the basis of persistent mood disturbances characterized by either depressed mood or lack of interest in all activities. Also, there should be clear evidence that these disturbances have been proven either from patient history, clinical data or through laboratory findings as a direct cause of substance use or intoxication or withdrawal. It is also important that the mood disorder does not occur during delirium and that the disturbance is not better accounted for by a mood disorder that is not caused by substance abuse.

One of the common causes of substance-induced disorder is alcohol. Major depressive disorder is linked to long-term alcohol intake. Previously, it was believed that people suffering from depression can
benefit from alcohol use to nullify their pain or curb their depression, but current research literature rejects this idea, suggesting instead that chronic use of alcohol directly causes major depressive disorder, especially in heavy drinkers. Furthermore, chronic alcohol use is associated with higher suicide rates.

In most cases, extensive history can help differentiate between preexisting depression and depression that may have resulted directly from chronic alcohol use. Similarly, chronic intake of benzodiazepines may also cause depression in certain predisposed individuals. Moreover, benzodiazepine withdrawal also causes rebound depression. Illicit drug use of substances like amphetamine, methamphetamine and cocaine, are associated with mania, hypomania, and depression.

*Mood disorders caused by an underlying medical condition*

This category includes mood disturbances that are direct results of underlying medical conditions. Neurological disturbances such as dementia and related states, metabolic disturbances including electrolyte balance, endocrine diseases, cardiovascular diseases, pulmonary diseases, and autoimmune diseases are known to cause mood disturbances.

**Dosage and Delivery: Infusion and Oral**

Psychotropic drugs like all other medications come in a variety of forms. They can either be taken in a pill form (tablet or capsule) orally
or in an injectable form (vial or ampule) intravenously. Some are inhaled and others applied directly onto the skin. Each route of administration has its own dosage formulation and magnitude of pharmacologic action. A diazepam tablet does not produce the same anxiolytic properties as its intravenous formulation. Dosages, in whatever form, present with their own unique advantages and disadvantages. The various formulations allow patients and clinicians the freedom to administer medications according to the patient’s circumstances and convenience, and clinical need.

*Routes of administration or delivery*

The route of administration plays a very important role in determining the dose of the drug to be delivered, the speed of its delivery to the target site and ultimately, the speed at which it exerts its pharmacological activity (onset of action). The route of administration affects not just the bioavailability of the drug, but its entire pharmacokinetic profile. The different routes of administration are broadly classified into three main categories: *enteral administration*, *parenteral administration* and *transdermal administration*. Each route offers its own set of advantages and disadvantages.

The table below lists the most common route from each category in comparison with each other’s advantages and disadvantages.
### Comparison of the advantages and disadvantages of the common types of routes of administration

<table>
<thead>
<tr>
<th>Effects</th>
<th>Oral</th>
<th>IV</th>
<th>Transdermal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>Unpredictable</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Onset of action</td>
<td>Fast, slow and extended</td>
<td>Fast</td>
<td>Slow and extended</td>
</tr>
<tr>
<td>Risk of toxicity</td>
<td>Present</td>
<td>High</td>
<td>Minimal</td>
</tr>
<tr>
<td>Dose</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Contamination / Infection risks</td>
<td>Low</td>
<td>High</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

**Enteral administration**

Drugs administered enteraally go through the gastrointestinal tract for absorption into the circulation. Examples include tablets, syrups, solutions, capsules and suspensions. However, this isn’t always necessarily the case. Sublingual tablets are placed under the tongue to be absorbed directly into the systemic circulation. The atypical antipsychotic, asenapine, is given sublingually.

Majority of the psychiatric drugs are given through the oral route. The route offers convenience and general patient acceptability. Almost all drugs mentioned in the previous sections come in a tablet form, *i.e.*, fluoxetine, quetiapine, diazepam, aripiprazole, *etc*. Psychotropic drugs that require multiple dosing throughout the day are formulated as extended release capsules or tablets to reduce the burden and
inconvenience of its frequent administration. An example is venlafaxine, and is available in an extended release capsule form.

**Parenteral administration**

Psychotropic drugs are also delivered parenterally. This particular route of administration allows for the direct administration into the central nervous system. One example is the injection of anesthesia directly into epidural space. Another example is the atypical antipsychotic, aripiprazole, which is given intramuscularly. Due to the drug entering the circulation directly and bypassing the liver, most of its active and non-active metabolites are found only in trace amounts, excreted via feces and urine.

Perhaps the most common route of parenteral administration is the intravenous route. It is particularly useful in managing emergency situations and acute episodes since its onset is the fastest. Drugs such as imipramine, morphine, propranolol, diazepam, and midazolam, undergo extensive first pass metabolism and have low oral bioavailability. But when delivered through the IV route, these drugs have almost 100% bioavailability.

Intravenous administration is known for its rapid effects, usually within seconds. However, another form of IV route, IV infusion, allows for the slow and steady administration of psychotropic drugs over a period of time. It does come with its own set of disadvantages such as phlebitis, extravasation, hypersensitivity, infection, embolism and fluid overload. Chlorpromazine is particularly irritating to the veins and may cause
swelling and redness at the site of administration. The intramuscular route allows for depot administration in patients that need a different treatment strategy than others and this is especially true for psychotropic drugs. Examples include those with frequent relapses, problems with oral medication adherence, need of a burst dosage. Haloperidol decanoate is an example. A starting dose of 50 mg is administered intramuscularly in the gluteal region. It is a long acting form of the drug that is designed to provide one-month therapy, sustained by the oral form of the drug. Other depot antipsychotic drugs that are administered as intramuscular injections are listed in the table below.¹⁰⁵

### Depot antipsychotics and recommended maintenance doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of administration</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zuclopenthixol</td>
<td>IM</td>
<td>200-400 mg bimonthly/monthly</td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>IM</td>
<td>12.5-75 mg monthly</td>
</tr>
<tr>
<td>Flupenthixol decanoate</td>
<td>IM</td>
<td>20-80 mg bimonthly/monthly</td>
</tr>
</tbody>
</table>

There are a few drugs that can even be administered intracerebrally in order to bypass the blood brain barrier. It is a fairly new route of administration that is still under research and development. An intracerebroventricular route also exists in which the drug is given
directly into the ventricles of the brain. It is not a common route of administration and is usually reserved for terminally ill cancer patients who need analgesia for pain that is refractory to medication administered through other routes.¹⁰⁶

*Transdermal administration*

Psychotropic drugs can also be administered via the skin. The transdermal route of administration allows for the absorption of the active drug through the skin and into the systemic circulation. An example of transdermally administered psychotropic drug is selegiline, which has been described in detail in the previous paragraphs. The transdermal route bypasses the notorious drug-drug and drug-food interactions exhibited by most of psychotropic drugs due to their oral pharmacokinetic profiles. As a result, it offers lesser side effects and decreased likelihood of overall incidence of adverse events when compared to the IV and oral routes.

Another transdermal patch containing a psychotropic drug is methylphenidate. It is usually prescribed for adolescents with ADHD.

*Miscellaneous routes of administration*

The intranasal route is the most favored administration technique by illicit drug users. This is because the nasal cavity is a highly vascularized port of drug entry. Legal drugs are also administered via this route as demonstrated by the intranasal nicotine (Nicotrol NS), a
drug used in the management of withdrawal symptoms associated with smoking cessation.

Dosing schemes or guidelines

The dosage of a psychotropic drugs depend on a number of factors such as age, gender, comorbidities, liver and kidney function, extent of disease, pregnancy status, side effects experienced by the patient, response to previously administered drug or tolerability of the drug, etc. Also, pediatric and geriatric doses for the majority of the medications differ from normal adult doses.

Another very important point about dose determination pertaining to psychotropic drugs is that dose increments with these drugs need to be made carefully to avoid toxicity. As mentioned previously in the other section, age, gender and comorbidities dictate the dose requirements of individual patients. Compromised renal and liver functions, older age and gender affect the pharmacokinetic and pharmacodynamics of drugs. The specific doses for the frequently used psychotropic drugs are discussed in detail below. An additional helpful quick reference drug sheet is shown at the end of this article.

Antipsychotics

Haloperidol is given in tablet form with an adult dose that ranges between 0.5-5 mg depending upon the severity of the disease. Its maintenance dose for such patients is between 1 mg to 30 mg in two
to three divided doses. The emergency parenteral dose of haloperidol is 2 mg to 5 mg given intramuscularly for prompt control, which may be repeated every 4-8 hours. A dose of 8-10 mg of the drug may also be administered via this route. When patients are excessively agitated, they may require regular hourly doses.

Haloperidol is not recommended for pediatric patients below 2 years of age or those who weigh less than 15 kg. Children between the ages of 3-12 years and those who weigh between 15 to 40 kg can be given an initial starting dose of 0.5 mg/day in two or three divided doses. In case the dose needs to be increased, it should be done every 5-7 days by 0.25 to 0.5 mg increments.

Parenteral forms of haloperidol are not recommended in pediatric patients below 5 years of age. For children between 6-12 years of age, 1-3 mg IM injections can be administered every 4 to 8 hours and the therapy should be switched to oral form as soon as possible. It is recommended that patients with renal or hepatic dysfunction be given the drug with caution.

Quetiapine is available in tablets 25, 50, 100, 200, 300 and 500 mg dosages. When prescribed for bipolar disorder, an initial dose of 25 mg is usually given twice daily. On the second and third day of therapy, dose increments of 25 to 50 mg to the drug regimen in 2 or 3 daily divided doses may be made. A total dose of 300 to 400 mg may be attained by the fourth day. When prescribed for schizophrenia, the dose ranges between 150 mg/day to 750 mg/day, however, doses
above 300 mg/day were not proven to be more efficacious than 300 mg/day. The safety of dosing regimen as high as 800 mg/day has not been proven. The dose for adolescent patients between the ages of 13 to 17 for the first five days of therapy is 50 mg, 100 mg, 200 mg, 300 mg and 400 mg at day 1, 2, 3, 4, 5, respectively. After this, the dose may be adjusted as required between 400 mg/day to 800 mg/day depending upon patient response and tolerability. An increment of more than 100 mg/day should not be made with quetiapine.

Schizophrenic adults with recurrent suicidal behavior may benefit from Clozapine, starting dose of 12.5 mg once daily, with dose increments of 25-50 mg/day, until the maintenance dose of 600-900 mg/day is reached. The safety of clozapine has not been studied in pediatric patients and should not be used in such populations. In geriatric populations, a lower initial dose of 12.5-25 mg/day is appropriate which may be titrated upward slowly to reach the maintenance therapeutic levels.¹⁰⁷

Risperidone may benefit adults with schizophrenia, usually started at a dose of 2 mg/day, with 1-2 mg dose increments made every 24 hours until a 4-8 mg/day maintenance dose is reached. In adolescents with schizophrenia, an initial dose of 0.5 mg is recommended with 0.5-1 mg dose increments made every 24 hours until the 3 mg maintenance dose is reached. The table below summarizes the maximum daily doses for each population that was discussed above.
Table 13: Maximum initial and maintenance doses of antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult Initial</th>
<th>Maintenance</th>
<th>Pediatric Initial</th>
<th>Maintenance</th>
<th>Geriatric Initial</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>0.5-5 mg</td>
<td>1-30 mg</td>
<td>0.5 mg</td>
<td>0.5 mg increase</td>
<td>0.5-2 mg</td>
<td>1-30 mg</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25-50 mg</td>
<td>400-800 mg</td>
<td>50 mg</td>
<td>400-800 mg</td>
<td>50-200 mg</td>
<td>200 mg or less</td>
</tr>
<tr>
<td>Clozapine</td>
<td>12.5 mg</td>
<td>600-900 mg</td>
<td>Not established</td>
<td>Not established</td>
<td>12.5-25 mg</td>
<td>25-150 mg</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2 mg</td>
<td>4-8 mg</td>
<td>0.5 mg</td>
<td>3 mg</td>
<td>0.25-1 mg</td>
<td>1 mg</td>
</tr>
</tbody>
</table>

**Antidepressants**

The dose and dosage form of fluoxetine depends upon the disorder it is prescribed to treat. In bulimia nervosa, a starting dose of 60 mg may be given; however, further dose titration may be necessary. In adult depression, a dose of 20 mg/day may be given initially for the first few weeks of therapy. If no clinical improvement is observed, the dose may be increased. The maximum total daily dose should not exceed 80 mg/day. Children less than 7 years of age should be started at 10 mg/day and succeeding dose increments made at least 2 weeks after initiation of therapy. For children above 8 years of age, a similar dose should be given with succeeding dose increments made after 1 week of treatment. When fluoxetine is to be administered with olanzapine, it is generally recommended that it be done in the evening as a once daily dose.
In children and adolescents weighing less than 70 kg, atomoxetine should be initiated at 0.5 mg/kg with increments made only after a minimum of three days therapy. The increments should not exceed the total dose of 1.2 mg/kg per day as a single dose or total divided doses. Generally, the dose should not exceed 1.4 mg/kg or a 100 mg in total when given to children (regardless of weight) and young adults. Patients who are co-administered with paroxetine and fluoxetine should not be given more than 80 mg/day since these two drugs are inhibitors of CYP2D6, the same enzyme that metabolizes atomoxetine. For children and adolescents above 70 kg or adults the starting dose is 40 mg, which may be increased after a minimum of 3 days therapy. It can be discontinued without tapering. Dose adjustments need to be made with patients who have hepatic insufficiency. Patients with moderate and severe hepatic dysfunctions may need to reduce their dose to as much as 50% and 75%, respectively.

Mirtazapine is administered orally in 15, 30 and 45 mg tablets. The initial dose in patients with major depressive disorder is 15 mg/day given at night. It may later be increased up to 45 mg/day if adequate clinical response failed to show with the starting dose. Dose changes should only be made after a 1-2 week interval. Geriatric patients should start at half the usual adult dose, at 7.5 mg, and not exceed more than 45 mg/day. Its safety and efficacy have not been established in pediatric patients. Drug clearance may be affected in
patients with renal or hepatic impairments and dose adjustments may be necessary to prevent toxic effects.\textsuperscript{197}

Venlafaxine is available in doses of 25 mg, 37.5 mg, 50 mg, 75 mg or 100 mg tablets. Extended release capsules are also available. The recommended dose at initiation of therapy is 75 mg given in 2-3 divided doses and preferably taken with food. If needed, dose increments of 75 mg may be made at 4-day intervals to reach a target of 225 mg/day. Some clinical trials showed that severely depressed patients responded to a dose of 375 mg. Dose adjustments are required in patients with moderate to severe renal and hepatic dysfunctions by as much as 25-50\%, respectively.\textsuperscript{198}

Trazodone is available in 50, 100, 150, 300 mg tablets. Extended release tablet formulations are also available. The usual adult starting dose is 150 mg/day in divided doses. A 50 mg dose increment may be made at 3 to 4 day intervals. The maximum allowable dose for outpatients is 400 mg/day and inpatients may be given up to 600 mg/day in divided doses. The latter is the maximum allowable total daily dose and should not be exceeded.\textsuperscript{200} Trazodone is available as a once daily-extended release dosage form for MDD in adults. Approved by the FDA in 2010, it provides sustained pharmacological effects minus the adverse effects associated with frequent dosing.\textsuperscript{199}

Bupropion is supplied in tablet form in 174 mg, 348 mg, and 522 mg doses. It is recommended in major depressive disorder and in patients
undergoing depressive episodes in seasonal affective disorder. It is administered in the morning as a whole pill. It should not be chewed nor crushed and its absorption is not affected by meals. The usual recommended dose for major depressive disorder is 174 mg once daily that may be increased gradually to 348 mg/day. Slow titration is important in order to prevent the risk of developing seizures. Patients with hepatic insufficiency are recommended a maximum dose of 174 mg/day. Like other antidepressants, it needs to be tapered before discontinuation.  

