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Adverse Effects of Selective Serotonin Reuptake Inhibitors (SSRIs)

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Abstract **-** Selective Serotonin Reuptake Inhibitors (SSRIs) are common medications taken by patients that are diagnosed with depression or anxiety, and examples of these medications are Fluoxetine, Sertraline, Paroxetine, Fluvoxamine, Citalopram, Escitalopram, and Vilazodone. However, SSRIs have been discovered to cause negative or adverse effects on patients, especially adolescents. This has caused the United States Food and Drug Administration (FDA) to become stricter with the administration of SSRIs, including the requirement for proper labels warning the patient of the adverse effects. This paper investigates adverse events that are associated with SSRI therapy. For example, the SSRI Fluoxetine has been shown to cause adverse effects such as insomnia, anxiety, anorexia, and seizures. Another SSRI is Sertraline, which causes excessive bleeding, which can further lead to platelet aggregation. Also, the SSRI Paroxetine can cause the patient to have drowsiness, sleep disturbance, appetite and Discontinuation Syndrome. Discontinuation Syndrome occurs when an antidepressant is not taken by the individual any more. To add on, the SSRI Citalopram can cause many adverse effects, including diaphoresis, nausea, and vomiting. The SSRI Escitalopram can cause hyponatremia, insomnia, and nausea. Finally, the SSRI Vilazodone can cause patients to experience arthralgia, palpitations, and fatigue. In addition to these adverse effects, there are also Serious Adverse Effects (SAEs). SAEs are adverse events that cause hospitalisation, permanent damage, and death to the patient. An example of an SAE is suicide, which is more likely to happen in adolescents. A study was conducted where 4582 patients were placed in 24 placebo-controlled trails that displayed that antidepressants caused increase in suicide in pediatric patients. Also, the FDA has administered black box warnings on SSRI packaging to notify patients 24 years of age and under that they are at risk of suicide. Many SSRIs cause serious damage, especially in teens, and may be ineffective.

Keywords**:** SSRI, Fluoxetine, Sertraline, Paroxetine, Fluvoxamine, Citalopram, Escitalopram, Vilazodone

1. Introduction

Mental health is an essential part of life, and is defined as something that affects a person's emotional and psychological health, decision making, and reactions to events. According to the U.S. Centers for Disease Control and Prevention (CDC), one in five adults living in the United States deal with mental health issues [1]. Depression is a loss of feelings of happiness or joy and can hinder day to day activities. According to the Substance Abuse and Mental Health Services Administration, six common types of depression are Major Depressive Disorder, Persistent Depressive Disorder, Postpartum Depression, Psychotic Depression, Seasonal Affective Disorder, and Bipolar Disorder [2]. Major Depressive Disorder is analogous to clinical depression, and is defined as a constant feeling of darkness or sadness which affects daily activities, and can also cause a decline in interest in certain hobbies or activities. Persistent Depressive Disorder is when an individual experiences a low mood for a long period of time. It is considered Persistent Depressive Disorder when adults have low mood for two years and for children, one year. The person can participate in day to day activities, but may experience episodes of Major Depressive Disorder. Postpartum Depression affects women after they give birth. Some symptoms are fatigue, uneasiness, and anxiety which make mothers have a tough time taking care of their newborn and themselves. Psychotic Depression occurs when a person gets depressed and simultaneously experiences hallucinations. Seasonal Affective Disorder (SAD) is described as a change in mood as the seasons change. SAD is most common in the autumn and winter months, in which the days get shorter and the amount of sunlight also decreases. Some symptoms of SAD are fatigue, anxiousness, weight gain, oversleeping, thoughts of death and/or suicide, and agitation. Finally, Bipolar Disorder is characterised by sudden shifts in mood or emotions. Extreme highs are described as mania or “manic” episodes and lows are titled depression or “depressive” episodes. There are many factors that cause Bipolar Disorder, such as heredity, Post Traumatic Stress Disorder (PTSD), and the misuse of drugs and/or alcohol. Some signs of having “manic” episodes are strong feelings of euphoria, restlessness, partaking in dangerous acts, and racing thoughts. Some symptoms for "depressive" episodes are feeling hopeless, thoughts of suicide, forgetfullness, feeling tired, and a decline in interest of hobbies the person used to enjoy. But, there is a range of the “episodes” that one might experience, which are titled as types of Bipolar Disorder. Bipolar I Disorder is diagnosed when

