

The anti-depression function of selective serotonin reuptake inhibitor

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Abstract. Depression is one of the world's most serious public health issues. What is worse, the number of people suffering from depression is expanding and shows a younger-age trend. The primary treatment for depression is drug therapy. Selective serotonin reuptake inhibitors (SSRIs), as the second generation of novel antidepressants, are highly recognized antidepressant medicines that are widely utilized in clinical practice and have become first-line drugs for the treatment of depression. This article provides a thorough and detailed introduction to SSRIs. It focuses mostly on the etiology of depression, the specific mechanism of SSRIs, the specific application of SSRIs, and properties of distinct SSRI drugs. This article looks at the superiority and significance of SSRI medicines in the treatment of depression. At the same time, the limitations and shortcomings of SSRI drugs were discussed, and the future development of SSRI drugs was envisaged.

Keywords: depressive disorder, selective serotonin reuptake inhibitor, antidepressant.

1. Introduction

We live in a rapidly changing society nowadays. The pace of people's life is accelerating continuously, and the psychological pressure on individuals of all ages is surging. Depression has become extremely frequent in modern society. More than 16 million individuals in the United States endure at least one episode of depressive disorder each year, according to the National Institutes of Health. A person's chances of developing depression at some point in their lives are roughly 10%. Depression is now one of the world's major public health issues. Finding effective medications to treat depression is both urgent and critical. At the moment, the most often utilized antidepressant medication are selective serotonin reuptake inhibitors (SSRIs). SSRIs have both obvious effect and high safety. Thus, they are widely favored by both doctors and patients, which is of great significance for overcoming the problem of depression. In this article, firstly, the link between depression and serotonin was discussed from the perspective of the pathogenesis of depression, and then the specific mechanism of SSRIs action was introduced. Furthermore, the applications and the characteristics of various types of SSRIs were discussed. Finally, the benefits and drawbacks of SSRI medications are brought up, as well as their potential future development.

2. Pathogenesis of depression

A psychiatric disease known as major depressive disorder (MDD) is characterized by a persistently down mood, low self-esteem, and a loss of interest in or enjoyment from normally pleasant events for at least two weeks. The pathophysiology of this mental condition is still not completely understood. However, hypotheses based on monoaminergic systems are widely accepted. According to monoamine theories, depression is correlated with low levels or inactivity of brain monoamines. Neurotransmitters and neuromodulators known as monoamine neurotransmitters have one amino group that is attached to an aromatic ring by a two-carbon chain.

Serotonin, norepinephrine, and dopamine are examples of neurotransmitters that are primarily released in the brain and adrenal glands. They are essential for brain growth, mood modulation, and stress response. Serotonin facilitates information transmission throughout the brain. It affects the majority of brain cells, including those involved in mood, sexual desire and function, appetite, sleep,

and various aspects of social interaction. The presence of serotonin generally improves our mood and increases our sociability. However, a serotonin deficiency makes a person more susceptible to stimuli in a negative way. People with low serotonin level tend to be less sociable and more introverted. Serotonin is thought to be correlated to depression based on the linkage between depression risk and polymorphisms in the 5-HTTLPR gene, which codes for serotonin receptors.[1]

Researchers discovered in the 1950s that a tiny proportion of people using the antihypertensive medication reserpine turned out to develop serious depression, and the treatment of tuberculosis drug isoniazid can obviously improve depressed mood. The reason may be that reserpine depletion can single amine neurotransmitter in the brain, and Isoniazid is a monoamine oxidase inhibitor that enhances the function of the serotonin and norepinephrine systems. Based on this, Coppen et al. proposed in 1965 that low serotonin levels in the central nervous system would cause depression; Subsequently, the monoamine neurotransmitter hypothesis was first proposed by Schildkraut et al. Most current antidepressants, are derived from this hypothesis, including serotonin reuptake inhibitors.[2]

3. What are SSRIs

SSRIs are a class of pharmaceutical antidepressant medicines, they are the most often prescribed antidepressants. SSRIs can alleviate the symptoms of depression ranging from mild to severe. They are comparatively safe, and have fewer adverse effects. Post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), social anxiety disorder (SAD) and generalized anxiety disorder (GAD) are some of the common mental illness. The good thing is that SSRIs are also permitted for their treatment.

selective serotonin reuptake inhibitors have a solid reputation for both efficacy and safety. They are typically the first choice for physicians when prescribing antidepressants.