Amitriptyline is available in oral and parenteral forms. In outpatient adults, an initial dose of 75 mg in daily divided doses is generally recommended. Usually, three doses of 25 mg are given throughout the day or at bedtime. It may be increased up to 300 mg if required. In inpatient adults, 100 mg-300 mg/day is usually given. In adolescents and elderly patients, a dose of 10 mg three to four times a day with 20 mg at bedtime may be given. The intramuscular injections may be given as 20 to 30 mg up to four times a day. It is not recommended for use in pediatric patients, specifically below 12 years of age. 

Selegiline transdermal patch has been recently approved for the treatment of major depressive disorder. Its efficacy has been tested in 6 week and 8 week-placebo-controlled trials. Selegiline is applied to dry, intact skin, usually applied on the upper torso, upper arm or upper thigh. The patch should not be put on any skin that is calloused, hairy, oily, scarred or broken. The patch is applied every 24 hours with
the initial recommended dose of 6 mg every 24 hours. In case increased dosage requirements, increments of 3 mg/day in two weekly intervals is advised. A maximum dose of 12 mg/day is allowed in special circumstances.

When selegiline is started, patients should be advised to avoid tyramine-containing foods and beverages and the same precautionary measure must be maintained until 2 weeks after dose reduction or discontinuation of the drug. Under no circumstances should selegiline transdermal patch be used in pediatric patients, even with strict dietary modifications (avoiding tyramine rich foods) in place.

Anxiolytics

Diazepam is particularly indicated for the short-term management of anxiety. It is usually recommended that patients starting treatment with diazepam be periodically checked to assess the efficacy and safety of the drug. Its long-term use (more than four months) including its efficacy and safety has not been clinically established.

Depending on the severity of the anxiety symptoms, diazepam tablets are usually started at 2-10 mg in repeated doses twice to four times daily. In the symptomatic relief of acute alcohol withdrawal, diazepam tablets may be given daily as 10 mg three to four times daily that may then be reduced to 5 mg three to four times until symptoms subside.
2-10 mg doses can be given for the relief of acute muscle spasms. In geriatric patients, the dose should generally be within the range of 2-2.5 mg once or twice daily and if the need requires, gradual dose increments may be made. It should not be administered to patients younger than 6 months of age. In older children, the lowest possible dose should be given with gradual dose increments made as required. Usually a 1-2.5 mg is given three to four times a day.\textsuperscript{202}

\textit{Mood stabilizers}

Lithium is formulated in its salt form as lithium carbonate capsules. A controlled release dosage form is also available that contains a higher dose. Immediate release tablets are usually administered thrice daily or four times and the controlled released tablets are given in no more than twice daily doses. Lithium toxicity is a very serious side effect that can occur if excessive doses of lithium are administered, underscoring the need for dose individualization. In patients with acute mania, lithium is administered as a total of 1800 mg daily, divided in four doses.

The desired lithium serum levels are between 1.0-1.5 mEq/L. Even slightly higher doses than 1.5 mEq/L can cause toxic (and even allergic) reactions such as tremor, renal impairment and ataxia, even death. For long term control and maintenance therapy, the desired lithium serum levels range between 0.6-1.2 mEq/L. The usual dose of lithium required to maintain these levels is between 900 mg to 1200
mg daily, depending on patient needs and responses. Serum levels should be monitored closely to prevent toxicity.\textsuperscript{109}

**Stimulants**

Amphetamine has a very high potential for abuse and prolonged usage may lead to altered behavior and drug dependence underlining the need for cautious prescribing habits and patient monitoring. Patients should be given the lowest possible dose and then maintained according to their clinical response. In children aged between 3-5 years with Attention Deficit Hyperactivity Disorder (ADHD), it is usually given at a dose of 2.5 mg once a day. It should not be administered at night as it may very well cause insomnia and disturb normal sleep patterns. In children above 6 years of age with ADHD, a 5 mg dose of the drug may be given once or twice daily. The respective doses for both age groups can be increased to double at weekly intervals if required. For adult patients with narcolepsy, it may be given as 5 to 60 daily in divided doses.

Methylphenidate is available in extended-release and immediate release dosage forms. For ADHD in adults, an initial dose of the 20 mg extended release in the morning is recommended with weekly increments of 10 mg, up to the maximum total daily dose of 60 mg/day. The immediate release form is usually administered as 20-30 mg in daily divided doses. The tablets are usually given every 6-8 hours before meals. The same dose is recommended for narcolepsy.\textsuperscript{194}
The recommended doses for methylphenidate in pediatric and adolescent patients are given in the table below.

<table>
<thead>
<tr>
<th>Doses</th>
<th>Methylphenidate-naïve patients</th>
<th>Patients already on methylphenidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 mg</td>
<td>Initial dose</td>
<td>If switching from 5 mg every 8-12 hrs</td>
</tr>
<tr>
<td>36 mg</td>
<td>Allowed increment after 1 week therapy</td>
<td>If switching from 10 mg every 8-12 hrs</td>
</tr>
<tr>
<td>54 mg</td>
<td>Maximum dose (6-12 years old)</td>
<td>If switching from 15 mg every 8-12 hrs</td>
</tr>
<tr>
<td>72 mg</td>
<td>Maximum dose (13-17 years old)</td>
<td>If switching from 20 mg every 8-12 hrs</td>
</tr>
</tbody>
</table>

A transdermal patch is also available for adolescents (13-17 years of age) with a starting dose at 10 mg applied to the hip for 9 hours.

**Sedative-Hypnotics**

At sub-hypnotic doses, phenobarbital may be used as an anticonvulsant in 50 to 100 mg daily divided doses. As a pre-anesthetic in pediatric patients, a dose of 1 to 3 mg/kg is generally given preoperatively. For daytime sedation in adults, the recommended dose is between 30 to 120 mg in two to three divided doses. For bedtime hypnosis the drug can be given as either 100 mg
or 320 mg dose depending upon the patient need. Geriatric patients and those with hepatic and renal impairments will need dose adjustments. Caution should be used when prescribing and administering it to geriatric patients since they are particularly more sensitive to the drug.\textsuperscript{203}

**Dose–response curve**

Dose response curve or the dose effect curve is defined as the graphic representation of the drug effect plotted against the dose. Essentially, it shows the relationship between the effect and changes in the dose. It is particularly useful in representing toxicity and therapeutic benefit relationship of a certain amount of drug.\textsuperscript{110} These drug response curves are used to graphically represent the results of many experiments pertaining to different drugs, their concentrations and the effects these variations produce.

On the dose–response curve the X-axis is the dose of the drug being studied that is plotted against the Y-axis, which is the response produced. When a full agonist is administered, it provokes a visible response on the graph. The dose response curve will shift from left to right, depending on the concentration of the agonist. A partial agonist is a drug that also provokes a response; however, the response will not be as substantial as the response produced by a full agonist. On the other hand, if an antagonist drug is administered, no response will be seen. In fact, antagonists are those drugs that do not produce a response, and instead they inhibit agonist-mediated responses. The
introduction of varying concentrations of antagonist drugs will produce a dose-response curve that either moves downhill or from right to left.

**Therapeutic versus toxic**

The therapeutic index is a measure of a drug’s safety. It demonstrates the relationship between its toxic dose and effective dose. Previously, it was calculated as the ratio of maximum tolerated dose to the minimum therapeutic dose. Its identification is an integral part of achieving the balance between a drug candidate’s safety and its efficacy for its proposed indication during drug development.\(^{111}\)

Currently, therapeutic index is calculated differently; it is the ratio of the median lethal dose to the median effective dose. Its current formula is shown below:

\[
\text{Therapeutic index} = \frac{\text{TD}_{50}}{\text{ED}_{50}}
\]

TD\(_{50}\) corresponds to the dose that produces toxic effects in 50% of the population. ED\(_{50}\) corresponds to the dose that produces a therapeutically beneficial effect in 50% of the population. Both those values are derived from quantal dose-response curves. Quantal dose-response curves are the graphic representation of the frequency with which each therapeutic and lethal doses of drug provoke the needed response or toxic effect in the population being studied.
Therapeutic indices of drugs readily inform clinicians and pharmacists of the relative safety profile of the drug. Drugs with a large therapeutic index are often very safe even when given in large amounts, having little risk of producing toxicity. Drugs with a narrow therapeutic index are drugs to watch out for and need close therapeutic monitoring because of the small difference between the therapeutic and lethal doses. The therapeutic index of drugs like warfarin, lithium, digoxin, phenytoin, gentamycin, Amphotericin B, 5-fluorouracil, AZT is narrow and the potential for toxicity at therapeutic doses is a big worry to prescribers and patients.

**Therapeutic indices of psychotropic drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>100:1</td>
</tr>
<tr>
<td>Morphine</td>
<td>70:1</td>
</tr>
<tr>
<td>Cocaine</td>
<td>15:1</td>
</tr>
</tbody>
</table>

**Summary**

Mental illness often co-exists with other chronic diseases that increase the risk of morbidity and mortality. The rate of mental illness is higher than other major diseases, such as cancer and heart disease. The Centers for Disease Control and Prevention (CDC), NHANES (national estimates) and BRFSS (state estimates) have estimated that depression in adults is 6.8% of the U.S. population. The prevalence of
mental disorders is highest in individuals residing in nursing homes. Older individuals with dementia often have complicated illnesses and are at higher risk of mental illness associated with treatment resistance and potential medication side effects. Alternatively, when a thorough patient history and physical assessment are performed, underlying medical conditions, which can cloud the clinical picture, can be included in the diagnostic criteria to help guide the treatment plan.

Multiple factors influence children who develop behavioral disorders and mental illness. These factors can be biological, i.e., malnutrition, brain damage, physical illness and inherited traits. Oftentimes, stressors in the child’s environment or at home can trigger the development of a mental illness. Children who suffer from abuse and neglect, or carry a diagnosis of post-traumatic stress disorder, often suffer from panic attacks, anxiety, depression and suffer tremendous somatic complaints, such as shortness of breath or digestion issues.

Individuals of all age groups with a history of substance abuse and depression often pose challenges to the health team. Substance abuse and mental illness involves a multidisciplinary team approach of therapists and psychiatric mental health professionals to help develop a multimodal treatment approach. Additionally, individual genetic variations can impact whether a patient is a fast or slow metabolizer of a drug category, and how effective a type of drug will be to treat a mental health condition. The DSM-5 manual has made diagnoses reliable and consistent, but its overall validity has led to controversy as
well as criticism. There have been five revisions since it was first published with some new criteria and guidelines for mental health disorders while other criteria have been revised or removed. Evidence of interventions that improve outcomes for individuals diagnosed with mental illness requires ongoing professional learning and participation in public resources.

**Psychopharmacology And Special Populations**

**Geriatric Patient**

An estimated 5.6 million to 8 million Americans over the age of 65 years have mental health or substance-use disorders. According to the Institute of Medicine (IOM), these numbers will continue to climb up to 14.4 million by 2030. To add to this dilemma is the decreasing number of geriatric psychiatrists working in this field. The American Geriatrics Society estimates that there are fewer than 1800 geriatric psychiatrists in the U.S., today and that by 2030 there will only be about 1650 left. These numbers mean that there will be less than 1 per 6000 older adults with mental health and substance-use disorders.

The IOM’s 2012 workforce report on this topic, subtitled *In Whose Hands?* confirms this shortage and states that the country simply cannot train a sufficient number of doctors specializing in geriatric medicine to meet the vacant positions. This report is backed by the fact that more than half the vacant fellowship positions in geriatric medicine or psychiatry remain unoccupied each year. Moreover, a separate survey by the American Psychological Association (APA)
found that only 4.2% of practicing psychologists have specialized training in treating older adults.\textsuperscript{112}

The shortcomings of the U.S., healthcare system put the mentally ill geriatric population at greater risk of disabilities, poorer treatment outcomes and higher rates of hospitalization and emergency visits than those with physical illnesses alone.\textsuperscript{113} The following are the four main challenges in the provision of appropriate mental health care to geriatric patients:

- Physiological changes to the body systems
- Presentation of psychiatric symptoms mimic many conditions that are part of the normal aging process (anxiety and, poor sleep, memory and concentration)
- As mentioned above, there’s limited number of specialized psychiatrists trained to handle geriatric patients
- Increased likelihood of existing comorbidities

As discussed in previous sections, there are physiologic changes to consider in the psychopharmacologic treatment of older adults. The pharmacokinetics of drugs including their renal and hepatic clearance, and protein binding are markedly different and at times unpredictable, adversely affecting its pharmacodynamics and therapeutic outcomes.\textsuperscript{114}

The kidneys are major routes of excretion for many non-lipid soluble drugs. One notable example is lithium, a popular mood stabilizer. It is almost completely renally excreted, a process strongly influenced by
sodium and water excretion. One important clinical implication of this type of elimination is its low therapeutic index, a marker for increased likelihood of toxicity. Renal dysfunction, use of NSAIDs, antidepressants and diuretics, are conditions that impair lithium excretion and increase the risk of toxicity. Older adults especially are at risk because many of them take maintenance medications concomitantly for their arthritis (NSAIDs), hypertension and heart conditions (diuretics).

**Physiologic changes to the kidneys in older adults**

<table>
<thead>
<tr>
<th>Renal changes</th>
<th>Pharmacokinetic implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in kidney size</td>
<td>Reduced elimination</td>
</tr>
<tr>
<td>Decrease in renal blood flow</td>
<td>Increased accumulation and toxicity</td>
</tr>
<tr>
<td>Decrease in functioning neurons</td>
<td>Increased / decreased absorption of other drugs *</td>
</tr>
<tr>
<td>Decreased renal tubular secretion</td>
<td></td>
</tr>
<tr>
<td>Decreased glomerular filtration rate</td>
<td></td>
</tr>
</tbody>
</table>

*Polypharmacy considerations: 25% of patients over the age of 70 take more than 5 drugs everyday.

Additionally, older patients with preexisting neurologic impairments such as dementia and Parkinson’s disease, and endocrine disorders such as hypothyroidism and testicular failure, are at a greater risk for acute lithium neurotoxicity. There have been several reports that
indicate persistent cerebellar and basal ganglia dysfunction after treatment with these special population groups.\textsuperscript{117}

These dysfunctions can manifest as neuromuscular excitability, irregular coarse tremors, fascicular twitching, rigid motor agitation, muscle weakness, ataxia, sluggishness, delirium, nausea, vomiting, and diarrhea.\textsuperscript{118} It is worth noting that some of these signs and symptoms occur in patients with Parkinson’s disease, which makes them easy to miss to the untrained eye. Therefore, careful plasma lithium level monitoring is necessary.\textsuperscript{117}

The liver is the most common site of drug metabolism (biotransformation). Thus, the aging liver adversely affects drugs that undergo extensive hepatic first pass effect. Many psychoactive drugs used in the treatment of various mental disorders are lipid soluble and thus, not freely excreted in urine. Instead, they are eliminated through the liver where they are excreted in the bile and transported to the intestine.\textsuperscript{116}

The SSRI, fluoxetine, is one such example. In the liver, it undergoes demethylation to form norfluoxetine, an active metabolite.\textsuperscript{115,116} A cirrhotic liver will delay its hepatic clearance, increasing the likelihood of toxicity.

