In choosing a topic on which to conduct our senior research as members of the LaGrange College Department of Chemistry, we established a set of criteria against which each possible topic was evaluated. First, we sought topics on which we had little to no prior knowledge so that our time spent engaged in research would be both interesting and enlightening. Secondly, we looked for topics which would effectively relate clinical applications to our undergraduate course of study and that would, therefore, be beneficial as we leave the department and pursue careers in medicine. We also sought topics on which we could provide detailed information that would be relevant not only to the trained scientist, but to the casual reader as well.

Through our academic endeavors as undergraduate students we have gained a broad background in the fields of psychology and biochemistry, both of which place some degree of emphasis on chemical processes in the brain. Having been exposed only to the basics of such processes in these courses, we developed a keen interest in the topic of neurochemistry. Though this topic is in itself extremely complex and continually developing, the existing links between serotonin and several neurological disorders provided a wide range of chemical and clinical applications into which we could delve. Furthermore, with serotonin being so closely associated with common neurological and psychological disorders, a body of work summarizing various serotonergic processes would, we feel, be beneficial to a broad spectrum of readers.

Synthesis of serotonin – also called 5-hydroxytryptamine – begins with the conversion of the amino acid L-tryptophan to 5-hydroxytryptophan by the enzyme tryptophan-5-hydroxylase.\(^1\) L-tryptophan is one of the nine essential amino acids, meaning that it is not synthesized in the body and must be obtained from external sources through the diet. The daily minimum requirement, 200 mg, of L-tryptophan can be satisfied by taking in adequate amounts of protein rich foods (such as red meat, fish, dairy products, and poultry).\(^2\) Once taken into the body, tryptophan can undergo conversion to either niacin or serotonin, with step one of the conversion to serotonin.\(^3\)

Tryptophan-5-hydroxylase – the enzyme involved in the first reaction in the synthesis of serotonin – can be inhibited by a variety of chemical compounds,

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**Neurochemistry: Serotonin and Clinical Disorders**

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such as p-chlorophenylanine, fenfluramine, p-chloroamphetamine and others.¹ For example, p-chlorophenylalanine is a selective and irreversible inhibitor of this enzyme.⁴ In a study published in General Pharmacology, the effects of p-chlorophenylalanine on serotonin were observed in rats who had been trained to discriminate between interoceptive stimuli produced by a variety of drugs, including amphetamine, fenfluramine and 3-4, methylenedioxyamphetamine (or ecstasy). Following the discrimination training, a group of the rats were pre-treated with p-chlorophenylalanine while another group was simply given saline before being tested on the discriminative tasks. Results showed that the p-chlorophenylalanine had no effect on their ability to discriminate between drugs that produced stimuli related to dopamine activity, such as amphetamine and cathinone. However, the results also showed that p-chlorophenylalanine significantly decreased their ability to discriminate between the serotonergic drugs, such as ecstasy, fenfluramine, and N-ethyl-3,4-methylenedioxyamphetamine. Those pre-treated with saline showed no decrease in discriminative ability between any of the drugs. After a period of 9-12 days following treatment with p-chlorophenylalanine, the normal brain serotonin levels were restored and the ability to discriminate between the serotonergic drugs returned. Analysis of these results led those who worked on this study to conclude that p-chlorophenylalanine “pretreatment lowers brain 5-HT and, in turn, significantly decreases the ability of rats to discriminate centrally active drugs whose interoceptive cueing stimuli are mediated by 5-HT neurons.”⁵

Following the initial conversion of tryptophan to 5-hydroxytryptophan, an aromatic amino acid decarboxylase converts 5-hydroxytryptophan to 5-hydroxytryptamine, or serotonin.³

Like tryptophan hydroxylase, aromatic amino acid decarboxylases can be inhibited by a variety of compounds. For example, benserazide is a central and peripheral decarboxylase inhibitor and carbidopa is a peripheral decarboxylase inhibitor.⁶ Other compounds which inhibit this enzyme include brocresine, difluoromethyldopa and monofluoromethyldopa.¹