someone only has one “manic” episode but can also experience “depressive episodes” sporadically. Bipolar II Disorder is when someone experiences mood changes from highs to lows commonly, but the highs aren’t as extreme. Finally, cyclothymia is characterised by mood changes from high to low, but not as frequently and also not as extreme as in Bipolar II Disorder. According to the CDC, depression affects 18.4% of adults in the American population and is the biggest contributor to mortality and disability costs in the country [3].

2. The Role of Serotonin in Depression

Depression results from the chemical imbalance of dopamine and serotonin in the brain, and raising the levels of these hormones can relieve the symptoms of depression. Serotonin is a neurotransmitter that is vital in many biological processes and is used in the central nervous system (CNS) and the peripheral nervous system (Figure 1). It is also commonly known as 5-HT (5-hydroxytryptamine). Serotonin is found in mammals, fungi, plants, and insects [4]. About 90% of serotonin concentration is in the enterochromaffin cells, which is where serotonin is synthesised in the gastrointestinal tract [4]. Some functions of serotonin are enabling happiness and reward, aiding with learning, memory, helping control behaviour and appetite, and assisting with the regulation of sleep [4]. Serotonin was first discovered by Roman scientist and researcher Vittorio Erspamer in 1953. It was found because he was looking for a molecule that was being released from platelets. After serotonin’s discovery, it was also discovered that it was a neurotransmitter. The different purposes of serotonin in the (CNS) are its actions on the brain stem, cerebellum, and forebrain. At a molecular level, serotonin is produced in two steps: a hydroxyl group (-OH) is added to the amino acid tryptophan, which creates 5-hydroxytryptophan (5-HTP) [4]. Next, the carboxyl group is removed from the 5-HTP in order to form 5-HT4. Serotonin is kept in the presynaptic neurons in the CNS after it is synthesised [4]. Serotonin is a very important neurotransmitter for the body, as it plays a significant role, by impacting the brain's cells indirectly and directly. Some examples are clotting, cell division, controlling appetite, and affecting bone metabolism [4]. Serotonin affects the bowel function by being in the GI tract where it controls bowel movement. Basically, the GI tract is lined with many enterochromaffin cells, which collect information of the food that has reached the stomach and release serotonin across various levels If there is an increase in serotonin levels, then the digestive process increases in speed, which mainly occurs with toxic and harmful food [4]. Serotonin levels also affect appetite, as serotonin decreases appetite when eating.

In addition, serotonin also plays a major role in mood [4]. This occurs in the brain, depending on the nerve stimulation and electrical impulse in the nervous system. Drugs such as LSD cause a rise in the levels of serotonin, which could lead to side effects such as appetite changes, feeling of euphoria, and the creation of hallucinations [4]. Also, serotonin controls blood clotting. When the serotonin gets released into the blood, it gets absorbed by the platelets in the blood, which causes an increase in the rate of metabolism. This affects a slow down in blood flow and causes the acceleration in clot formation. In addition, serotonin facilitates nausea. This happens when there is an excess amount of serotonin absorbed into the bloodstream, which is caused by the release of serotonin in the gut that can't be digested fast enough. While in the bloodstream, the serotonin interacts with 5-HT3 receptors, activating chemoreceptor trigger zones, and the activation of those zones instruct the brain to remove the food eaten, which in turn causes nausea [4]. Finally, the neurotransmitter affects bone density, although there isn’t much proof to support this claim. The claim is that certain people have increased levels of serotonin in their bloodstream, which causes a normal or an increase in bone density [4]. To be more specific, the 5-HT1B receptor is deemed to be the connection between bone density and blood serotonin [4].