### Physiologic changes to the liver in older adults

<table>
<thead>
<tr>
<th>Hepatic changes</th>
<th>Pharmacokinetic implications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease in liver blood flow</td>
<td>Reduced metabolic clearance</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Decrease in liver size</td>
<td>Increased accumulation and toxicity</td>
</tr>
<tr>
<td>Decrease in liver mass</td>
<td></td>
</tr>
</tbody>
</table>

Another pharmacokinetic consideration to take into account is the distribution of drugs via protein (albumin) binding. Like renal clearance, the amount of protein in the body is governed by a number of conditions. Generally, older adults are more likely to suffer from hypoalbuminemia due to any of the two main conditions:

1. Malnutrition:
   - Lack of protein in the diet

2. Increased excretion of albumin resulting from:
   - Renal (kidney) dysfunction
   - Liver disease such as cirrhosis or hepatitis
   - Heart disease: leads to congestive heart failure, or pericarditis
   - Gastrointestinal disorders: reduces protein absorption
   - Cancer such as sarcoma or amyloidosis
   - Medication side effects
   - Infections such as tuberculosis
The body can only use non-protein bound drugs. Therefore, clinicians will do well to consider the comorbidities of geriatric patients prior to prescribing psychoactive drugs.

Decreases in protein-binding results in an increase in circulating free drug fractional amounts; and, hence, its effects. An example of a highly protein bound (>90%) drug is phenytoin. Its use in the setting of hypoalbuminemia in an elderly patient requires dosage adjustment and cautious titration after administration of the initial dose. Usually, a total daily dose of 3 mg/kg is appropriate in this case. Due to the poor correlation of the total drug level with clinical response and risk of adverse effects, an appropriate therapeutic range may be 5–15 mcg/mL rather than the 10–20 mcg/mL recommended for young adults. Also, if phenytoin is administered concurrently with diazepam, the latter displaces the former from plasma proteins, resulting in an increased plasma concentration of free phenytoin and an increased likelihood of unwanted effects.

Other considerations to keep in mind when dealing with mentally predisposed geriatric patients are adherence to therapy, medication errors, and safety and efficacy problems. Clinicians and pharmacists need to make it easy for the patient. They need to go the extra mile with this population group using certain measures such as:

- Ease of administration
- Possible dose reduction
• Avoidance or reduce medications that produce visual and motor impairment

**Pregnancy**

There are two types of women that fall into this population group; women who were already on psychoactive drugs when they fell pregnant and the ones who started the medication during pregnancy. A good reference is the Harvard women’s health website at http://www.womensmentalhealth.org/.

Contrary to popular belief, the hormonal changes do not naturally protect women from mental disturbances during pregnancy. Studies in the last few years have dispelled this myth and confirm that up to 20% of women suffer from stress, mood and anxiety during gestational and postpartum periods. These difficult diagnoses pose tricky challenges to the mother, baby and the clinician during the entire delicate transition. The management approach requires a balance between keeping the disorder under control and maintaining the health of the mother and the growing fetus.

For women already on psychoactive medications, there are general guidelines that are usually followed, which are listed below.

• Cessation of pharmacotherapy:

  This is a common approach given that it minimizes fetal exposure to psychoactive drugs during its most vulnerable
period of development (1st trimester). But it is not always the best approach because psychiatric instability is not a benign condition; it poses a risk to the fetus too. There have been reports of higher rates and risk of relapse in women with bipolar disorder who discontinued their mood stabilizers than those who maintained treatment (37.0%). Optimally, the clinician should present the risks and benefits of this approach to the patient so the latter can share the responsibility of making well-informed decisions regarding the treatment.120

• If the risks posed by the first option outweigh the benefits, drugs that have long history of relative safe use in pregnant women should be used. The FDA Pregnancy Category Designations introduced in 1975 can be used in this instance though it is important to be aware of its limitations. For one, the category designations often lacked sufficient human data. Second, there is no clear differentiation between categories C and D.120

A systematic review on the use of first and second generation antipsychotics during early and late pregnancy found that the latter was more likely associated with gestational metabolic complications and higher than normal birth weight of babies compared with the former. Another study reports that the drug-induced weight gain and visceral-fat accumulation of second generation antipsychotics in non-pregnant women also applies to their pregnant counterparts, exposing them to higher risks of gestational diabetes, hypertension and pre-eclampsia.122,123
The teratogenic risk of amisulpride, ziprasidone, and sertindole is considered unknown due to insufficient human data. Clozapine, another second generation antipsychotic, is known to cause agranulocytosis in both pregnant and non-pregnant populations. The risk of infection to the baby and mother is therefore increased, meritng careful monitoring of WBC counts for the next 6 months after initiation of therapy. In contrast, the first generation antipsychotics, haloperidol and chlorpromazine, are associated with fetal malformations (mostly limb defects) and spontaneous abortions, respectively.\textsuperscript{121}

Lithium is generally avoided in pregnancy. It is associated with high risk (13-fold) of heart malformation when used during the 1\textsuperscript{st} trimester of pregnancy. When used in the 3\textsuperscript{rd} trimester of pregnancy, it may cause lethargy and listlessness in babies accompanied by irregular suck and startle responses. Additionally, it may cause congenital hyperthyroidism and poor oxygenation resulting in the appearance of “blue babies”. When used in the second trimester, lithium is safe. It is contraindicated in breastfeeding women since it enters the breast milk and causes unwanted side effects on babies.\textsuperscript{124}

The guideline, \textit{Use of Psychiatric Medications During Pregnancy and Lactation}, published by the American College of Obstetricians and Gynecologists (ACOG) in 2008, issues the following recommendations and conclusions based on good and consistent scientific evidence (Level A):\textsuperscript{125}
• Lithium exposure in pregnancy may be associated with a small increase in congenital cardiac malformations, with a risk ratio of 1.2 to 7.7.

• Valproate exposure in pregnancy is associated with an increased risk of fetal anomalies, including neural tube defects, fetal valproate syndrome, and long term adverse neurocognitive effects. It should be avoided in pregnancy, if possible, especially during the first trimester.

• Carbamazepine exposure in pregnancy is associated with fetal carbamazepine syndrome. It should be avoided in pregnancy, if possible, especially during the first trimester.

• Maternal benzodiazepine use shortly before delivery is associated with floppy infant syndrome.

On the other hand, there are 5-30% of women who reportedly suffer from depression at the onset and during perinatal period. Untreated depression leads to substance and alcohol abuse, and poor pregnancy outcomes such as inadequate prenatal care, low birth weight and, retarded fetal growth. Depression is also associated with premature birth. These data highlights the need for careful analysis and reevaluation of the risk-benefit ratio of initiating and maintaining use of psychoactive drugs during pregnancy.
A higher risk for persistent pulmonary hypertension (PPHn) in the newborn has been linked to the use of SSRIs like fluoxetine during the last trimester of pregnancy. Persistent pulmonary hypertension of the newborn is a cardiovascular condition usually seen within 12 hours of delivery. When this happens, the infant’s pulmonary vascular resistance does not decrease as normally expected and blood is shunted away from the lungs. This diversion results in an insufficiently oxygenated blood that causes respiratory distress in the infant, which may require assisted ventilation. PPHM occurs in approximately 2 in 1000 births.\textsuperscript{127}

Anxiety disorders can also be triggered or worsened by pregnancy. Panic disorder, obsessive-compulsive disorder, and generalized anxiety disorder appear to be as common as depression. Fluoxetine is the most prescribed and thoroughly researched antidepressant in the United States. There is a large pool of data collected from over 2500 cases that indicates no increase in risk of major congenital malformation in infants exposed to this drug. Studies of other SSRI antidepressants show the same results, though these have not been backed by such large data. Older antidepressants such as MAOIs are generally not recommended during pregnancy because of their extensive dietary restriction requirements that can compromise the mother’s nutritional status, induce hypertension, and adversely react with terbutaline, a drug used to suppress premature labor.\textsuperscript{126}

**Pediatric Patient**
Children are not untouched by mental illness. According to cumulative research data, 1 in 5 children and adolescents in the United States suffer from a behavioral or emotional disorder. ADHD, pediatric conduct disorder, depression, bipolar disorder, oppositional defiant disorder, mood disorders, obsessive-compulsive disorders, mixed manias, social phobia, anxiety, sleep disorders, borderline disorders, assorted “spectrum” disorders, irritability, aggression, pervasive development disorders, personality disorders, and there are others discussed in the pediatric psychiatry literature. The field of pediatric psychopharmacology is a rapidly growing area of care, and an indispensable part of pediatric psychiatric treatment.\(^{128}\)

Perhaps the greatest concern in the psychopharmacologic treatment of pediatric patients lies in the fact that there’s a huge potential for over diagnosis and overtreatment without adequate clinical data supporting the efficacy and safety of psychotropic agents in this particular population.\(^{129}\)

Below are the three main challenges in the provision of appropriate psychopharmacologic treatment to pediatric patients:\(^{130}\)

1. Inadequate medication response:
The lack of efficacy is one of the two most commonly cited reasons for nonadherence to pharmacotherapy.

2. Significant adverse drug reactions:
The second most commonly cited reason for noncompliance is the crippling side effects, disabling the child to function normally at school and among his peers. This is an important area of management wherein clinicians need to tread carefully because children may very well develop a negative view towards medication that may have proved helpful. Since many adult psychiatric disorders have an onset at an early age, a past error in psychopharmacologic treatment choices can spur a lifetime of consequences for the patient, the family and the present clinician.

3. Lack of specialized child and adolescent psychiatrists:\textsuperscript{131} In the face of ongoing shortages of specialized child and adolescent psychiatrists, the responsibility of providing psychopharmacologic treatment often falls on adult psychiatrists, family physicians, and pediatricians.

\textit{Atypical antipsychotics}

In 2007, risperidone received FDA approval for the treatment of schizophrenia in adolescents age 13 to 17 and single therapy in short-term treatment of manic or mixed episodes of bipolar I disorder in children and adolescents age 10 to 17. A study made recently suggests that this drug elevates prolactin levels in children age 7-17 treated with it. The implication of this finding is especially important for those children entering puberty as they may develop more than normal increase in breast size and galactorrhea.\textsuperscript{132}
Antidepressants

There is a rise in the research, current expert guidelines and consensus statements that back the efficacy of SSRIs and the tricyclic antidepressant (TCA), clomipramine, in the treatment of obsessive compulsive disorder (OCD) in psychiatric pediatric patients.

The use of sertraline, paroxetine and fluoxetine in pediatric patients show that they exhibit similar pharmacokinetic profiles as in adults. Although the half life of these drugs do tend to be shorter because of the more rapid metabolism and hepatic blood flow in children, the dosing schedules remain the same, i.e., fluoxetine and sertraline are given once a day and fluvoxamine twice a day when doses are above 100/mg day total. The slight difference in pharmacokinetic data does not have clinical significance in the overall pharmacodynamics of the drug.\textsuperscript{133}

A study found that a quarter of pediatric subjects treated with SSRIs and clomipramine exhibited agitation that could potentially cause mania and hypomania. The paradoxical effects warrant further investigation and careful monitoring since these drugs may very well induce the onset of another potentially serious mental illness, bipolar disorder.\textsuperscript{133}

Paroxetine has a short half-life and may cause withdrawal symptoms after as few as 6-8 weeks of treatment. Therefore, the FDA has recommended clinicians who prescribe it to closely monitor patients,
with at least a weekly face to face follow up during the first 4 weeks of therapy and specific visit intervals thereafter.\textsuperscript{134}

It is the clinician’s responsibility to inform parents and patients about adverse effects, the dose, the timing of therapeutic effect, and the danger of overdose of the administered antidepressants, especially TCAs, prior to initiation of psychopharmacologic treatment. With TCAs, clinicians need to determine the exact dosage for patients because these drugs are known to cause fatal overdose at therapeutic dosages. On the other hand, parents need to take an active role in the drugs’ storage and administration, especially parents of younger children or children with suicidal tendencies.\textsuperscript{135}

The TCAs have been surpassed by the SSRIs when it comes to safety. As such, they are no longer the first line of drug for pediatric depression. Moreover, they require a baseline electrocardiogram (ECG), resting blood pressure, pulse, and weight monitoring prior to initiation of treatment. SSRIs have no such laboratory test prerequisites in healthy individuals.\textsuperscript{135} The risk of QT-prolongation is rare but nevertheless present in patients with risk factors for arrhythmias. These patients are best managed by another antidepressant.

\textit{Stimulants}

More than 80\% of stimulant medication use in the world occurs in the U.S. A study conducted in 2008 attributes this huge number to cultural
influence on the identification and management of psychiatric disorders than any other field in medicine.\textsuperscript{136}

At the heart of ADHD management is psychopharmacology, which consists of stimulants, norepinephrine reuptake inhibitors, alpha-2 agonists and antidepressants. Stimulants like amphetamine and methylphenidate rank the best evidenced-based medications for improving attention dysfunction in children and adolescents.

The past 50 years have seen the development of various methylphenidate (MPH) formulations, ranging from sustained tablet (long acting) release to patches. A systematic review and meta-analysis conducted by Punja \textit{et al.}, found that long-acting MPH formulation had little effect on the severity of inattention and overactivity, and hyperactivity and impulsivity, according to parent reports; whereas, the short-acting formulation was preferred according to teacher reports for hyperactivity.\textsuperscript{137} Despite the long history of effectiveness, MPH type of medications comes with side effects that can discourage patients from following through with recommended drug regimen.

\textbf{Stimulant medications and their notable side effects.}\textsuperscript{138}

<table>
<thead>
<tr>
<th>Medication</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate (MPH)</td>
<td>Addiction, insomnia, decreased appetite, agitation, headache, heart palpitations,</td>
</tr>
<tr>
<td>Drug</td>
<td>Side Effect</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Magnesium pemoline</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>Depression, dysuria, bladder pain</td>
</tr>
</tbody>
</table>

A community based study conducted by the Department of Pediatrics, School of Medicine at Yale found that MPH have growth suppression factors, with children taking the drug at doses 10-80 mg/day exhibiting significant height differences when compared to untreated biological siblings at the same age.\(^{139}\)

Another ADHD medication, atomoxetine, also carries an FDA warning. Studies show that children and adolescents with ADHD who take atomoxetine are more likely to harbor suicidal thoughts than who do not take it. Magnesium pemoline is associated with hepatic failure and comes with the FDA Black Box Warning. It is not considered the first line drug for ADHD and when a clinician does plan to start a patient on it, a written informed consent should be obtained prior to initiation of therapy.\(^{140}\)

**Psychopharmacology: Limitations Of Treatment**

Psychopharmacology, with its advances in theories and practice, still comes up short to actually addressing the root cause of mental illness. The SSRIs is a good example. Even after decades of research, the serotonin and norepinephrine hypothesis as the cause of depression is
still largely controversial. This will be discussed in depth in the section, ethical dilemma, but suffice to state for now that the financial stakes are high on these hypotheses.