Once the serotonin is synthesized it must then be stored for later use. While the greatest concentration of serotonin in the body is found in the enterochromaffin cells of the GI tract, we will focus on the storage and action of serotonin in the central nervous system.⁷ Like other neurotransmitters, serotonin is stored by neurons in small synaptic vesicles from which it can be quickly and easily released. A study published by the Journal of Neuroscience proposed that such storage of serotonin in central and peripheral serotonergic neurons involved the formation of a complex between serotonin-binding protein (SBP) and the serotonin itself.⁸
To test this hypothesis, a labeled form of serotonin, [3H]5-HT, was used as a probe. A group of rats were perfused intraventricularly with [3H]5-HT and strips of rabbit enteric nervous system tissue were incubated with [3H]5-HT in the presence of desipramine. Both sets of tissues were homogenized in order to disrupt the synaptic vesicles and release any [3H]5-HT/SBP complexes that had been formed. Following the filtration of the resulting supernatant on Sephadex G-50, the obtained volume of [3H]5-HT complex was then subjected to a procedure known as SDS-PAGE, or sodium dodecyl sulfate-polyacrylamide gel electrophoresis.

Results of the electrophoresis procedure showed that the [3H]5-HT/SBP complexes migrated on the gel with measured molecular weights of 45kDa and 56kDa. The results also showed that the 45kDa complex was predominant when the complex was formed in vivo, while the 56kDa complex was predominant when the complex was formed with extracted SBP. After establishing that the newly taken up serotonin preferentially labeled the 45kDa SBP, the supply of endogenous, or naturally synthesized, serotonin was depleted in the animal test subjects by placing them on a tryptophan-deficient diet. This resulted in an increase in the amount of exogenous, or artificially introduced, serotonin bound to SBP in vivo. By illustrating that the endogenous serotonin was competing with the labeled probe for binding sites on the protein, the researchers were able to conclude that endogenous serotonin is normally bound to SBP. Such binding, as suggested by this study, may be important in reducing the osmotic pressure that would result if serotonin were free in the synaptic vesicle solution.

Following storage in synaptic vesicles as a complex with SBP and subsequent transport to the axon terminals, or terminal buttons, of the neuron, the serotonin is ready to be put to use. For it to be used it must first be released from the presynaptic neuron into the synaptic cleft where it can migrate to receptor sites on the postsynaptic neuron. This release is caused by the direct receipt of a level of stimulation beyond the threshold of excitation at a particular neuron or by the indirect receipt of such stimulation through spatial or temporal summative processes. Though this stimulation may be received at several points along the neuron, for the sake of simplicity we will say that this stimulation is received by the postsynaptic neuron at its dendrites.

Prior to this stimulation the neuron exists with a charge difference of approximately -70 mV between the inside and outside of the neuron by maintaining both an electrical and a chemical gradient across its membrane. This difference in charge is known as the resting potential. The gradients responsible for maintaining the resting potential are themselves maintained by the combination of the membrane’s selective permeability and its sodium-potassium pumps.
When at rest the inside of the neuron is negative relative to the outside of the neuron. This is so because when the neuron is at rest the sodium channels in the selectively permeable membrane are closed which prevents the influx of the positively charged sodium ions. Also, the potassium channels are very nearly closed when the neuron is at rest and since opposing forces in the forms of an electrical gradient pulling the potassium into the neuron and a chemical gradient driving it out are acting on the potassium (which is also positively charged), no net charge difference can be directly attributed to the potassium despite its high concentration within the resting cell relative to its concentration outside of the cell. Therefore, the selective permeability of the membrane is key in the maintenance of the electrical and chemical gradients created by the action of the sodium-potassium pumps which will be discussed later.9

When a sufficient stimulus - one at or above the threshold of excitation - reaches the neuron, the neuron becomes depolarized and the permeability of the membrane increases as the voltage-activated sodium channels open. Sodium ions then rush into the cell and further depolarize the neuron until such time that the sodium channels snap shut. The action potential, or period of rapid depolarization followed by slight hyper polarization of the neuron, is conducted along the length of myelinated axons through a process called salutatory conduction. On such axons, the myelin exists in individual segments along the axon and the gaps between these segments are called nodes of Ranvier. When an action potential reaches the axon hillock it is transmitted along the axon until it reaches the first node. The segment of axon covered by the myelin is practically impermeable to sodium ions so the action potential cannot regenerate along these sections of the membrane. Instead, sodium ions enter at the nodes11 and diffuse in both directions, with reverse conduction being prevented by the resistance of previous nodes to production of further action potentials for a period of time called the refractory period.9