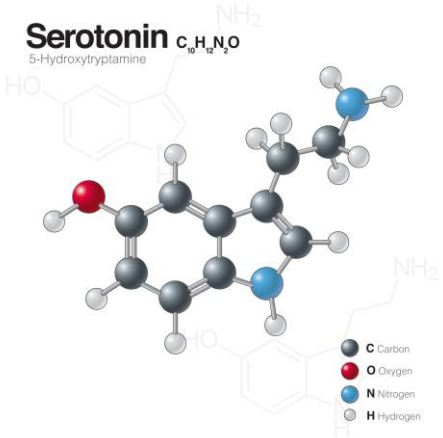

Fig. 1: Chemical structure of serotonin

3. Safety and Efficacy of SSRI Therapy

Selective serotonin reuptake inhibitors (SSRIs) are the most common antidepressant medication prescribed [5]. SSRIs work by increasing the levels of serotonin in the brain [5]. The first SSRI that was introduced to the market was Fluoxetine, in 1987 and was named as Prozac [6]. The seven main SSRIs approved include Fluoxetine, Sertraline, Paroxetine, Fluvoxamine, Citalopram, Escitalopram, and Vilazodone. The SSRI Fluoxetine is an Food and Drug Administration (FDA) approved antidepressant that aids individuals that suffer from bulimia, binge eating disorder, bipolar depression, obsessive compulsive disorder, and panic disorder [7]. But, fluoxetine can also be utilised for non-FDA approved disorders, such as post-traumatic stress disorder (PTSD), borderline personality disorder, and social anxiety disorder [7]. In the prefrontal cortex, the dorsal raphe nucleus contains presynaptic serotonin, also known as 5HT1A. Fluoxetine affects this by obstructing the reuptake of the serotonin, which is then further stopped by the reuptake transporter protein, which resides in presynaptic terminal [7]. Fluoxetine stops the reuptake of serotonin, so it initiates an activating effect, and causes the effect of antidepressants to rise between 2-4 weeks after initiation of therapy. In addition, the SSRI Sertraline is a drug used to treat FDA approved disorders such as obsessive compulsive disorder, PTSD, social anxiety disorder, and major depressive disorder [8]. The medication can also be utilised for non-FDA approved disorders: Binge Eating Disorder, Bulimia Nervosa Disorder, and Generalised Anxiety Disorder. Sertraline is an antidepressant that affects the reuptake of presynaptic serotonin reuptake [8]. Sertraline also affects norepinephrine and dopamine uptake, making it a highly effective drug on mental health disorders. Another SSRI is Paroxetine. Paroxetine is an antidepressant that is a selective serotonin reuptake inhibitor that blocks the serotonin reuptake transporter, which in turn increases the concentration of synaptic serotonin [9]. This causes an increased in downregulation of related serotonin receptors, which makes the concentration normal.9 Paroxetine is used for major depressive, obsessive compulsive disorder, PTSD, and anxiety disorder, but Paroxetine is not approved for children or people less than 18 years old [9]. The SSRI Citalopram is also an important SSRI. Citalopram is a hydrobromide that acts by controlling serotonergic activity in the CNS, elevating brain-derived neurotrophic factor (BDNF) in the hippocampus and the preferential cortex [10]. Citalopram can be used to treat depression in adults (FDA- approved), Obsessive-Compulsive Disorder (OCD), Panic Disorder, Separation Anxiety Disorder, Binge Eating Disorder, and PTSD [10]. Citalopram is strongly discouraged for pregnant women and should be cautioned when used on patients over the age of 65 years old. Additionally, the SSRI Escitalopram is widely used to treat depression. Escitalopram attaches to the sodium-dependent serotonin transporter protein (SERT), which is in control of reuptake of serotonin from the synaptic cleft [10]. When SERT is not activated, it leads to an increase in serotonin levels. Escitalopram is used to treat major depressive disorder in patients older than 12 years of age (FDA approved) [10]. This medication can also be used off-label for disorders such as Panic Disorder, PTSD, OCD, and social anxiety disorder [10]. When the use of escitalopram is stopped suddenly, it can cause withdrawal symptoms, such as nausea, dizziness, and lethargy [10]. Escitalopram should also not be mixed or used with other drugs, as this can cause adverse effects, increasing the risk of excessive bleeding and QT prolongation. Patients with