**Cure Versus Control**

In the context of mental illness, psychopharmacologic interventions are only modest palliative care measures. In other words, it is all about control of symptoms to improve the quality of life. Psychiatry, the mother tree of psychopharmacology, is largely governed by the mission to protect public health, to the extent of creating a forceful barrier against those who pose a danger to it. The asylums and rehabilitation facilities are evidence of this endeavor. On the other hand, because public safety is the driving directive of this field, the patients that are governed by it sometimes take secondary importance.

Psychoactive drugs alter antisocial behavioral tendencies, allowing mentally ill individuals to function in society. But this seemingly positive benefit comes with a price; the altered behavior makes the families and public feel safer while the patient may not necessarily feel better. For instance, schizophrenia is managed with neuroleptic medications that target its destructive symptoms such as hallucinations, delusions and thought disorders at doses that cause significant debilitating side effects such as sedation, lethargy, emotional blunting, impotence, Parkinsonism, and agitation. As a
result, many patients not only skip these drugs but the entire psychiatric treatment plan altogether.

Indeed, a lot of patients require legal-coercion in order to take their prescribed drugs and they are not entirely to blame. The bottom line is optimal public safety does not always equate to patient’s well being, nor are they always compatible. Either one has to give in to the other.

Since the patients are the ultimate expert in their own subjective psychiatric health, it makes sense that they take a more active role in their psychopharmacologic therapy. This type of approach is not new; the patient controlled analgesia (PCA) is proof of that. A lot of clinicians are wary of this type of approach, and their fears are warranted. Psychoactive drugs are known to cause psychological and physical dependence, which are potential risks that sometimes outweigh the benefits, resulting in under-dosing and needless suffering. The idea of enhancing psychological well being to augment suffering in the name of palliative psychopharmacological treatment is still a highly debated topic to this day.

Not all psychiatric patients respond to psychoactive drugs the same way. This is why there is a need for an established plan that includes regular and frequent consultations throughout the course of treatment (usually lifetime). The pharmacotherapy tenet, “start low, go slow,” needs to be followed especially for these medications. But more than this, the challenge to the clinicians lies in the fact that it takes a considerable amount of time to find the right drug for each patient and
even longer to find the minimum effective dose that balances the risks and benefits.\(^{141}\)

**Toxicity Levels**

According to a report published by the National Center for Health Statistics (NCHS) in 2011, the number of adolescents and adults that use antidepressants in the U.S. climbed to a staggering 400% in the last three decades. What’s more, more than 60% of them have taken it for 2 years or longer, with 14% having taken the medication for 10 years or more. But perhaps the most chilling part of this report is that less than one-third of them and less than one-half of those taking multiple antidepressants have seen a psychiatrist in the past year.\(^{142}\)

Perhaps the class of antidepressants that concerns clinicians the most is SSRIs because although they have lesser incidence of toxicity, they are the most widely prescribed in the U.S. Serotonin toxicity, a common adverse effect of this class, encompasses a wide range of signs and symptoms affecting the neuromuscular, autonomic, cardiovascular, nervous and gastrointestinal systems, where the highest concentrations of serotonin receptors are found. In its most severe form, it is known as serotonin syndrome and its most frequent cause is the co-administration of SSRIs with MAOIs.\(^{143,146}\)

The drug interaction can occur after as little as 2 doses have been administered. It may then trigger a series of acute symptoms such as agitation, gastrointestinal disturbances, and tremor that worsen
rapidly. Patients who experience milder forms may not recognize these as manifestations of toxicity and thus, not seek treatment. Aside from drug interactions, serotonin syndrome can also occur due to excessive dosage for suicide purposes, although this rarely happens.¹⁴⁶

The mechanisms and their precipitating factors that cause an abnormal increase in serotonin levels are:¹⁴⁴

- Direct stimulation of 5HT-receptor: buspirone, triptans, lithium, carbamazepine, peyote

- Direct release of 5HT from presynaptic storage: amphetamines, MDMA, cocaine, reserpine, levodopa, monoamine oxidase inhibitors, opioids such as codeine and pentazocine

- Greater availability of 5HT precursors - L-tryptophan from tyramine containing foods

- Reduced reuptake of 5HT: SSRIs, trazodone, nefazodone, venlafaxine, tricyclic antidepressants, dextromethorphan, meperidine, St. John's wort, amphetamines, carbamazepine, methadone, linezolid

- Reduced metabolism of 5HT: Monoamine oxidase inhibitors, St. John's wort

- Presence of comorbid conditions such as serotonin-secreting tumors
Citalopram has the highest fatality rate among all SSRIs.\textsuperscript{145} It exerts a dose-dependent QT prolongation resulting in the revision of the drug’s prescribing information to include it in 2011. It is contraindicated in individuals with congenital long QT syndrome, with the recommended daily dose not exceeding 40 mg.\textsuperscript{144}

Tricyclic antidepressants (TCAs), though not the first line drugs for depression, are still used in some patients. The pharmacologic mechanisms that cause TCAs toxicity are:\textsuperscript{147}

- Norepinephrine and serotonin reuptake inhibition at nerve terminals
- Anticholinergic activity
- Inhibition of alpha-adrenergic receptors
- Blockade of cardiac sodium channels in the myocardium

Among the TCAs, amitriptyline toxicity has the highest number of fatalities.\textsuperscript{148} Patients exhibit major cardiac toxicity symptoms when drug concentration and that of its metabolite, nortriptyline, exceed 300 ng/mL. This is most apparent with QRS widening that leads to ventricular tachycardia and asystole. Because their relative plasma levels are highly variable, toxicity can also occur at lower concentrations.\textsuperscript{149}

Monoamine oxidase inhibitors (MAOIs) are older antidepressants with well-documented dietary-induced toxicity. They are last resort drugs in the treatment of resistant depression, usually reserved for cases
where patients do not respond to SSRIs. Additionally, MAOIs have high oral absorption with peak plasma concentrations occurring within 2-3 hours of ingestion.

Monoamine oxidase inhibitors inhibit the degradation of catecholamines norepinephrine, dopamine, and serotonin, resulting in symptoms that reflect excessive excitable neurotransmitters such as hypertension, tachycardia, tremors, seizures and hyperthermia. MAOI toxicity is the result of three main events:150

- Intentional poisoning:
  Uncommon but happens nonetheless. Symptoms appear late, up to 32 hours after ingestion.

- Drug-food interaction:
  This is the famous “tyramine reaction” which results in fatal hypertensive emergencies. It has a rapid onset, usually within 15-90 minutes after ingestion.

- Drug-drug interaction:
  It occurs when co-administered with serotonin reuptake inhibitors and several analgesics. Essentially, any drug that releases catecholamines can trigger hypertensive crisis in individuals also using MAOIs.

### Significant interactions with MAOIs

<table>
<thead>
<tr>
<th>Drug-food interactions</th>
<th>Drug-drug interactions</th>
</tr>
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</table>


Depressants are favorite drugs of choice to overdose on, particularly, barbiturates. However, newer classes such as benzodiazepines, which also happen to be the most commonly prescribed depressant in the U.S., are now the first line drugs for anxiety. These drugs have better safety profiles owing to their relatively high therapeutic index, but when taken concurrently with alcohol can lead to severe central nervous system (CNS) depression.

Symptoms of depressant overdose include sluggishness, drowsiness, reduced mental faculties, and in severe cases, respiratory depression and coma.

Reports in the recent years pointed to the possible increased likelihood of propylene glycol toxicity in neurocritical patients treated with high dose barbiturates. Propylene glycol is a pharmaceutical vehicle in the IV formulations of phenobarbital and pentobarbital. Its accumulation in
the body to toxic levels may trigger the very seizures that the barbiturates intended to treat.\textsuperscript{151}

Barbiturates, in certain countries where euthanasia is legal, are used in combination with muscle relaxants for physician-assisted suicide (PAS). Depressants should not be taken when operating machineries or driving.\textsuperscript{152}

Lithium poisoning is another concern with psychopharmacologic treatment. Due to its therapeutic dose often overlapping with its toxic dose, the drug is known to cause frequent toxicity among its users, especially those with renal insufficiency and on diuretics. Lithium clearance is predominantly based on the glomerular filtration rate (GFR). Diuretics increase the reabsorption of lithium at the proximal tubule, the site where carbonic anhydrase inhibitors (\textit{i.e.}, acetazolamide) exhibit their effect.\textsuperscript{153}

\textbf{Patient Consent}

The patient’s mental capacity is largely influenced by the severity of diagnosed disorder and plays a crucial role in determining the patient’s ability to give an autonomous and informed consent for psychiatric therapy, including the initiation of psychopharmacologic medications.

Essentially, informed consent is both a legal and medical standard that is made up of three important components:\textsuperscript{154}

1. Ability to process information logically
2. Capacity to make decisions based on a set of given information
3. Voluntary action in the absence of coercive factors

Decisional capacity in psychiatric patients has been studied extensively in the last decade using the MacArthur Competence Assessment Tool for Treatment (MacCAT-T). These studies found that decisional incapacity is common only in 20–30% of chronic psychiatric patients with acute and cognitive disorders, although this differs from state to state. Additionally, it has also identified several strong predictors.

**Predictors for decisional incapacity**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive symptoms</td>
<td>Hallucinations</td>
</tr>
<tr>
<td></td>
<td>Delusions</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>Social withdrawal</td>
</tr>
<tr>
<td></td>
<td>Apathy</td>
</tr>
<tr>
<td>Severity of symptoms</td>
<td>The more severe the depression, the greater the likelihood of incapacity</td>
</tr>
<tr>
<td>Involuntary admission</td>
<td></td>
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<tr>
<td>Treatment refusal</td>
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</table>

Incapacity was noted mostly in patients with organic mental disorders such as dementia, psychosis and delirium. The remainder majority is
actually capable of making treatment decisions. These include patients with personality and adjustment disorders.

Despite these predictors, the decision-making capacity of patients is not dependent on diagnostic categories of mental disorders; rather, it is the functional abilities such as understanding and practical reasoning that are the crucial elements in the assessment of decisional capacity. Informed consent, based on appreciation, understanding and reasoning of the treatment proposed, varies across different diagnostic categories.\(^{155}\)

**Schizophrenia**

Studies show that schizophrenic patients’ appreciation, understanding and reasoning adversely affect MacCAT-T scores. In particular, they show, if at all, limited insight into their illness.

**Mood disorders**

Mania is a significant risk factor for incapacity, while mild to moderate depression has little effect on the decisional capacity of patients.

**Mental retardation**

Adults with mild mental retardation experience significant loss of appreciation and reasoning abilities, deeming them most of the time incapable of making informed decisions regarding their treatment.
**Substance use disorder**

Patients with this disorder are judged to have the full mental capacity to make autonomous treatment decisions, unless they also suffer from dementia or other issues due to substance use.

**Anorexia nervosa**

Since patients with this disorder experience distorted body image or denial of the consequences of abnormally low body weight, they generally show a loss of appreciation to the treatment proposed.

Primarily the clinician, prior to the start of treatment, psychopharmacological or otherwise, obtains informed consent. Obtaining informed consent follows a two-step process:\(^{55}\)

1. Ensure that the patient has been given all information relevant to the treatment proposed – the risk, benefits, and prognosis both with and without treatment, alternative treatments and their risk and benefits.

2. Ensure a voluntary choice free from coercion.

**Legal Considerations**
The clinician must be aware of the state laws governing the involuntary treatment of psychiatric patients, especially its limitations. As discussed in the previous sections, public safety is a powerful persuasion in eliciting legal action when compared to the wellbeing or even preservation of individual rights of the mentally ill individuals. For example, in Rhode Island, the state can impose involuntary treatment of the mentally ill based on two legal premises:

1. *Parens patriae*, meaning “parent of the country,” gives the state sovereign authority to intervene and act on behalf of the mentally ill when they become mentally or physically incapable of caring for themselves.

2. Police power gives the state the authority to intervene on behalf of the public when its safety is threatened. Interventional actions include isolation and confinement of dangerous individuals. It applies to criminals, persons with contagious diseases and the mentally ill.

The question now becomes, can states make involuntarily hospitalized patients take their psychotropic medications? The answer is both *yes and no*. The majority of U.S. states respect personal decisions of patients, whether to initiate a treatment or forego it. This is true, even for many mentally ill individuals. However, when found legally incompetent by law the refusal of medications may be overridden by a court order.
Many states appoint legal guardians to consent for these patients. A few states recognize the right of voluntary patients to refuse psychotropic medications. The reasons for refusal may be due to any of the following reasons:156

1. Delusional thinking (less likely)
2. Previous intolerable side effect to the medication in question (more likely)

The second reason underscores the need for clinicians to explain the recommended psychopharmacologic treatments, including the benefits, adverse effects, and risks to their patients. The clinicians also need to explore fully the reasons behind the patient’s refusal. They may also opt to switch the patient to an alternate medication of the same class or another medication with more favorable side effects.156

A second and third question follows the first one: Can involuntarily hospitalized patients be given emergency medications? How do these differ from involuntary medications? Emergency medications are ordered when imminent danger to self or others is present. An example includes the use of short acting benzodiazepines and neuroleptics in restrained, dehydrated and delirious manic patient who continues to physically resist and bang his or her head against the bed frame. These emergency medications must be ordered acutely and their clinical need reassessed frequently (every few hours). They are only used when needed and no longer than a few days at the most.156
Involuntary medications are those that need to be regularly taken by patients as per court’s order. As such, they are time-limited and their extension requires a clinical reevaluation of the patient, overall response to therapy and present endangerment to public safety. The criteria for involuntary medications vary across states, but commonly include the following:\textsuperscript{156}

1. Incompetence to participate in decisions about treatment
2. Poor prognosis leading to dangerous behavior to self or others without the medications
3. History of noncompliance

Once these criteria are met, the clinician can then apply for the administration of involuntary medications with an accompanying affidavit supporting them. Another ethical issue that emerged during the 1980s is the covert administration of psychotropic drugs during emergencies. Today, 25 states have included psychiatric advance directives (PADs) in the state legislatures to protect the autonomy of mentally ill patients during their periods of mental incapacity. PADs enable these patients to uphold their right to exercise choice and control over their own treatment during episodes when they are mentally incapable of making the decision.

**Safety**

Most psychoactive medications are either illicit or controlled drugs because of their propensity to cause dependence among its users.
Drug dependence is implicated in four medical events, which are outlined below.

1. Withdrawal and physical dependence:

Physical dependence is characterized by the normal physiological adaptation of the body to the presence of a chronically administered drug. A drug dependent person needs to keep using the drug in order to prevent a withdrawal syndrome. Withdrawal syndrome results from abrupt discontinuation or dosage reduction, which has consequences ranging from mild to severely unpleasant and life-threatening complications.

2. Tolerance:

A physiological state marked by a substantial decrease in drug sensitivity due to its chronic administration.

3. Psychological dependence:

Psychological dependence refers to the intense and compulsive craving for the chronically administered drug. It is created when the “high” fades and the user administers another dose for an additional “fix”. While physical dependence will go away in days or weeks after drug use, psychological dependence can continue for years. This is the hallmark of “addiction”.
4. Overdose:

Overdose is the administration of an excessively large and lethal dose of a drug (more than the therapeutic dose), leading to possible life-threatening complications.