The influx of positively charged sodium ions into the axon at the node of Ranvier causes the already present positive ions to be repelled further down the axon to the next node. When these ions reach the next node along the axon they cause the voltage-activated sodium channels along the node to open and thus allow the action potential to continue being conducted. The benefit of such conduction is that the flow of ions within the axon is much faster than having to continually regenerate the action potential. Plus, it saves energy by reducing the amount of sodium that must be pumped out by the sodium-potassium pump to restore the gradients. Therefore, conduction along myelinated axons occurs much faster and more efficiently than along unmeditated axons.9

Upon reaching the axon terminals, the action potential activates the
voltage-gated calcium channels in the terminals which allows calcium ions to flow into the cell. The influx of calcium stimulates the excretion of neurotransmitter molecules from the presynaptic terminals into the synaptic cleft through exocytosis\(^9\) - a process which involves the fusing of synaptic vesicles with the presynaptic membrane. \(^{12}\)

There appear to be several proteins which are involved in the process of neurotransmitter release, each of which seems to have a specialized function. When the calcium ions rush into the cell they are thought to be detected by the protein synaptotagmin, which possesses a calcium binding domain. Once this protein detects the calcium influx it is thought to initiate the vesicle fusion process. \(^{13}\)

Among the other proteins involved in this process are Rab3a and Rab3b, which are thought to be actively involved in guiding the vesicles to “active zones” where they can dock with the presynaptic membrane. Once the vesicles reach the active zone two proteins seem to work together, with synaptobrevin (a vesicle membrane protein) being involved in the recognition of the presynaptic membrane and syntaxin (a membrane protein) being involved in the recognition of the vesicle membrane. Following the mutual recognition of both membranes the SNAP-25 protein snares the presynaptic membrane and the four proteins in the synapsin group (which includes synapsin I and synapsin II) seem to play a role in holding docked vesicles in place during the fusion process. Other proteins, including physophilin, N-ethylmaleimide sensitive fusion protein (NSF) and soluble NSF attachment protein (SNAP), then seem to create a fusion pore through which the neurotransmitters are released. \(^{13}\)

After the action potential peaks, the resting potential is restored by the flow of potassium along its concentration gradient out of the cell since the potassium channels remain wide open and gradually return to their original state as the resting potential is restored. In fact, the outflow of potassium can be so great that the cell experiences a temporary hyperpolarization. By the end of the action potential the cell has been restored to its original resting state, with the only difference being that at this point the cell has slightly more sodium ions and slightly less potassium ions than before. By pumping out three sodium ions for every two potassium ions it pumps in, the sodium-potassium pump eventually restores the original distribution of ions. \(^{9}\)

Once the neurotransmitters are released into the synaptic cleft they travel the width of the cleft and interact with receptors on the postsynaptic membrane. The neurotransmitters released by the presynaptic cell may also interact in some cases with special receptors – known as autoreceptors – on the presynaptic membrane. Such interaction with presynaptic receptors is often used
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as a negative feedback mechanism, inhibiting further release of the neurotransmitter once enough has been supplied. In fact, a study in the most recent publication of *Proceedings of the National Academy of Sciences of the United States of America* shows that serotonin binding to presynaptic G-protein coupled autoreceptors exerts such inhibitory effects by altering the synaptic vesicle fusion properties.

Results of this study indicated that the interaction between serotonin and the presynaptic G-protein coupled autoreceptors caused vesicles to transiently or partially fuse with the presynaptic membrane. Fluorescence measurements taken after such inhibition had occurred indicated that the synaptic vesicles withdrew from the membrane with little or no loss of the labeled lipid. The altered fusion properties are the result of the interaction between the α-subunits of the G-protein and the C-terminal of SNAP-25 protein. By essentially blocking the vesicle docking site, these G-protein subunits severely limit the degree to which the vesicles may fuse with the membrane. These results were further supported by the fact that injection of a G-protein α-scavenger prevents such inhibition. Inhibition was also prevented by injection of botulinum toxin A, which cleaves most of the C-terminal residues of SNAP-25.

Interaction between a neurotransmitter molecule and a receptor site can take place in two general ways: ionotropically or metabotropically. When a neurotransmitter exerts ionotropic effects on a receptor, it binds to the receptor site and quickly opens a channel for some type of ion to enter the postsynaptic cell through. It may also cause a channel to close, obstructing the flow of ions into the postsynaptic cell. For example, when acetylcholine attaches to a nicotinic receptor it causes a rotation in the receptor protein which opens a channel through which sodium can pass. Effects brought about in this manner are typically very rapid and short-lived, making them “useful for conveying information about visual and auditory stimulation, muscle movements, and other rapidly changing events.”