QT syndrome in their family history should be tested before given Escitalopram. Finally, the SSRI Vilazodone is commonly used to treat depression. Vilazodone ($C_{26}H_{27}N_5O_2$) is used to aid in the activity of serotonergic in the CNS, which is done through selective inhibition of serotonin reuptake [12]. Viladozone is most commonly known for treating Major depressive disorder [12].

Although SSRIs can improve depression and other mental disorders in weeks, there are also many negative and harmful side effects that the patient may experience. The side effects of SSRIs can range in severity from non-serious to life-threatening; however, it is critical to recognize that even non-serious side effects can compromise patient compliance with medication, and ultimately affect the success or failure of treatment. For example, the SSRI Fluoxetine has many adverse effects that have been reported by adults, such as nausea, suicidal thoughts, seizures, anorexia, insomnia, drastic changes in weight, and many more symptoms [7]. Some side effects can vanish with adjustments over time, as the adverse effects are caused by the timing and dosage of medication. For instance, if the adverse effect was insomnia, the patient can take the medication in the morning. Fluoxetine also can have toxicity when taken with alcohol, which could cause respiratory depression and ataxia. [7] When Fluoxetine is taken with other SSRI medication or medication that grows serotonin levels, it could lead to an SSRI overdose. But, Fluoxetine is infrequently dangerous if it is the only medication taken by the patient. Another SSRI that has harmful side effects is Sertraline. The age of the patient can affect the different side effects. For example, teens and children are more likely to have suicidal thoughts if they are taking Setraline for major depression [8]. Other adverse effects are excessive bleeding and can later cause platelet aggregation [8]. The withdrawal of this medication can cause detrimental effects on the body and the mind. Some symptoms include: nausea, vertigo, tremor, anxiety, and confusion [8]. To reduce the risk when stopping intake of Sertraline, it's best to gradually decrease the amount of dosage. Sertraline toxicity can cause muscle rigidity, diaphoresis, hyperthermia and serotonin syndrome [8]. Serotonin syndrome is when the body has too much serotonin in the body due to medication. To treat serotonin syndrome, the medication should stop being ingested.

The SSRI Paroxetine also possesses harmful effects. Many of these harmful effects take effect depending on the dosage that is administered. Some side effects are loss of appetite, sleep disturbance, sweating, and drowsiness [9]. Discontinuation syndrome is more commonly found with the administration of Paroxetine when compared to other SSRIs [9]. Discontinuation syndrome is a condition that can occur if an antidepressant suddenly is stopped by the patient. Some of the symptoms from discontinuation syndrome are lethargy, headache, fever, anxiety, vomiting, and dizziness [9]. Also, children and adults ages eighteen to twenty-four, are more at risk for suicide. Finally, different organs and systems acquire adverse effects. When the nervous system is affected, headaches, dizziness, and tremors can form [9]. In terms of metabolism, weight gain can occur in the body [9]. When the cardiovascular system is affected, it can cause edema, chest pain, palpitations, and tachycardia [9]. Photosensitivity and alopecia can occur when the skin is compromised [9]. To add on, when the gastrointestinal system is affected, diarrhea, nausea, and constipation can occur [9]. In addition, the SSRI Citalopram has many adverse effects, affecting over 10% of patients that are administered this SSRI [10]. The most common effects include the influences the SSRI has on the CNS, which are insomnia, headache, and dizziness, diaphoresis, nausea, vomiting, and constipation [10]. Some uncommon effects are hemorrhage, serotonin syndrome, suicidal thoughts/suicide, and mania [10]. Another SSRI that causes adverse effects is Escitalopram. The most common adverse effects are nausea , fatigue , and insomnia. Escitalopram can also cause hyponatremia, a condition that is caused by low sodium levels, which causes the body to have more water than it needs. Some symptoms of hyponatremia are nausea, vomiting, fatigue, and anorexia [11]. Some extreme symptoms include a change in mental state, seizures, and coma [11]. Serotonin syndrome can also be developed, and some of the symptoms are dizziness, vomiting, hallucinations, and coma [11]. Finally, the SSRI Vilazodone has many adverse effects. For example, diarrhea affected 28% of patients reporting adverse events; nausea (23% of patients reporting adverse events); vomiting (5% of patients reporting adverse events); and insomnia (6% of patients reporting adverse events) [12]. Some other effects include palpitations, dry mouth, fatigue, arthralgia (joint stiffness), and dizziness [12].