Statistics On Teen Substance Use

The 2008 Monitoring The Future (MTF) survey indicates use of illicit (street) drugs among teens has decreased in the U.S. However, more teens misuse prescription and OTC medications than any other illicit substance, except marijuana. A survey of 8th, 10th and 12th graders in public and private schools found in 2011 found that 2.1% of these teens reported that they had abused Ritalin and 4.1% reported that they had abused Adderall in the past year. In fact, the psychotropic medications, Adderall, Xanax and Valium are among the top 5 prescription drugs abused by teens, behind only the opioids, OxyContin and Vicodin.\(^{157}\)

According to the CDC, there was a 91% in drug poisoning deaths among teens between the ages of 15-19 from 2000 to 2009 due to prescription drug overdose.

Commonly prescribed and abused psychoactive drugs.

<table>
<thead>
<tr>
<th>Commonly abused psychoactive drugs</th>
<th>Symptoms of overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulants (amphetamine,</td>
<td>Agitation, increased body</td>
</tr>
<tr>
<td></td>
<td>temperature,</td>
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<td></td>
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</tr>
<tr>
<td>phentermine, benzphetamine, methylphenidate</td>
<td>seizures, hallucinations, death</td>
</tr>
<tr>
<td>Depressants / sleeping pills (barbiturates, benzodiazepines)</td>
<td>Respiratory arrest, clammy skin, dilated pupils, rapid pulse rate, coma, death</td>
</tr>
<tr>
<td>OTC dextromethorphan from cough syrup</td>
<td>Paralysis, loss of memory</td>
</tr>
<tr>
<td>Narcotics (codeine, methadone)</td>
<td>Respiratory depression, pinpoint pupils</td>
</tr>
</tbody>
</table>

**Causes of drug dependence**

The exact causes of illicit drug use is unclear, however, the genetic make up and innate psychoactive properties of the drug combined with peer pressure, emotional upheavals, anxiety, depression, and environmental stressors are all thought to play a role. Among adolescents, peer pressure is a large contributing factor to drug abuse with 50 percent of those who become addicted eventually suffering from mental disorders such as depression, attention deficit disorder (ADD), and post-traumatic stress disorder (PTSD).

Family behavior and habits also play a role in adolescent drug abuse. Children with parents who are drug abusers themselves are more likely to experiment with drugs and develop an addiction when they become adults.
Generally, there are five factors that are attributed to the development of drug dependence:  

- Existing mental illness such as depression, bipolar disorder, anxiety disorders, and schizophrenia  
- Accessibility to illicit drugs  
- Low self-confidence and poor family and social relationships  
- Stressful lifestyle  
- Cultural acceptance of drug use

Curiosity, an inherent human trait, is known to be a precipitating factor for both discoveries and disasters. Drug dependence proceeds through several stages from experimental use to downright addiction. Age is a determining factor in the speed at which a person moves through the stages. Generally, the younger the person is, the faster he is likely to move quickly through the stages.

The first table below lists the stages leading to drug dependence; and, the second table, the common psychoactive drugs and corresponding street names.

<table>
<thead>
<tr>
<th>Stages leading to drug dependence</th>
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<tbody>
<tr>
<td>Stages</td>
</tr>
</tbody>
</table>

### Experimental use
- Introduction by peers for recreational use

### Regular use
- Develop physical dependence, marked tolerance to drug; seek higher and frequent doses

### Daily preoccupation
- Deal drugs to support habit, social withdrawal, use of other drugs

### Addiction
- Psychological dependence, loss of control over drug use, legal and financial problems, denial of existing drug problem

### Street names of psychoactive drugs

<table>
<thead>
<tr>
<th>Psychoactive drugs</th>
<th>Street names</th>
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<tbody>
<tr>
<td>Amobarbital</td>
<td>Yellow jackets</td>
</tr>
<tr>
<td>Butalbital</td>
<td>Blue devils</td>
</tr>
<tr>
<td>Secobarbital</td>
<td>Seconal</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Downers, goofballs</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Roofies, Vallies, blues</td>
</tr>
<tr>
<td>Amyl nitrate capsules</td>
<td>Poppers, snappers</td>
</tr>
<tr>
<td>Marijuana</td>
<td>Roach, weed, MJ, Mary Jane, grass</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Speed, crystal</td>
</tr>
<tr>
<td>Methadone</td>
<td>Dollies</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>Laughing gas</td>
</tr>
</tbody>
</table>
Drug tests and screening

Illicit drug use can be detected using urine samples to test for the presence of the drug’s metabolites.

- Marijuana:
The drug is detected in urine for 48-72 hours after single use and up to 12 weeks after chronic use.

- Barbiturates:
Two of the most commonly detected tranquilizers are butalbital and phenobarbital. Butalbital is prescribed for migraine while phenobarbital is primarily prescribed for seizure disorders. Their period of detection varies between the short acting to long acting drugs of this class, but generally, they are detected 2-10 after last use.

- Benzodiazepines:
Benzodiazepines such as diazepam and alprazolam are found up to 7 days after the last chronic use, depending on its half-life.

Treatment of Substance Use

The first step in the treatment of a drug use disorder is its recognition as a problem. Recent research has found that addicts will less likely “deny” their drug abuse as a problem when confronted with empathy
and respect. Treatment, much like the process that resulted in full-blown drug addiction, occurs in a series of stages: 158

1. Cessation of drug use either gradually or abruptly. Since abrupt cessation can lead to severe withdrawal symptoms, professional detoxification in a controlled environment is encouraged along with peer support, and abstinence. Detoxification or “weaning off” sometimes require the administration of a drug with similar effects to reduce the side effects and risks of withdrawal. Depending on the severity of the dependence and health status of the patient, detoxification can be done on inpatient or outpatient basis.

2. Emergency treatment for acute toxicity due to overdose. Patients who overdosed usually present in the ED unconscious and on respiratory arrest. Antidotes are often used in these cases to bring down the toxic levels of the offending substance.

3. Behavior modification through counseling. Many rehabilitation facilities have long after-care plans in place (when the user is released from the medical facility) for both the patient and the family.

4. Psychosocial support after overcoming addiction. The treatment of drug addiction does not stop when the patient leaves the clinic facility. Friends and family are needed to help the person
establish some level of normalcy after a long period of social withdrawal.

**Ethical Issues**

Psychopharmacology does not, in itself, cure mental illness any more than aspirin cures an infection. Pharmaceutical companies are powerful players in the field of psychopharmacology. They protect and continue to advocate past hypotheses based on monoamine deficiency that initially influenced the widespread use and acceptance of psychoactive drugs more than 50 years ago. A lot has happened since then, but these hypotheses (serotonin and norepinephrine hypotheses) are actively used to justify and promote expensive psychoactive medications. In fact, these companies exert great influence on the prescribing habits of clinicians, sometimes more than patient history and evidence-based studies. What’s more, these hypotheses are wrought with limitations and dubious integrity.¹⁶⁰

**Selective serotonin reuptake inhibitors**

Selective serotonin reuptake inhibitors (SSRIs) treat depression by inhibiting the breakdown or reuptake of serotonin from the synapse, thus keeping the serotonin bound to the postsynaptic receptor and active for a longer period. The selectivity of SSRIs is misleading because the drug affects other neurotransmitters, not just serotonin. For instance, fluoxetine and paroxetine, also indirectly affect the activity of another neurotransmitter, norepinephrine. The indirect
effect is clearly seen in the aggression tendencies of patients prescribed with these drugs.

The neurochemical mechanisms of the brain are poorly understood let alone the specific effects of serotonin in the brains of depressed individuals. Consistent evidence-based research has not been established yet, even after all these years. Although there is little doubt that SSRIs do act on the serotonin system, what is still questionable is the role of serotonin deficiency in depression. Even one of the leading scientists of initial serotonin research, George Ashcroft, did not pursue further studies on the idea of lowered serotonin levels being the cause of depression in the 1970s. Ashcroft pointed out that, “what we believed was that 5-Hydroxyindoleacetic acid (5-HIAA) levels were probably a measure of functional activity of the systems and not a cause. It could just as well have been that people with depression had low activity in their system and that 5-HIAA was mirroring that and then when they got better it didn't necessarily go up.”

The SSRIs improve depressive moods by targeting the serotonin system but as Ashcroft implied, clearly there are factors other than neurochemical balance at play in the etiology, course and outcome of depression. The serotonin hypotheses clearly advanced the psychopharmacological treatment aspect of depression but the way that pharmaceutical companies have held onto it, despite its insufficient and inconsistent evidence, to make a solid marketing case to the public is also clearly unethical and most often, unchallenged.
The therapeutic significance of SSRIs in depression is akin to aspirin in pain and fever. Just like aspirin that does not treat the cause of fever (i.e., infection); SSRIs do not treat the root cause of depression, and they merely elevate serotonin levels. It merely demonstrates a causal relationship between the symptom (depression) and serotonin levels. Symptomatic control of the disease is not treatment of the disease itself. Another problem with the serotonin hypotheses is that there are other agents such as reserpine that cause depletion of serotonin levels in the brain; yet do not cause depression.¹⁶⁰

Perhaps, the blame is not entirely on the pharmaceutical companies alone. The Food and Drug Authority (FDA) has played a hand in it too. They only require two positive clinical trials to demonstrate that an investigational antidepressant is better than placebo in order to approve it. Now all pharmaceutical companies need to do is conduct numerous studies until they come up with at least two that show positive results. This takes on the appearance of the FDA setting a minimum standard for the pharmaceutical companies; and, in so many words stating: show us two evidences that make it better than nothing and we’ll give you the green light.

Many of the clinical trials concerning the effectiveness of SSRIs that were approved by the FDA show time and again that they do not offer a clinically significant advantage over placebo in the treatment of depression. According to recent global data on antidepressant studies,
there is a less than 10% difference in the effect of FDA approved antidepressants versus placebo. Also, as for the small number of studies that did provide positive results, they catch the public’s eye through numerous publications in well-respected and peer-reviewed journals and FDA databases. But the remainder majority that provided negative and less than promising results were obscured and never mentioned. Sometimes, these trials are stopped even before they could be completed because of the alarming side effects found, which do not make it to the journals either.

Manipulation of the release of clinical data on antidepressants makes them less of a threat than the mental disorder that they were studied to treat. The hidden dangers are ugly and when do they become known, are often blamed on the underlying disorder rather than caused by the drug treatment. A good example is the increased risk of suicidal tendencies in patients on SSRIs. Because SSRIs were initially developed to study the serotonin levels of suicide victims, this particular finding is a tough pill to swallow by the very same companies who spearheaded the studies. After all, these drugs were studied to treat depressed individuals who were at risk of harming themselves and others. To protect the company’s interests, they’ve assigned the blame on the disorder, a practice known as “defending the molecule”. Other scientists are catching up on this practice and have released studies that undermine it such as those that emerged in the early 1990s showing healthy and non-depressed volunteers
increased likelihood to develop suicidal thoughts after treatment with SSRIs for other indications.\textsuperscript{164,165}

Another ethical dilemma to be considered in the administration of psychopharmacological treatment is the unethical manipulation of the mentally ill. Despite their refusal to treatment, the law sometimes forces them to sign up for one anyway. As mentioned in the previous section, such an action is the result of the law acting on behalf of the public’s best interests at the expense of the patient’s personal freedom.

**Patient Advocacy**

Unlike antihypertensive treatments with a well-defined and measurable outcome, psychopharmacologic treatments are hard to measure let alone quantify in a patient’s chart. There’s simply so much subjective data to sort out and make sense of. There isn’t a consistent measuring tool that tells both clinicians and patients that full mental stability has been regained that is in keeping with practice guidelines. Even mental illness is a poorly understood disorder. Moreover, treatment costs money, even with Medicare in place. These facts plus the risks that the treatment present to the well being of the patient are serious considerations that must be weighed in by the patient themselves before committing to it.

**Medicare**
The government has several insurance health policies in place to share the burden of healthcare costs of its citizens. Medicare provides insurance coverage for the mentally ill when they are hospitalized (Medicare Part A) or receive services in the facility but not confined in it (Medicare Part B). Prescription medications are also covered by Medicare under Medicare Part D. Additionally, the government gives patients the choice of an additional coverage called the Medicare Supplement Insurance (Medigap) policy to fill in the void that the first two policies leave. These policies, though helpful, still leave a substantial hole in the complete treatment of the mentally ill.\textsuperscript{166}

\textit{In-patient care}

Medicare Part A measures the patient’s use of hospital services (\textit{i.e.}, psychiatric and skilled nursing facilities) in benefit periods. A benefit period begins the day the patient is admitted as in an inpatient facility and ends after 60 consecutive days of non-treatment from the same facility. Should the patient be hospitalized again after 60 days, a new benefit period begins, and must pay a new deductible for any new services rendered. Patients have the advantage of multiple benefit periods when admitted to a psychiatric hospital with a limit of 190 days.\textsuperscript{166}

For each benefit period as a hospital inpatient, the following fees applied in 2012:\textsuperscript{166}

- $1,156 deductible per benefit period
- $0 for the first 60 days of each benefit period
- $289 per day for days 61–90 of each benefit period
• $578 per "lifetime reserve day" after day 90 of each benefit period (up to a maximum of 60 days over the patient’s lifetime)

An inpatient will be partially covered by Medicare Part B for mental health services (80% of the Medicare-approved amount) provided by doctors and other health care professionals while confined.

**Outpatient care**

Medicare Part B covers outpatient mental health services, including those from clinics, providers’ or therapists’ offices, and hospital’s outpatient department. In some cases, it covers partial hospitalization costs and allows for a more intense treatment than what the primary provider’s office can provide and patient confinement during the day (no overnight stay).

As of 2010, it covers the following services, with possible deductibles and copayments:\(^{166}\)

- Individual and group psychotherapy with doctors and other licensed professionals
- Family counseling
- Tests to evaluate the effectiveness of treatment and services given
- Psychiatric evaluation
- Medication management
- Occupational therapy as part of mental health treatment
- Non-self administered prescription drugs (i.e., injectables)
• Individual patient training and education
• Diagnostic tests
• Partial hospitalization may be covered

The deductibles pertain to the amount the patient must pay for health care or prescriptions before Medicare, prescription drug plans, or other insurance begins to pay. Copayment pertains to the amount the patient may be required to pay as share of the costs for medical service or supply, like a doctor’s visit, hospital outpatient visit, or prescription rendered and received. It is a set amount rather than a percentage of the total bill.

Additionally, Medicare Part B fully covers several preventive measures to mental illness (upon agreement of assignment by the therapist or doctor) such as:¹⁶⁶

• A one-time “Welcome to Medicare” preventive visit which includes a review of potential risk factors for depression. It is covered within the first 12 months of Medicare Part B issuance.

• A yearly “Wellness” visit. Medicare covers a yearly “Wellness” visit once every 12 months (if the patient had Part B for longer than 12 months).

• A yearly depression screening. Medicare covers one depression screening per year. The screening must be done in a primary
care doctor’s office or primary care clinic that can provide follow-up treatment and referrals.