The other way in which neurotransmitters can interact with postsynaptic receptors involves the action of a secondary messenger. When the interaction of a neurotransmitter and a receptor exerts metabotropic effects, the neurotransmitter binds to a specific recognition site (which is typically located on the extracellular portion of the receptor but may also be located within its hydrophobic core) of a G-protein-coupled receptor, also called a 7-transmembrane segment protein. Binding of the neurotransmitter to the receptor site induces a conformational change in the receptor that activates a G-protein (or GTP-binding protein) on the inside of the postsynaptic cell. The newly activated G-protein then increases the concentration of a secondary messenger, such as cyclic adenosine...
monophosphate or cyclic guanosine monophosphate, inside the postsynaptic cell. These secondary messengers are then able to communicate with areas within the cell.\textsuperscript{16}

Serotonin interacts with a number of receptors and, depending on the specific receptor subtype, can exert either ionotropic or metabotropic effects. For example, 5-HT\textsubscript{1A} receptors are G-protein coupled receptors and they are found at high densities within the hippocampus, septum, amygdale, and cortical limbic areas of the brain. The main therapeutic potential of these receptors has been related to the treatment of anxiety and depression, as many 5-HT\textsubscript{1A} receptor ligands with agonist activity (which is activity that enhances or mimics the effects of serotonin\textsuperscript{17}) seem to possess anti-anxiety and antidepressant properties. The anti-anxiety actions of these agonists seem to primarily involve presynaptic autoreceptors which causes a reduction in the release of serotonin terminal areas. On the other hand, the antidepressant actions of such agonists involve postsynaptic receptors and the enhancement of the effects of the serotonin.\textsuperscript{18}

5-HT\textsubscript{1A} antagonists may also possess clinically relative properties. For example, by blocking the 5-HT\textsubscript{1A} autoreceptors with a silent 5-HT\textsubscript{1A} antagonist the postsynaptic concentration of serotonin would increase. Such an increase in postsynaptic concentration could lead to the activation of other receptor subtypes. Perhaps, then, “pretreatment of patients with agents possessing silent and selective 5-HT\textsubscript{1A} antagonist character may accelerate the onset of effects of selective serotonin reuptake inhibitors (SSRIs) and enhance their clinical efficacy.”\textsuperscript{18}

Other 5-HT\textsubscript{1} subclasses include 5-HT\textsubscript{1B}, 5-HT\textsubscript{1D}, 5-HT\textsubscript{1E}, 5-HT\textsubscript{1F}, 5-HT\textsubscript{1P}, and 5-HT\textsubscript{1S}. Of these remaining subclasses, 5-HT\textsubscript{1D} and 5-HT\textsubscript{1F} appear to be the most clinically significant. With regard to the 5-HT\textsubscript{1D} subclass (which includes the sub-subclasses 5-HT\textsubscript{1D?} and 5-HT\textsubscript{1D?}), a drug known as sumatriptan (which is used clinically in the treatment of migraines) is an effective agonist. The link between the agonistic effects of sumatriptan on 5-HT\textsubscript{1D} receptors and its effectiveness in the treatment of migraines suggests that these receptors may play a role in this disorder. However, sumatriptan binds equally well with both of the 5-HT\textsubscript{1D} sub-subclasses as well as with 5-HT\textsubscript{1F}. Therefore, it is not known which of these receptors is actually involved in migraines. Since the ? sub-subclass seems to be involved in neurogenic inflammation and the ? sub-subclass seems to be involved in vasoconstriction, it has been suggested that these two receptors be targeted in the development of new migraine treatments. Binding of sumatriptan also occurs at 5-HT\textsubscript{1F} receptor sites, a sub-subclass of receptors that is expressed in both neural and vascular tissue, which suggests a link for these receptors to migraines as well.\textsuperscript{18}