Even though an antidepressants purpose is to help heal clinical depression, it causes an increase in suicidal behavior and thoughts. The United States Food and Drug Administration (FDA) have even enforced the use of warnings and labels on antidepressant packaging (black box warning) that say patients under the age of 24 are at risk of suicide [13]. A meeting was organized by the FDA in 1991 to discuss the concerns of the behavior the patients exhibited when treat fluoxetine, as many

patients expressed their suicidal behavior when taking the medication [13]. In March of 2004 FDA urged that patients taking antidepressants to be monitored to study the worsening of depression and suicidal thoughts in the patients [13]. There have been reports on suicidality when the antidepressants fluoxetine, paroxetine, and sertraline are ingested [13]. Many studies and experiments have supported that suicidal behavior is increased in teenagers and adolescents [13]. For example, 4582 patients were placed in 24 placebo-controlled trails that showed that antidepressants caused increase in the suicide in pediatric patients [13]. Another study was conducted of 159,810 users of the following SSRIs: amitriptyline, fluoxetine, paroxetine, and dothiepin showed increased in thoughts of suicide in the first month, specifically the first nine days [13]. To add on, another study titled Meta-analysis by Stone et al placed 99,231 patients with either antidepressants or placebo, and found that most group of patients exposed to suicidal behavior were patients under the age of 25 years old [13].

Overall, adverse events can compromise patient compliance with SSRI therapy, and lead patients to discontinue therapy prematurely. This can be shown through a study that was conducted in 1997 by administering fluoxetine to subjects, with 10.4% of patients discontinuing the treatment [14]. Another trial was done among children and adolescents with the drug paroxetine, and 8.9% of patients had to discontinue due to the adverse effects [14]. Also, the same trial was done on subjects with the SSRI sertraline and 9% also discontinued treatment [14]. Of the 9%, most were children that discontinued, and the most common reason for discontinuation is suicidal thoughts, suicidal attempts, and aggressive behavior [14]. To add on, an adverse effect that is caused by SSRIs is suicide. A study was taken where the risk of suicide was recorded, for many SSRIs through a 95% confidence interval. For example, when using the drug Effexor XR for Major Depressive Disorder, the risk for suicide increases 8.84 times [14]. Another drug titled Luvox causes suidice risks across all trials to increase by 5.52 times and another drug titled Zoloft causes the likeliness of suicide to increase 2.16 times for major depressive disorder [14].

Serious adverse events (SAEs) from SSRI therapy are not merely an inconvenience for patients, these events are severe and threaten patient safety [14]. An SAE is defined as events that cause death, the risk of death, the patient to be hospitalized, the formation of a disability or permanent damage, birth defects, and an event that needs medical attention/intervention to prevent further damage [14]. Many patients have discontinued their treatment due to SAEs, for example, 12% of patients taking Paroxetine stopped treatment, 8% of venlafaxine patients also stopped treatment [14].

4. Conclusion

To conclude, SSRIs are used to elevate the levels of serotonin in the brain and are used for mental disorders such as anxiety and depression. But, SSRIs cause adverse effects to the patients, which could be severe and life threatening. More awareness has been brought to this issue, and alternatively medication is also being researched. Patients are given antidepressants with caution and are advised to not take large doses according to the FDA [5]. Ultimately, SSRIs can even worsen a person's mental state, suggesting that there are opportunities for improving medications used to treat mental health disorders.

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