After payment of the yearly Medicare Part B deductible, how much each patient pays for mental health services will depend on the purpose of the visit to the therapist or doctor:166

- **Diagnosis**: For visits with the intent to diagnose a mental disorder, patients pay 20% of the Medicare-approved amount.

- **Treatment**: For outpatient treatment of a diagnosed mental disorder (i.e., psychotherapy), patients paid 40% of the Medicare-approved amount in 2012.

According to the Patient Protection and Affordable Care Act (PPACA), commonly called Obamacare that was passed in 2010, the price of outpatient mental health treatments will be reduced to 35% in 2013 and 20% in 2014. However, if these services are rendered in a hospital outpatient clinic or outpatient department, an additional copayment or coinsurance amount may need to be paid to the hospital. This amount will vary depending on the service provided; somewhere between 20%–40% of the Medicare-approved amount.

**Prescription coverage**

Medicare Part D is offered by various insurance companies, both private and government, approved by Medicare. Patients who are subscribed to the policy, Medicare Prescription Drug Plan, have access
to its formulary. A formulary is a list of drugs that the Medicare plans cover. Medicare drug plans do not cover all drugs, but they’re required by law to cover all or almost all anti-depressant, anticonvulsant, and antipsychotic medications. Nonetheless, before enrolling into a treatment, patients need to ask their doctors and plan providers which drugs are covered by the Medicare plan.¹⁶⁶

In certain cases wherein a doctor needs to prescribe a drug that’s not covered by the formulary of the patient’s Medicare plan; both the patient and the doctor have the right to request a coverage determination to possibly accommodate the intended prescription. Coverage determination is the first decision made by the Medicare drug plan (not the pharmacy) provider about the drug benefits that the patient is entitled to such as:¹⁶⁶

- Whether a particular drug is covered
- Whether the patient have met all the requirements for getting a requested drug
- How much the patient is required to pay for a drug
- Whether to make an exception to a plan rule when requested

The situations that warrant coverage determination are:¹⁶⁶

- When a drug deemed necessary by the doctor isn’t covered
- When a drug deemed necessary by the doctor is covered but at a higher cost
- When a drug deemed necessary by the doctor needs prior authorization before it can be given
• When a drug is not covered by the existing Medicare plan of the patient because the plan provider have not deemed it necessary for that patient

If the drug plan does not provide a prompt decision and the requestors (patient or doctor) can show substantial proof that the delay would affect the patient’s health, the plan’s failure to act is considered to be a coverage determination. On the other hand, if the decision made by the provider is not agreeable to the needs of the patient, the requestors can file an appeal.

Coverage determination allows for exception requests; formulation exception and tiering exception. The requestors can file a request for formulary exception to cover a drug that’s not on its drug list or to waive a coverage rule. A tiering exception allows for charging a lower amount for a drug that’s on a drug plan’s non-preferred drug tier. The doctor or other prescriber must send a supporting statement (compelling medical reasons) justifying the need for such an exception.

Every person with Medicare is entitled to certain rights and protection. To learn more about these, visit www.medicare.gov/publications to view the booklet “Medicare Rights and Protections”, or call 1-800-MEDICARE. There are various federal and state sponsored programs in place for mentally ill individuals with limited resources and income to allow them access to treatment.
Extra Help

Extra Help is a Medicare program to help pay for Medicare prescription drug costs. Generally, qualification is based on certain income amounts. Even if patients do not automatically qualify for Extra Help, they can still apply. For more information, patients should be advised to:

• Visit www.socialsecurity.gov or visit www.socialsecurity.gov/i1020 for online applications.

• Call Social Security at 1-800-772-1213. TTY users should call 1-800-325-0778 for phone and paper applications.

• Visit or call the State Medical Assistance (Medicaid) office. Visit www.medicare.gov/contacts, or call 1-800-MEDICARE (1-800-633-4227) to get the phone number. TTY users should call 1-877-486-2048.

State Pharmacy Assistance Programs (SPAPS)

Many states have SPAPs in place to help certain patient groups pay for prescription drugs based on their financial need, age, or medical condition.

For more information, patients should be advised to:

• Call the State Health Insurance Assistance Program (SHIP) or,
• Visit www.medicare.gov/contacts, or call 1-800-MEDICARE (1-800-633-4227) to get the phone number of a particular SPAPS office. TTY users should call 1-877-486-2048.

Medicare Savings Programs

Patients with difficulty paying for deductibles and coinsurance as part of their Medicare costs can receive state assistance in the form of Medicare Savings Programs. For more information, patients should be advised to:

• Call or visit State Medical Assistance (Medicaid) office, and ask for information on Medicare Savings Programs. To get the phone number for a specific state, visit www.medicare.gov/contacts, or call 1-800-MEDICARE.
• Visit www.medicare.gov/publications to view the brochure “Get Help With Your Medicare Costs: Getting Started.”
• Contact the State Health Insurance Assistance Program (SHIP). Visit www.medicare.gov/contacts, or call 1-800-MEDICARE to get the phone number.

Medicaid

Medicaid or Medical Assistance also provides health coverage to certain people who have limited income and resources. Each state has its own set of criteria for eligibility that must be met. Other factors such as age and co-existing physical disabilities also count. For more information, patients should be advised to:
• Call the State Medical Assistance (Medicaid) office. Visit www.medicare.gov/contacts, or call 1-800-MEDICARE (1-800-633-4227) to get the phone number. TTY users should call 1-877-486-2048.
• Learn about the Medicaid program by visiting www.medicare.gov/publications to view or print the brochure, “Medicaid: Getting Started.”

Homelessness

Approximately 200,000 of the severely mentally ill population in the U.S. are homeless. Homelessness limits a person’s access to appropriate health care and employment opportunities. In children and adolescents, this experience translates to school absences. The homeless have higher rates of hospitalizations for physical illnesses, mental illness, and substance abuse than any other population groups.\textsuperscript{167} The housing needs of the severely mentally ill homeless are categorized into two groups:

1. Decent, affordable housing
2. Supportive assistance

The first category applies to all citizens. According to the Johns Hopkins article, \textit{The Severely Mentally Ill Homeless: Housing Needs and Housing Policy}, there are numerous studies that point to the risk
of homelessness being an immediate consequence of discharge from hospitals. This finding implies that housing arrangements and continued support should be given to the treated individuals as they rejoin the community. The need for supportive assistance by the severely mentally ill patient requires new approaches to housing policy to be based on three factors.\textsuperscript{168}

1. The continuity of symptoms, behaviors, and functional disabilities even after discharge from a mental hospital and placement into a housing setting.

2. The varying impairments and symptoms of mental illness and the volatility of episodes between “controlled” phase and the active phase of illness.

3. The availability and stable supply of appropriate mental health services.

The main public sector sources of funding for supportive housing for the severely mentally ill persons include:\textsuperscript{168}

- State supplements to the Supplemental Security Income (SSI) program
- Two optional programs under Medicaid (Targeted Case Management, and Rehabilitative Services)
- Social Services Block Grant
- HUD Section 811 program (formerly Section 202/8)
• McKinney Act, including the Projects for Assistance in Transition from Homelessness (PATH) program and the Shelter Plus Care program

Majority of those programs can only afford a fraction of the capital necessary to develop and operate a supportive housing setting. On their own, they are insufficient stand-alone sources of funding for housing costs. The limited budgets of these programs affect the depth of funding assistance and numbers that can be assisted. For example, Medicaid, is a useful source of funds for case management, but is not indicated primarily to pay for housing costs alone. Another example are the SSI payments for special residential settings that can only go as far as cover operational costs but not necessarily bankroll new housing developments nor pay for any large capital costs.

Addiction

As reiterated in the previous sections, patients need to be informed of their rights when receiving psychopharmacological treatment. As required by law, clinicians and their guardians, if any, must disclose all treatment information to the patient and obtain his consent prior to its initiation.
On the other hand, patients need to keep themselves aware of their rights by visiting or contacting various patient advocacy groups in their state. Patient advocacy organizations such as New York’s Office of Alcoholism and Substance Abuse Services (OASAS) protect the rights of mentally ill patients, especially alcoholic and drug addicts, while receiving treatments. The organization operates in accordance with Mental Hygiene Law and Regulations as well as other applicable state and federal laws. According to its website, patients have the right to:  

- Be informed of the program’s rules and regulations.
- Receive considerate and respectful care.
- Receive services without regard to race, color, ethnicity, religion, sex, sexual orientation or source of payment.
- Receive confidential treatment. Except for a medical emergency, court order, child abuse or crimes committed on program premises, a program generally cannot release information about the treatment without written consent.
- Be fully informed of the treatment plan and participate in its development. This includes setting goals and measuring progress with the counselor.
- Refuse treatment and be told what effect this could have on the health or status in the program.
- Discontinue treatment at any time.
- Obtain, in writing, an explanation of the reason(s) for the discharge from treatment and information about the program’s
appeal process. And, if necessary, receive help obtaining treatment at another program.

- Avoid inappropriate personal involvement with counselors, staff or other patients. Patients have the right to be free from sexual harassment and sexual misconduct.

On the other hand, according to the website, patients also have the responsibility to:

- Act responsibly and cooperate with the staff from the program.
- Treat the staff and other patients with courtesy and respect.
- Respect the right of other patients to receive confidential treatment.
- Participate in the development and completion of the treatment plan, which includes becoming involved in productive activities, such as work or school and not using drugs.
- Pay for treatment on a timely basis.
- Talk with a counselor about problems that affect the treatment progress and recovery.
- Offer suggestions on improving program operations.
- Talk with a counselor before ending treatment; do not just stop or leave.
- Ask questions about any part of the treatment that wasn’t understood.

**Communication With The Patient And Health Team**
Patient and Family Collaboration

The impact of mental illness is not lost on the families. When it first strikes, the first reaction of those closest to the patient may be to deny the existence of such illness.

Signs of denial include but not limited to:\textsuperscript{170}

- Wanting to put the painful episodes behind right away

- Believing that the symptoms will not recur in the future after treatment of an acute episode

- Looking for stressors and problems and removing the patient from its presence. For example, some families relocate their mentally ill patient from their present environment into a new one in the hopes that a “fresh start” will alleviate the illness.

Families may also be ill equipped to understand the diseases. Without the proper information, they may not be optimistic about the patient’s future and chances of normalcy. It is crucial that families educate themselves to help them understand how the illness affects their loved ones and that with psychotropic medications, psychotherapy and treatment monitoring, mentally ill individuals actually have increased control over their symptoms and episodes and can function normally in a social environment.\textsuperscript{170}
Sometimes, even when all members of the family have understood the illness and their role in the recovery of their loved ones, the family is often reluctant to discuss the person with others because of fear of judgment. The families may also withdraw from social interactions at home for fear of triggering a symptomatic episode with the disruption and presence of visitors. The stigma associated with mental illness results in social withdrawal, not just by the patient but also by the families involved.

Mentally ill patients need a support system to cope with their illness, and the most logical choices to include are the family members, both blood relatives and patient-defined caretakers. In fact, clinicians must consider both the patient and the family as fellow collaborators in the long-term treatment of patients. Evidence-based studies underscore the significance of patient and family participation, working together with the health team in a collaborative endeavor. The main goal of family interventions is to reduce the risk of patient relapse along with other goals such as reduction of family burden and improvement of patient and family performance. Effective family interventional measures include:

- Education about the illness and its course
- Training and using problem-solving skills within the family
- Improving communications between family members and the patient
- Reducing stress among members by way of hobbies and social engagement away from home
These interventions when coupled with somatic treatments such as psychopharmacologic medications and behavioral therapy have been proven to reduce episodes of psychiatric disturbances. Studies have consistently found that patients who received family interventional measures for more than 9 months fared better (reduced relapse, better symptom control, medication and therapy adherence) than those who received it for less than that amount of time. The clinician needs to be open to the type and depth of family interventions, factoring in the patient’s needs and family preferences. A well-defined family psychoeducation approach is best implemented, whenever the resources allow it. Referrals and membership to family support groups and peer-based non-clinical programs such as the National Alliance for the Mentally Ill's *Family-to-Family Education Program* are also helpful.

**Consultation With Peers**

*Cognitive Behavioral Therapy*

Essentially, Cognitive Behavioral Therapy is a type of psychotherapy that makes patients more conscious and aware of their thoughts and behavior in order to be able to change them. The National Alliance on Mental Illness (NAMI) defines Cognitive Behavioral Therapy (CBT) as a form of psychotherapy that focuses on “examining the relationships between thoughts, feelings and behaviors. By exploring patterns of thinking that lead to self-destructive actions and the beliefs that direct
these thoughts, people with mental illness can modify their patterns of thinking to improve coping”. For example, a depressed patient may often express feelings that question self-worthlessness with statements such as “I am worthless” and believe it to be the definitive truth. The role of the CBT therapist, in this case, is to challenge the patient’s version of the truth, present it as a hypothesis and proceed to test its validity by a series of “experiments” that undermine its rationality.

Patients involved with CBT are given tasks or assignments. For example, a sociophobic may be asked to buy milk from the local grocery. Another example is patients being asked to write down their dysfunctional thoughts as they happen in a diary or journal, which is then reviewed by the therapist for patterns in their thinking that triggered them. CBT and psychodynamic therapy has three main differences, all of which are listed on the table below.

**Differences between CBT and psychodynamic therapy**

<table>
<thead>
<tr>
<th>Features</th>
<th>CBT</th>
<th>Psychodynamic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target mechanisms</td>
<td>It aims to relieve symptoms of distress by recognizing and replacing dysfunctional thoughts and patterns.</td>
<td>It aims to relieve symptoms of distress by attempting to uncover its root causes such as childhood trauma.</td>
</tr>
<tr>
<td>Period of therapy</td>
<td>Relatively brief (3-6 months)</td>
<td>Long term &gt; 6 months</td>
</tr>
<tr>
<td>Structure</td>
<td>Elements of homework and assignments for patients</td>
<td>Typically without homework and assignments</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Patient participation</td>
<td>Therapist sets the agenda for each session based on mutually agreed objectives</td>
<td>Patients set the agenda of each session by talking about their thoughts</td>
</tr>
<tr>
<td>Role of therapist</td>
<td>Relationship with therapist is not part of the focus of the treatment</td>
<td>Relationship with therapist is an essential part of the focus of the treatment</td>
</tr>
</tbody>
</table>

As mentioned above, Cognitive Behavioral Therapy facilitates a structured consultation, enabling patients to actively practice the proposed solutions during therapy sessions. CBT’s Five Areas assessment model developed by the NHS provides a clearly defined summary of the problems and challenges that mentally ill patients face. These are listed as:

- Life situation, relationships, practical problems and difficulties
- Altered thinking
- Altered feelings (also called moods or emotions)
- Altered physical feelings or symptoms in the body
- Altered behavior or activity levels.

According to the Canadian Counseling and Psychotherapy Association, the major techniques commonly employed by CBT are:

- Relaxation training
• Presence of mind
• Systematic desensitization
• Assertiveness training
• Social skills training

Cognitive Behavioral psychotherapy is especially effective in the management of specific psychological disturbances such as depression, anxiety and mood disorders, certain phobias, post-traumatic stress disorder and insomnia.

*Depression*

Some studies have found that the effectiveness of CBT in treating depression comparable to antidepressant medications, yielding similar positive therapeutic outcomes, and may even be superior in the prevention of symptom relapse in certain individuals. But more importantly, studies have also shown that when these two treatment approaches are combined, they produce better outcomes than when each is employed alone.