The 5-HT\textsubscript{2} subclass of serotonin receptors, which includes the 5-HT\textsubscript{2A}, 5-HT\textsubscript{2B}, and 5-HT\textsubscript{2C} sub-subclasses, has also been shown to be clinical-
ly relevant. $5\text{-HT}_{2A}$ receptors act metabotropically and are coupled to the phosphoinositol secondary messenger system. They are found throughout the brain in varying densities, though they are found in high densities within the neocortex. These receptors are involved in several normal physiological functions, including appetite control, thermoregulation, sleep, cardiovascular function and muscle contraction. Interestingly, several antipsychotic medications seem to bind with high affinity to these receptors, suggesting that the $5\text{-HT}_{2A}$ receptors may play a role in several psychological disorders. For example, many antagonists of these receptors bind also to dopamine receptors and the combined effect has been shown to be helpful in the treatment of certain types of schizophrenia. Other $5\text{-HT}_{2A}$ antagonists have also been used in the treatment of anxiety.\(^{18}\)

$5\text{-HT}_{2C}$ receptors possess a high sequence homology, particularly within the seven transmembrane segments, with the $5\text{-HT}_{2A}$ receptors. Consequently, many of the agents that bind to $5\text{-HT}_{2A}$ receptors also bind with similar affinities to the $5\text{-HT}_{2C}$ receptors. Therefore, many of the pharmacological effects exerted by the $5\text{-HT}_{2A}$ receptors are also exerted by the $5\text{-HT}_{2C}$ receptors. With regard to the $5\text{-HT}_{2B}$ receptors, little is known and studies are still being done to develop selective agents for this sub-subclass.\(^{18}\)

$5\text{-HT}_{3}$ receptors are a unique subclass among the family of serotonin receptors. Rather than acting metabotropically, they exert ionotropic effects by acting as nonselective sodium/potassium ion channel receptors.\(^{18}\) These receptors are found in both the peripheral and central nervous systems, particularly in the frontal cortex\(^{19}\), the hippocampus\(^{19}\), the entorhinal cortex\(^{20}\), and the postrema.\(^{21}\)

$5\text{-HT}_{3}$ antagonists have been used clinically in the treatment of chemotherapy-induced or radiation-induced nausea and vomiting. Studies have also suggested that such antagonists may be effective at treating migraines, anxiety, depression, and dementia. Perhaps the most interesting clinical implication of $5\text{-HT}_{3}$ antagonists is in their potential ability to treat drug withdrawal and its associated symptoms (which, depending on the nature of the abused drug, often involves migraine-like headaches). While there are certainly other drugs which treat withdrawal, $5\text{-HT}_{3}$ antagonists are particularly attractive because they seem to lack to the side effects characteristic of those other treatments.\(^{18}\)

The potential for use of $5\text{-HT}_{3}$ antagonists in the treatment of withdrawal from highly abused drugs such as alcohol, nicotine (which is excluded in the latest edition of the DSM from the list of drugs that can be abused but remains on the list of drugs which can cause dependence), cocaine and amphetamines, stems from their ability to function as anxiolytics. $5\text{-HT}_{3}$ antagonists can also aid in curbing the effects of various drugs by lowering the level of dopamine in the mesolimbic pathways (a major component of the neuronal circuitry

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Citations
involved in drug abuse) which increases upon activation of these receptors by 5-HT$_3$ agonist drugs.$^{22}$ A study published in the journal *Biochemistry* confirmed that both nicotine and cocaine bind to 5-HT$_3$ receptors and thereby exert agonistic effects at these receptors.$^{23}$

Recent development of 5-HT$_4$ selective agents has led to studies which have proposed clinically relevant roles for 5-HT$_4$ receptors. They are found at a high density in the nucleus accumbens$^{24}$ which suggests a link to the brain’s reward system and may influence self-administration behavior.$^{18}$ In a famous study done by James Olds and Peter Milner, rats were placed in Skinner boxes where they could “produce self-stimulation of the brain by pressing a lever for electrical brain stimulation as a reinforcer.”$^9$ They found that rats would work very hard to stimulate certain areas of the brain, sometimes to the point of exhaustion. Later studies showed that brain stimulation must stimulate dopamine release to be reinforcing, and the nucleus accumbens happens to be an area which is rich in both dopamine and 5-HT$_4$ receptors.$^9$

Naturally, then, it has been suggested that 5-HT$_4$ antagonists may be useful in the treatment of dopamine-related disorders. It has also been suggested that these receptors may play a part in memory and learning due to their decreased presence in the brains of people with Alzheimer’s disease. It follows that 5-HT$_4$ agonists may help restore cognitive deficits, but use of such agonists may result in unwanted cardiovascular side effects.$^{18}$

Various antipsychotics, particularly atypical antipsychotics, and antidepressants bind with high affinity to 5-HT$_6$ receptors which suggests a connection between these receptors and certain psychiatric disorders. Antipsychotics such as clozapine and olanzapine – those which produce the fewest extrapyramidal side effects (such as pseudoparkinsonism and tardive dyskinesia)$^{25}$ - bind with high affinity to 5-HT$_6$ receptors. This high affinity for these receptors may help differentiate between typical and certain atypical anti-psychotics. Also, prevention 5-HT$_6$ receptor expression in rats has been shown to increase cholinergic function. Therefore, these receptors may play a role in controlling “cholinergic neurotransmission.”$^{18}$

Little is known about the other 5-HT receptor sub-classes, however 5-HT$_7$ receptors seem to play a role in the regulation of circadian rhythms. Accordingly, 5-HT$_7$ selective agents may be useful in the treatment of jet-lag or “sleep disorders of a circadian nature.”$^{18}$

Naturally, with the actions of serotonin being seemingly involved in a wide range of behavioral and physiological processes, some common disorders (such as migraine, schizophrenia, and depression) that have their roots in altered serotonin activity typically require some type of treatment. Often times this
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treatment is medical, however many psychological forms of treatment have also been proven effective. For the purposes of this paper we will focus on medical treatments for such disorders, many of which a becoming progressively more effective. In order to achieve further advancements, individual’s must understand that “medical science is entering a golden age, but the keys to longer, better lives are not all hidden in the lab. The biggest challenge we face is to translate knowledge into action.”

Let us begin our exploration of such medical treatments by examining one of the most common mental disorders – depression. The article “Sadness, Gladness—and Serotonin” defines depression from a medical viewpoint as, “a syndrome, or group of concurrent symptoms, that manifests itself in varying pathological forms.” There are nine basic symptoms associated with depression; however, each clinically depressed person exhibits different ones in varying degrees. These nine symptoms are: “depressed mood, problems experiencing pleasure, low energy, disrupted sleep, diminished or increased appetite, mental or physical agitation or slowing, feelings of worthlessness or guilt, difficulty concentrating, and suicidality.” In order for a patient to be diagnosed with depression, they must exhibit extreme distress and five of the nine symptoms over a period of at least two weeks. Once a patient is diagnosed, they can be properly treated for the disorder.

The most common and effective treatment for depression is antidepressants, a class of drugs which includes tricyclics, MAO-I's, SSRIs and various atypical antidepressants. “Ever since the first antidepressants were developed in the 1950’s—these were the monoamine-oxidase inhibitors, or MAOI’s—it has been known that the neurotransmitter serotonin, like another neurotransmitter, norepinephrine, profoundly affects mood.” While the molecular transactions are vastly complex compared to the basic figures, research has proven a link between low levels of serotonin and depression as well as high levels of serotonin with well being.

Each type of antidepressant (with the exception of atypical antidepressants) has a specific mechanism of action. For example, the tricyclics block reuptake of serotonin and catecholamine neurotransmitters. This result of this blockage is a prolonged length of stay for the neurotransmitters in the synaptic cleft which allows for more stimulation of the postsynaptic cell. Of the antidepressants, this class produces the most side effects and is used less often as a result. Examples of tricyclic antidepressants include imipramine HCL, amitriptyline HCL, and doxepin HCL. SSRI’s – Selective Serotonin Reuptake Inhibitors - have a similar mechanism of action, though the block reuptake of only serotonin and not the catecholamines. Examples of SSRIs include fluoxetine HCL (trade name: Prozac) and sertraline (trade name: Zoloft).
MAO-Is use of an inherently different mechanism of action. Rather than blocking the reuptake of neurotransmitters, MAO-I’s inhibit the enzyme responsible for metabolizing the catecholamines and serotonin: monoamine oxidase (which exists in two classes, A and B). By preventing their degradation, MAO-Is allow these neurotransmitters to remain in the cleft longer and continue stimulating the postsynaptic cell. They also can speed up release of these neurotransmitters by eliminating the need for the presynaptic cell to continually synthesize them. Commonly used MAO-Is include phenelzine (trade name: Nardil) and selegiline (a MAO-B inhibitor). Recently, selegiline was approved by the FDA to be administered by a skin patch to treat depression.