The main element of CBT is the recognition of irrational self-destructive thoughts and replacing them with positive ones. One of the ways CBT therapists execute this is by encouraging patients to introduce positive activities into their daily schedules. The more pleasure they receive daily, the less likely that negative thoughts will
intrude. Additionally, therapists encourage patients to develop regular sleep patterns as it improves symptoms of bipolar disorder and depression.

Anxiety and panic disorders

Cognitive behavioral therapy is also useful in the treatment of anxiety and panic disorders. Patients with panic disorders may have irrational fears of being in danger, voicing them out with statements such as “I am in danger of being suffocated” or “I’m going to die alone”. CBT therapists encourage such patients to test out these specific fears and develop realistic responses when these feelings (panic attacks) arise. An example is exposing them to these very fears in a safe and controlled therapeutic environment. Fears of contamination, death, illness, physical harm, etc. are identified and replaced to reduce the anxiety connected with them.

Phobias

The CBT approach used in anxiety and panic disorders is the same for patients with phobias. The therapists expose the patients to their specific fears and help them change their response to them.

Post-traumatic stress disorders (PTSD)

Cognitive behavioral therapy has been used in the management of posttraumatic stress disorders in adults and children for many years.
Several expert consensuses find trauma-focused CBT to be effective in PTSD that is precipitated by various life events.

CBT for PTSD in adults:

- **Terrorism:**

  CBT has been found to be effective for PTSD in the survivors of the 9/11 terrorist attack on the World Trade Center, the 2005 London bombings, and the 1998 bomb explosion in Omagh, Northern Ireland.

- **War trauma:**

  Soldiers exposed to combat while on a tour of duty are at high risk for PTSD. Combat veterans with severe and chronic PTSD can be managed with multidimensional CBT that includes greater social engagement and interpersonal functioning.

- **Assault:**

  CBT is effective in reducing the symptoms of PTSD in female victims of assaults such as childhood abuse, rape and sexual assaults. There is evidence that the benefits are long term and measureable at future follow-up assessments.

- **Road traffic accidents:**

  Motor vehicle accidents (MVAs) are commonly cited triggers of PTSD. CBT components such as imaginal reliving and facilitating of post-
traumatic growth have been employed in MVA survivors with subsyndromal PTSD, which has resulted in psychological stabilization when assessed at subsequent follow-ups.

- Refugee status:

Refugees with PTSD present with a wide range of symptoms resulting from prolonged and repeated exposure to traumatic events, displacement and acculturation. The latter presents a particular challenge to therapists since the culture and language of the refugees need to be incorporated into the CBT. Refugees who are resistant to medications have also benefitted from CBT.

- Disaster workers:

A CBT composed of brief-focused measures is effective in disaster workers who are exposed to shocking scenes and humanitarian suffering.

**CBT for PTSD in children and adolescents**

CBT has long been recommended as the first choice of treatment of PTSD in children and adolescents.

- Natural calamities:

After the 1999 earthquake in Athens, the implementation of short-term CBT in a group of children survivors with PTSD symptoms showed a significant reduction in overall symptoms across intrusion,
avoidance, and arousal symptom clusters, as well as in depressive symptoms immediately after the intervention and better psychosocial functioning.

- **Man-inflicted traumas:**

  Child abuse victims are supporters of the effectiveness of trauma-focused CBT. A study of Palestinian adolescent victims of armed conflict suggests that trauma-focused CBT addressing negative coping and fatalism may produce positive results.

- **Sexual abuse:**

  Studies show that trauma-focused CBT for symptomatic children has been successful within the first 1–6 months after experiencing sexual abuse. Compared with child-focused therapy, trauma-focused CBT has demonstrated significantly more improvement with regard to PTSD, depression, behavior problems, shame, and abuse-related attributions in sexually abused children.

  Resistance to CBT and consequent dropouts are common in PTSD patients. Although CBT has been proven to be beneficial in reducing the recurrence and intensity of depression, stress and panic attacks, there are certain studies pointing to its limited usefulness in dealing with unidentified causes of psychological illnesses.
Group therapy and counseling

Group counseling is a form of psychotherapy that operates on the idea that an individual will be much more likely to identify and understand one’s maladaptive patterns and issues through sharing of thoughts and experiences with a group of people. Essentially, people learn more about themselves through interpersonal interactions. Group counseling sessions are supervised and facilitated by one or two group therapists. These sessions operate as a closed system.

Much like CBT, the therapeutic environment upon which these sessions take place is controlled, seldom allowing the intrusion of external forces. The intense emotional charges and complex vulnerabilities uncovered by such sessions need to be protected in order to preserve the patient’s sense of safety and trust in the group.¹⁷⁶

Group therapy can be divided into two groups:

• Psychoeducational group therapy:
This type of therapy aims to provide information about specific topics in order to educate patients.

• Process-oriented group therapy:
This type of therapy seeks to provide patients the experience of being in a group and the vehicle to exercise interpersonal sharing in order to heal.
Listed below are some of the issues and dysfunctional patterns, which patients who take part in group counseling share:177

- Sense of isolation
- Shyness
- Excessive dependence in relationships
- Superficial relationships
- Frequent disagreements
- Anxiety in social settings
- Trust issues
- Low tolerance for criticisms
- Lack of self-confidence
- Fear of rejection
- Lack of intimacy in relationships

Topics commonly addressed in group therapies include:

- Substance abuse
- Depression
- Anxiety
- Post-traumatic stress
- Divorce
- Eating issues
- Domestic violence
- Sexual identity crisis
- Parenting issues

According to Irvin Yalom, an influential American existential psychiatrist, there are therapeutic principles (nine of which are used in
group counseling and listed below) that explain the various counseling factors used to address those maladaptive issues and patterns listed above.\textsuperscript{175}

- **Universality:**
The shared experiences among patients help clients’ triumph over pervasive sense of isolation and low self-esteem.

- **Altruism:**
The idea of helping others improves one’s own self-esteem and encourages better coping styles and interpersonal skills among patients.

- **Instillation of hope:**
The idea of coping together inspires hope among those who are not optimistic about recovery.

- **Cohesiveness:**
The sense of belonging to a group promotes validation and assurance of a functioning therapy and ultimately, successful recovery as a unit. The patients, feeling a sense of belonging to the group, value it and its endeavors, thus promoting its shared interest to help each member recover.

- **Corrective recapitulation of the primary family experience:**
The inevitable development of closeness among patients immediately instills a sense of more than just camaraderie but also a sense of familiarity that is akin to family.
• **Self awareness:**
The input of other patients gives patients a greater insight and diverse views into their own problems and issues.

• **Catharsis:**
The feelings of guilt and shame attached to deeply personal experiences are purged out through frequent interpersonal sharing.

• **Imitative behavior:**
The positive actions and behaviors of the senior patients and those with more advanced skills influence the others to copy them.

• **Existential factors:**
The recognition and acceptance of inherent limitations and inevitabilities of life such as death, aging and choices help promote personal growth.

**Ethical considerations**

Group therapists are legally required to inform clients of the following information prior to the start of sessions:

• Type of therapy
• Patient’s obligations to participate
• Patient’s rights within the therapeutic group
• Confidentiality issues
• Anonymity of other members
Patients are expected to keep the contents of the session confidential and the identity of fellow patients anonymous. Unless a patient has authorized release of information, both patients and therapists are not allowed to discuss another’s personal history with other patients or individuals outside the group therapy circle.

Requirements from the therapist:
- Obligated by law to inform the proper authorities if a patient has expressed intent to harm one’s self or others
- Responsible for keeping a professional environment devoid of discrimination and inappropriate behavior
- Responsible for upholding each patient’s rights
- Responsible for ensuring a collaborative and productive progression of sessions

*Psychological support*

Psychological support is the provision of psychosomatic aid to improve a patient’s ability to function under enormous stress levels in the context of a critical environment. The emotional support has been implicated in studies as a significant factor in speeding up the recovery process. Traditionally, members of one’s own family usually provided psychological support. However, the last 50 years have seen the weakening of family ties and emerging community awareness that
makes psychological support from outside the family circle an ideal prospect.

In cases of natural disasters, international aid workers are often deployed to the site to offer physical, medical and emotional aid to the victims. Below is a list of guiding principles, which should be considered during the implementation of psychological support to an unfamiliar culture.

- **Community-based approach:**
  
The employment of local resources, provision of training and upgrading of local structures and institutions contributes to the success of this type of approach. It allows for locally taught volunteers to share their knowledge with fellow community members becoming instrumental in providing successful relief.\(^{178}\)

- **Use of trained volunteers:**
  
The training of local volunteers is an integral part of helping the community as a whole. They already have access to the community, and the confidence of the survivors. Their inside knowledge of the local culture enables for the easy facilitation of appropriate and adequate assistance to the affected population.\(^{178}\)

- **Empowerment:**
After disaster strikes, the community members will be left helpless and reliant on external help, setting the ground for bitterness at both the helpers and the situation. The passive recipient may look at acceptance of the external aid as a sign of weakness despite the motivation of the helpers stemming from human compassion, protest against injustice, love, or other equally well-meaning emotions. Psychological support in this instance should be targeted at empowering the victims so they can regain self-respect and autonomy. This can be achieved by encouraging community participation.

- **Community participation:**

It allows for feelings of ownership and “being in control” to be fostered in the victims instead of being helpless passive recipients of help.

- **Care with terminology:**

The wrongful use of certain words during stressful situations can lead to victims closing themselves off and erecting walls to guard their pride and what they believe are their best interests. Choosing words carefully and refraining from putting discriminatory labels on people and situations can help circumvent those self-protective measures.\(^{178}\)

- **Active involvement:**

To prevent further victimization and promote self-empowerment, helpers should focus on measures that underscore competence rather than on symptoms and deficits of the community members. These measures should target the following:\(^{178}\)
- The identification and strengthening of mechanisms that will contribute to better coping
- The active involvement of people in sorting out their problems
- The recognition of people’s skills and competence

Self-help measures and strategies adopted by the victims are crucial to their successful recovery.

- Early intervention:

  Early psychological support is a crucial preventive factor against severe depression and chronic distress. Ignoring emotional reactions can result in passive victims rather than active survivors, delaying the recovery process.

- Viable intervention:

  Disasters precipitate short-term and long-term emotional challenges. The distress that people experience after a disaster may not become apparent immediately, continuing mentoring and follow-up is essential if the initial psychological support is to remain effective in the long term.

**Lifestyle Precautions**

Family members, no matter the age, living with a mentally sibling or parent are inadvertently affected by the symptomatic episodes that
may or may not occur frequently. The decision to live with a mentally ill individual is based on several patient and family considerations that may present positive and problematic outcomes for both parties.

The positive factors include but are not limited to some of the following:

- Reduced episodes of disruptive symptoms
- Accessibility to activities outside the home
- Contribution to family workings
- Skilled family training
- Minimal disruption of family function
- Bigger support network

The negative outcomes and factors of living at home may include any of the following:

- Difficulty in controlling the patient
- Less likelihood of social interaction
- Activity restrictions put in place
- Chaos and disruption of normal activities
- Family may have no social and psychological support
- Inability to support and direct patient
The National Alliance on Mental Illness (NAMI) has established several guidelines to help family members cope at home. One of these guidelines focuses on establishing clear communications with the affected member.

The table below lists various possible symptoms and the suggested corresponding course of actions to take.

<table>
<thead>
<tr>
<th>Symptoms/actions of affected member</th>
<th>Suggested course of action to take</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have trouble with reality</td>
<td>Be simple and truthful</td>
</tr>
<tr>
<td>Are fearful</td>
<td>Stay calm</td>
</tr>
<tr>
<td>Are insecure</td>
<td>Be accepting</td>
</tr>
<tr>
<td>Have trouble concentrating</td>
<td>Be brief, repeat</td>
</tr>
<tr>
<td>Are over stimulated</td>
<td>Limit input, don’t force discussions</td>
</tr>
<tr>
<td>Easily become agitated</td>
<td>Recognize agitation, allow escape</td>
</tr>
<tr>
<td>Have poor judgment</td>
<td>Not expect rational discussion</td>
</tr>
<tr>
<td>Have changing emotions</td>
<td>Disregard</td>
</tr>
<tr>
<td>Have changing plans</td>
<td>Keep to one plan</td>
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<tr>
<td>---------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Have little empathy for you</td>
<td>Recognize as a symptom</td>
</tr>
<tr>
<td>Believe delusions</td>
<td>Ignore, don’t argue</td>
</tr>
<tr>
<td>Have low self-esteem</td>
<td>Stay positive</td>
</tr>
<tr>
<td>Are preoccupied</td>
<td>Get attention first</td>
</tr>
<tr>
<td>Are withdrawn</td>
<td>Initiate relevant discussion</td>
</tr>
</tbody>
</table>

Dr. Brian D. Eck, a licensed psychologist and professor created a guideline for creating a “low-stress home environment for a mentally ill person”. The contents of the guidelines are listed below:

- Go slow:
  Recovery and growth take time. Rest is important.
- Keep It Cool:
  Enthusiasm is normal. Disagreement is normal. Emotions are normal. Help your family members to keep thing in perspective and obtain some degree of balance.
- Give People Space:
  Private time and space are important for everyone. It is okay to offer or to refuse and offer.
• Set Limits:
Everyone needs to know what the rules are. A few good rules that are consistently enforced will help keep things calm.

• Ignore What You Cannot Change:
Let some things slide. Do not ignore violence.

• Keep It Simple:
Say what you have to say clearly, calmly, and positively. When you address them, your family members will most likely respond only to the first couple sentences that you say to them at one time.

• Follow Medical Provider’s Orders:
Encourage your family members to take their medications as prescribed and only those that are prescribed. If you can, have them sign a release of information so that you and the doctor can discuss your family member’s treatment program.

• Carry On Business As Usual:
Reestablish routines as quickly as possible when they are disrupted. Encourage your family members to stay in touch with their supportive friends and relatives.

• No Street Drugs Or Alcohol:
Emphasize that illegal drugs and alcohol make symptoms worse. Help them find creative ways to avoid or limit the use of those substances in social situations.
• Recognize Early Signs Of Relapse:

Note changes in your family member's symptoms and behaviors, especially those which usually occur just before a relapse. Help your family members to recognize these changes and to make contact with their doctor.

• Solve Problems Step By Step:

Help your family members make changes gradually. Work on one thing at a time and be patient as they learn from the consequences of their behavior. Let them experience the non-dangerous consequences of their choices.

• Establish Personal Measures Of Success:

Help your family members set realistic goals, and then chart these personal goals from week to week and month to month. Remember that success for your relative is in comparison to how they were personally doing last month, not how they were doing before they got ill, or how others their age are doing.