Also, atypical antidepressants including venlafaxine (trade name: Effexor) and buproprion (trade name: Wellbutrin) are used to treat depression. However, their mechanisms of action vary greatly and the way in which they exert antidepressant effects is largely unknown. Hence, they are called atypical.

Though antidepressants have been proven quite effective at treating depressive symptoms, treatment with antidepressant drugs alone does not necessarily prevent the recurrent nature of the episodes. Often, drug therapies must be combined with other forms of therapy to prevent relapse. Other options available to patients suffering from depression, according to the article “Treatment and Prevention of Depression,” include electroconvulsive therapy, interpersonal therapy, and cognitive behavior therapy. Electroconvulsive therapy is most effective for individual’s experiencing the most severe cases of depression; however, there are many concerns surrounding the deleterious effects on cognition and memory. Interpersonal psychotherapy (IPT) provides delayed effects in improving interpersonal and social skills. This treatment typically reduces acute distress and aids in the prevention of relapse. Even though IPT has proven great success, it is not available in all clinics or readily accessible for all patients.

Finally, cognitive behavior therapy (CBT) can be used to treat severe cases of depression with experienced doctors. This treatment is not only useful in reducing the chance of relapse; it may also be used preventatively with patients at high risk for developing depression. While many breakthroughs have been made over the past few decades, much is left to be discovered and revolutionized in the treatment of depression.

Another common disorder associated with serotonin activity is migraine disorder. By definition, migraines are severe recurring headaches incorporated with sharp pain, sensitivity to light and noise, nausea, and vomiting. Robin L. Brey stresses that “the exact cause of migraine is unknown, but may be related to low brain levels of […] serotonin. During an attack, changes in brain activity may cause blood vessels and nerves around the brain to become inflamed.”
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in depression, patients suffering from migraines may have varying symptoms, but the most common include: moderate to severe headaches lasting 4 to 72 hours, throbbing pain-typically on one side, increased pain following movement, nausea or vomiting, and sensitivity to light, odor, or sound. In order to be clinically diagnosed as suffering from migraines, individuals must provide details of their headaches to their doctor and undergo a neurological examination.

Upon diagnosis, there are several treatments proven to ease and often prevent migraines. The most common way to treat migraines is with medication. The medications can be classified into three groups: “nonprescription (over-the-counter) medications, such as aspirin, ibuprofen, or acetaminophen combined with aspirin and caffeine, prescription nonsteroidal anti-inflammatory drugs and analgesics, and specific drugs used to stop migraine attacks such as triptans and ergot alkaloids.”

Individuals suffering from migraines on a daily basis can take “antidepressants, beta-blockers, calcium channel blockers, medicines also used to treat epilepsy, and alternative treatments, such as vitamin B2, magnesium, and feverfew,”. Some patients can be treated on a preventative level without medications by using techniques which are focused on controlling migraine triggers such as diet, sleep, stress, and environmental factors.

“Research has shown that some cognitive and behavioral treatments can help prevent migraine(s): relaxation training, thermal biofeedback with relaxation training, electromyographic biofeedback, and cognitive-behavioral therapy (also called stress management training).”

The combination of all treatments still leaves a lot of room for major breakthroughs in migraine related research. Unfortunately, one out of four people in U.S. households will continue to suffer chronic migraines and three out of four of these individuals will be female.

Research has also implicated serotonin in the development of schizophrenia. Schizophrenia is defined by Fountain House as the most disabling and chronic mental disorder, usually developing in an individual’s late teens or early twenties. Typical symptoms include bizarre thought patterns, hallucinations, and delusions - “These are the positive symptoms that typically lead to psychiatric treatment and hospitalization. Often neglected are the ‘negative’ symptoms — social isolation and withdrawal, blunting of emotional expressiveness, poor communication skills and decreased motivation and self-care.” Treatment of the positive and negative symptoms has expanded through extensive research and the understanding of the effects caused by serotonin (5-Hydroxytryptamine, 5-HT).

A serotonin (5-HT) hypothesis of schizophrenia was developed through research of the “interactions between the hallucinogenic drug LSD (D-lysergic acid diethylamide) and 5-HT in peripheral systems.” Research reported by
Mark J. Millan stressed the reproducible elevation in 5-HT1A receptor density in studies of schizophrenic brain. This particular increase is “specific to schizophrenia because depressed patients revealed a diminution in 5-HT1A sites.” While the underlying mechanism of this increase is not yet understood, post-transcriptional processes are deemed to be involved since mRNA encoding 5-HT1A receptor levels are not modified. “A final, intriguing finding was an elevation in levels of 5-HT1A receptors in the cerebral vermis of schizophrenic patients, a structure implicated in sensory-attentional processes and motor function.”

Overall, positive symptoms may be improved by “selective activation (or blockade) of 5-HT1A receptors” and negative symptoms such as cognition or mood may be improved by activation of “input by 5-HT1A autoreceptor agonists.” In regards to specific treatment of schizophrenia, the main focus is on antipsychotic drugs.

“Antipsychotic drugs provide the most effective schizophrenia treatment to patients with predominately positive symptoms.” These drugs provide a varying degree of relief to schizophrenic patients and serve to block certain dopamine and serotonin receptors in the brain. Traditional first generation antipsychotic drugs prescribed to patients include chlorproazine, loxapine and prolixin, all of which belong to phenothiazine class of antipsychotic drugs and act primarily as antagonists of the dopamine D2 receptors. These may work well because schizophrenic patients have nearly twice as many D2 receptors as normal people.

To establish the number of D2 receptors, a radioactively labeled drug (IBZM) was used to occupy all unoccupied D2 receptors and then a count was made. Following this count, dopamine synthesis was inhibited by administering a drug called AMPT. With dopamine synthesis blocked, the second round of IBZM was able to label all D2 receptors and a second count was made. By subtracting the first count from the second count, a total number of D2 receptors was obtained.

The butyrophenone drugs constitute another class of first generation antipsychotic drugs. This class includes the common drugs haloperidol (trade name: Haldol) and droperidol (trade name: Inapsine). A major drawback to treatment with both classes of first generation antipsychotics is that they seem only to alleviate the positive symptoms of schizophrenia.

However, treatments have evolved with the emergence of “atypical” (or 2nd generation) antipsychotic drugs which seem to treat both the positive and negative symptoms. These drugs act by blocking dopamine receptors as well as some serotonin receptors, particularly 5-HT1A and 5-HT2A receptors. By treating schizophrenia with 2nd generation antipsychotics that have action at serotonin receptors, we can eliminate certain mood-related symptoms associated with serotonin, thus explaining their ability to relieve negative symptoms.
A Note on Research Ethics by Nicole Gonzalez

Jon Merrills defines ethics as “the systematic study of what is right and good with respect to conduct and character.” In the sense that values are what we believe, our attitude, actions, and judgement must be driven by those values. For health care professionals, such values are codified in the Hippocratic Oath of doctors. “There are two main elements in the Hippocratic Oath: Inward-looking rules about respecting teachers, colleagues, etc. Generalized rules to care for the patient, which can be criticized as being little more than definitions of a doctor.”

Overall, the key is to find the balance for one patient amongst all patients. In recent years, a great debate has developed over the treatment of depression. One of the most prevalent debates surrounds pharmacoeconomic studies. The most common problems involve: inability to set values on treatments, variations on measurements and definitions of disorders, and difficulty to make a reliable prognosis with the combination of “cognitive, environmental, and biochemical factors.”

Similarly, studies in the ethical diagnosis and treatment of schizophrenia can be centered around five broad categories. According to Laura B. Dunn, et al, these categories include:

1. Scientific designs (e.g., placebo-controlled studies and medication-free intervals, prodromal and high-risk research, and genetics research);
2. Informed consent and decision-making capacity, including assessment of decisional abilities, as well as intervention studies;
3. Understanding and perceptions of risk and benefit (including the therapeutic misconception);
4. Influences on research participation (including voluntarism, altruism, and other motivations);
5. Key participant safeguards, such as protocol review and participant advocates.

Another great ethical importance which must be stressed involves the national drug insurance systems which in and of themselves are centered on many “values.” The problem with this system is “the classification of drugs and medical conditions that determine which drugs and medical conditions should be paid for by the insurance system.” Unfortunately, these are the reasons many individuals are unable to obtain the proper medicinal treatments for these detrimental disorders. Thus, as research in these fields is expanding and constantly updating, the values that drive the passion for a cure should not be concentrated solely on the pill; instead, it should reach beyond to those anticipating relief.
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Notes


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