Christopher Amenson, a psychologist created a guideline in fostering helpful attitudes and environments and setting the tone to productive approaches to coping and living with mentally ill family members. These are outlined below:209

Develops hope and expectations based on realistic information and prognosis.
• Full acceptance
  – Mourn the loss, but not in the presence of the relative
  – Never discuss or lament the past or what the future could have been
  – Avoid comparisons to peers
• Demonstration of worth and dignity even in the face of certain limitations
  – Treat as an adult
  – Include in decisions
  – Ask to help do chores
• Allow freedom to pursue own goals
• Facilitate the achievement of goals
• Focus efforts everyday toward fulfilling those goals
• Help attain a unique version of fulfillment

Foster a healing environment
• Assign no blame
• Communicate clearly the appropriate and realistic expectations and limits to the patient
• Create an undemanding and structured environment
• Create a predictable routine

• Make way for a calm environment with limited stimulation

• Maintain consistent environment

• Engage the patient in non-stimulating activities

• Offer chances to fulfill major personal and competence requirements

• Give praise and encouragement

• Tutor and provide incentives on the acquired vocational and social skills

• Ensure that medication and treatment programs are adhered to

• Be ready to handle emergency attacks and worsening episodes to minimize commotion and prevent major relapse

Maintaining a sense of normalcy for other family members living at home

• Recognize the needs of family members and develop means to meet them

• Stay socially active

• Seek support from persons and families who understand

• Foster and promote skills and activities which promote overall health

• Streamline personal energy to making life better for every member
• Grant privacy and extend support for personal tastes and endeavors

Employment Options

Due to poor understanding of mental illness and perpetuation of wrongful information in the media, a chronic form of the disease is not just socially debilitating, it also often results in employment discrimination.¹⁸⁰

Benefit from employment of the mentally ill

Contrary to popular belief, employing mentally individuals actually have their own merits. They offer traits and features that can be beneficial to the company such as:¹⁸⁰

• Creativity
• Imagination

Mentally ill individuals are among the most creative and imaginative members of the workforce. Numerous studies have pointed out that psychopharmacologic medications used by such individuals actually help them become more productive.

Re-employment as part of the reintegration process
Securing and keeping a significant employment is valuable to the mentally ill person. Daily work and the predictability it provides keep their minds preoccupied and engaged in productive endeavors, replacing the negative thoughts. Many psychologists agree that that employment is a vital tool in fostering mental wellness and warding off its reverse - mental illness.

Work offers five features that endorse mental wellness:

- Time frame
- Social contact
- Communal effort and common goals
- Personal identity through affiliation
- Routine activity

Essentially, employment is an important part of the long-term recovery process. As mentioned above, advances in psychopharmacology make it possible for those with chronic mental illness to make a valuable contribution to the workplace.

**Surviving the stigma**

Despite the advances in psychopharmacologic treatments of mental illness, there is a pervasive ignorance surrounding it. Listed below are some of the myths associated with it.\(^{180}\)
• **Myth #1: Mental illness and mental retardation are one and the same.**
  The Facts: Mental illness and mental retardation are completely different disorders when it comes to intellectual function. Mental retardation chiefly illustrates limited intellectual performance, while individuals with mental illness have varying intellectual capacities that are as diverse as the general population.

• **Myth #2: There is no cure or sure recovery from mental illness.**
  The Facts: While these mental illnesses are chronic, studies have found that with the appropriate treatment, the majority of sufferers attain genuine symptom control over time, allowing them to lead stable and productive lives. Additionally, sure recovery from mental illness is a subjective ideal; the reintegration of sufferers into mainstream society especially in the employment area is a clearer and well-defined therapeutic outcome.

• **Myth #3: Mentally ill employees are mediocre workers.**
  The Facts: Mentally ill individuals may in fact be better compared to their co-workers without mental illness. Employers have reported them to be superior in punctuality and work attendance. Additionally, they are motivated and as productive as their coworkers without mental illness.

• **Myth #4: People with mental disabilities have low tolerance for stress related to the job.**
The Facts: The response and perception of job-related stress vary among individuals, whether mentally ill or not. Also, optimal productivity is directly and proportionally related to the employees’ needs and working environment.

• *Myth #5: Mentally ill and mentally restored individuals are unpredictable, potentially violent, and dangerous.*

The Facts: This is the one myth that has been perpetually portrayed by the media to the public about individuals with mental illness. The truth is, this might be true for certain uncontrolled psychotic individuals but is not necessarily true for all mentally ill people.

**Legalities of hiring mentally ill individuals**

During his first term in office, President George H.W. Bush signed into law *The Americans with Disabilities Act of 1990* (ADA). The ADA is a comprehensive civil rights law that forbids the discrimination against people with physical and mental disabilities in employment, public accommodations and commercial entities, public transportation, public telecommunications, and other miscellaneous provisions. Congress enacted the Title I of the Americans with Disabilities Act to help mentally ill individuals fight against the stigma and employment discrimination in the workplace.

Under Title I of the Act employers are prohibited from discriminating against qualified individuals with disabilities in activities pertaining to
employment such as job applications, hiring, job assignments, fringe benefits, promotion and discharge. Employers may require medical entrance examinations after offering employment positions to all applicants, regardless of disability. The results should be held in safe keeping as a confidential medical record. Qualified individuals do not include those who are actively engaged in substance abuse and misuse. Substance abusers are not legally covered by the ADA. The ADA has overlapping responsibilities in both Equal Employment Opportunity Commission (EEOC) and Department of Justice (DOJ) for employment by state and local governments; all three government offices coordinate and support each other’s efforts to avoid duplication in investigative and enforcement activities.

**Responding to discrimination**

Mentally ill individuals who believe they have been discriminated against in terms of employment should contact the nearest located U.S., EEOC offices. Basically, discrimination charges should be filed within 180 days of the alleged discrimination. However, if state and local authorities provide relief for discrimination on the basis of mental disability, individuals may have up to 300 days to file charges. It is strongly advised to contact the EEOC immediately after the alleged discrimination to protect the individuals’ rights.

*Contact details*
For information and instructions on reaching the local EEOC office, patients should be advised to call:

- (800) 669-4000 (Voice)
- (800) 669-6820 (TDD)
- In the Washington, D.C. 202 Area Code, call 202-663-4900 (voice) or 202-663-4494 (TDD)

**Entitlements**

According to the EEOC website, discriminated individuals are entitled to one or more of the following remedies that will place that individual in the position had the discrimination not occurred such as:\(^{181}\)

1. Hiring
2. Promotion
3. Reinstatement
4. Back pay
5. Reasonable accommodation including reassignment
6. Attorneys fees

How the government benefits from the employment of the mentally ill

The cost of reemployment and reintegration of the mentally ill individuals is less than that of keeping them confined to hospitals and unemployed. A concrete example of this took place in Canada. The World Health Organization and the International Labor Organization noted how 240 persons with mental illness fared over a 10-year period with the aid of formal work reintegration program. Surprisingly, these
persons kept meaningful and earned a collective sum of $5 million, paid $1.3 million in income taxes, and saved the government an estimated $700,000 in welfare costs.182

**Social Interactions And Response To Treatment**

The social circumstances and membership to a group have deep impact on the patient’s adherence and response to treatment. These social circumstances include living arrangements, legal status, sexual orientation, and family resources.

**Psychosocial treatment**

Schizophrenic patients are often prescribed with psychosocial treatments in combination with psychopharmacological drugs and counseling. Studies have demonstrated that the patients who exhibited symptom control and normal functional abilities (stable) have had psychosocial treatment incorporated into their overall treatment plans. One of the debilitating consequences of schizophrenia is social function impairment characterized by difficulty creating and maintaining interpersonal relationships, abnormal function in social roles such as a student, parent, or worker, self-care skills, and reduced participation and pleasure in recreational activities. Other severe to moderate psychiatric disorders may experience similar social impairments too.

Similar to the development of tailored psychopharmacological interventions for each patient, the selection of psychosocial treatments
should also correspond to key factors in each patient’s life. Listed below are factors to consider in this endeavor:\(^{171}\)

- Social circumstances
- Patient’s social needs
- Patient’s clinical needs

**Social stressors**

While social interactions have its benefits, a variety of psychosocial stressors can trigger the recurrence of symptoms in a mentally susceptible person. These stressors are listed below:\(^{170}\)

1. Stressful life events
   - Interpersonal loss
   - Long periods of separation (\textit{i.e.,} military deployment, job assignment)

2. Socio-cultural stress
   - Poverty
   - Homelessness
   - Disrupted social network
   - Distressful emotional climate (\textit{i.e.,} hostile coworkers and fellow members of a social group).
The knowledge and awareness of the listed stressors can help in its identification and prevention. In a social environment, psychosocial interventions include preventing the onset or accumulation of stressors and teaching the patient coping mechanisms to combat them.

As discussed throughout the course, psychosocial treatments overlap with some of the other psychiatric interventions, such as:

- family interventions
- supported employment
- assertive community treatment
- social skills training
- cognitive behaviorally oriented psychotherapy

Since family interventions, supported employment, assertive community treatment and cognitive behavioral therapy have been discussed already; the primary focus of this section will be to discuss social skills training.

**Social skills training**

The fundamental principle of social skills training is that intricate interpersonal skills involve the smooth assimilation of a blend of simple behaviors and mannerisms.

**Simple behaviors with examples**
<table>
<thead>
<tr>
<th>Simple behaviors</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannerisms</td>
<td>Facial expression, eye contact</td>
</tr>
<tr>
<td>Paralinguistic features</td>
<td>Voice loudness and affect</td>
</tr>
<tr>
<td>Verbal behavior</td>
<td>Appropriate language</td>
</tr>
<tr>
<td>Interactive balance</td>
<td>Response latency, time spent talking</td>
</tr>
</tbody>
</table>

These specific skills can be systematically taught, and, through the process of shaping (i.e., rewarding successive approximations toward the target behavior), complex behavioral repertoires can be acquired.

Social skills training is conducted in groups with a universal format that includes the following steps:  

1. Rationale conception for learning the skill  
2. Grouping and discussion of each skill  
3. Skill demonstration using role play  
4. Client engagement and participation in the role play  
5. Acquisition of positive feedbacks from group members  
6. Appreciation of well executed efforts  
7. Provision of constructive criticisms of a subpar execution of a skill
8. Client engagement in another role play

9. Designation of homework to create opportunities for external practice

Learning a particular social skill takes time, usually several sessions with one scenario at a time. In later group sessions, role-plays can focus on actual situations recently experienced by patients or scenarios that are most likely to occur in the future.

**Benefits of social skills training**

Multiple studies have pointed out that effectiveness of social skills training to patients with mental illness. Moreover, the same studies have pointed out that these effects were maintained over time even in the absence of sustained training. These benefits translate to better quality of life but not necessarily clinical recovery such as reduction of symptom relapses or re-institutionalization.

**Social networking**

Social networking among the general population is a popular means of communication and social interaction. The majority of young adults use some sort of social networking site.
A survey of persons with psychological issues, spearheaded by Gowen, et al., of the Research and Training Center at Portland State University in Oregon, found that Facebook and Twitter are helpful in activity planning and provide opportunities for social interaction. Moreover, the survey also that majority of the respondents searched for other mentally ill individuals in order to extend help to them. Moreover, these sites provide patients the means to maintain long distance relationships, thus strengthen existing bonds. The results of the survey present risks too. Since individuals and not qualified professionals run these sites, the most blatant risk to patients is exposure to wrong information. Therapists need to educate their patients on the safe and useful sites to visit and the ones to avoid. The second disadvantage to social networking is the rampant cyber-bullying and uncensored violent content that may result in exacerbated feelings of isolation, depression, and anxiety.

With social skills in place, mentally ill individuals can learn to cope with their illness and prevent social exclusion or isolation. Social exclusion violates the values of human social equality and undermines social solidarity. Moreover, the psychosocial stressors mentioned above are both a cause and consequence of social exclusion.

**Risk of violence**
According to the “Fact sheets about mental illness and violence” produced by the University of Washington’s School of Social Work, violence is the least of all worries when it comes to interacting with mentally ill individuals.  

_Fact 1: The vast majority of people with mental illness are not violent._
"Although studies suggest a link between mental illnesses and violence, the contribution of people with mental illnesses to overall rates of violence is small, and further, the magnitude of the relationship is greatly exaggerated in the minds of the general population”.  
_Institute of Medicine_
"...the vast majority of people who are violent do not suffer from mental illnesses.”  
_American Psychiatric Association_

_Fact 2: The public is misinformed about the link between mental illness and violence._

A longitudinal study of American’s attitudes on mental health between 1950 and 1996 found, “the proportion of Americans who describe mental illness in terms consistent with violent or dangerous behavior nearly doubled.” Also, the vast majority of Americans believe that persons with mental illnesses pose a threat for violence towards others and themselves. 

_Fact 3: Inaccurate beliefs about mental illness and violence lead to widespread stigma and discrimination:_
The effects of stigma and discrimination are profound. The President’s New Freedom Commission on Mental Health found that, “Stigma leads others to avoid living, socializing, or working with, renting to, or employing people with mental disorders - especially severe disorders, such as schizophrenia. It leads to low self-esteem, isolation, and hopelessness. It deters the public from seeking and wanting to pay for care. Responding to stigma, people with mental health problems internalize public attitudes and become so embarrassed or ashamed that they often conceal symptoms and fail to seek treatment.”

New Freedom Commission

Fact 4: The link between mental illness and violence is promoted by the entertainment and news media. "Characters in prime time television portrayed as having a mental illness are depicted as the most dangerous of all demographic groups: 60 percent were shown to be involved in crime or violence."  

Mental Health America

Summary

Mental disorders, despite various attempts at understanding them throughout human history, remain a poorly defined group of illnesses. There is a large area of research that has not yet been uncovered. As a result, experts in the field, psychiatrists, therapists, clinicians and other healthcare professionals, are left with the daunting task of relying on what medical literature and training has taught them about
symptomatic control. Since the root causes are unknown, trying to treat symptoms of mental illness is very challenging. Three aspects of treatment predominantly guide mental health professionals: alleviate the symptoms and establish some degree of normalcy, protect the safety of the patient and the public, and improve the patient's overall quality of life.

Various interventions, both clinical and nonclinical, have been introduced in the last fifty years. Freud’s groundbreaking research in psychology put forward the use of somatic treatments in mental illness. The acceptance of somatic treatment introduced to the world the use of psychotropic medications to correct biochemical disturbances in the brain, which was Freud’s proposed pathology of mental illness. Research in recent decades brought to light many of the adverse effects of these older medications, prompting pharmaceutical companies to develop novel therapeutic agents that are safer, though not necessarily more efficacious. There has been a growing trend of “medicalization” of almost, if not all, known mental disturbances. The DSM-5 added many new criteria to guide clinicians to diagnose abnormal and normal human psychological responses.

Psychopharmacologic interventions have undoubtedly made the lives improve of those who are mentally ill. The presence of individuals with mental illness in society is not just tolerated but increasingly accepted. However, like many medical advances, the rise in public awareness of mental illness is also associated with several pitfalls. Namely, studies
have failed to demonstrate the efficacy of medical treatments as being superior to placebos, ethical issues regarding specific treatments, and their propensity to cause fatal adverse effects (i.e., suicide tendencies and cerebrovascular events).

Currently, mental illness is dealt with by numerous measures, not just by psychopharmacological therapy. Counseling, family interventions, group therapy, social training, and government and nonprofit organization sponsored programs have made mental illness a very manageable lifelong disorder. These measures combined with federal and state legislations have allowed the mentally ill to blend into society, function in a social environment, and to contribute meaningfully as part of the collective whole to its overall endeavors.

References

The reference section of in-text citations include published works intended as helpful material for additional reading.


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