Chimedrine, an antihistamine-based selective serotonin reuptake inhibitor medication, was created by neuroscientists in the late 1970s. It was introduced in 1982 and marketed under the names of Normud, Zimeldine and Zelmid. Unfortunately, the drug has been reported to cause Guillain-Barre syndrome, a polyneuropathy that affects the peripheral nervous system. This incident led to the drug having to be withdrawn from the market. Since then, a new class of SSRI drugs has emerged. The scientists produced two new SSRI drugs called fluvoxamine and fluoxetine.

After the release of Zoloft and Paxil in the early 1990s, Fluoxetine, often known as Prozac, was first released. Fluoxetine is currently one of the most commonly used medicines that doctors prefer to deal with depression worldwide. A study for molecules with monoamine receptor affinity led to the appearance of fluoxetine. The purpose of this study was to uncover chemicals which do not interfere with cholinergic adrenoceptor, or histamine receptors. It was first regarded as a wonder medicine for treating depressive disorder. By 1990, it had become the most prescribed antidepressant in the world, generating pharma firms more than one billion dollars annually on its own. This medicine is appropriate for individuals of wide range of ages, from adolescents to the elderly, and it may even be used to heal animals.

As one of the first pharmaceuticals to be sold on a large scale to consumers, fluoxetine offers several new opportunities for the psychotherapy. However, it is not perfect. It contributed to the pathologizing of therapeutic methods, and many patients thus restricted their depression treatment to mere medication. Numerous in the medical profession think the medicine is over-administered and, in some cases, ineffectively provided when it is not used in conjunction with another sort of treatment, such as psychotherapy.

Following the discovery of SSRIs, there was considerable interest in developing antidepressant medicines having a wider mechanism of action. Venlafaxine, whose brand name was Effexor, was released in 1993 as the first antidepressant of the serotonin-norepinephrine reuptake inhibitor (SNRI) family. SNRIs differ from SSRIs in that they inhibit the reuptake of both 5-hydroxytryptamine and

Norepinephrine. Following the SSRI, currently SNRI is also the most widely used antidepressants. [3]

SSRIs belong to the second generation of antidepressants. The SSRI antidepressants that are marketed today include Fluoxetine, Citalopram, Escitalopram, Sertraline and Paroxetine, they have been approved by Food and Drug Administration. Among the available drugs, Indalpine and Zimelidine have been discontinued. Additionally, some never SSRI drugs to market, such as Alaproclate, Cericlamine, Femoxietiene, and others, which may be at high risk, are still not fully developed. Furthermore, certain SSRI medicines, such as Alaproclate, Cericlamine, Femoxietiene, and others, have never been commercialized, which may be at high risk or are still in the early stages of development.

4. Basic mechanism of SSRIs

In general, SSRIs target the serotonin transporter (SERT or 5-HTT), which delivers serotonin back to the presynaptic neuron from a synaptic cleft. Synapses contain these critical transporters. In terms of chemical structure, these receptors belong to glycoproteins. Their role is to extract excess neurotransmitters from these synapses and transport them back to presynaptic neurons for further usage; this is known as serotonin reuptake. SSRIs are referred to as "selective" since they have little or no influence on body's other neurotransmitters like norepinephrine and dopamine.

The binding of 5-HT to SERT is prevented by SSRI. At the presynaptic terminal, 5-HT is metabolized by monoamine oxidase or stored in secretory vesicles. Therefore, serotonin levels are elevated in the growing dendritic region of 5-HT neurons, but not in the axon terminal region. Desensitization of somatodendritic 5-HT_{1A} autoreceptors occurs as the concentration of 5-hydroxytryptamine rises, which means the receptors no longer reacts to its specific ligand. Autoreceptors collectively refer to receptors that are responsive to the transmitter released by the neuron on which they are located. They often serve as the main building block of an extremely short negative feedback loop in which the neuron's production of one neurotransmitter prevents it from releasing another. 5-HT_{1A} autoreceptors can be found in synapses (both presynaptically and postsynaptically) or nerve terminals. 5-hydroxytryptamine release at nerve terminals is inhibited when 5-HT_{1A} autoreceptors are stimulated. These autoreceptors will no longer impede the 5-HT neuron's impulse flow when they are down-regulated. After that, the impulse flow is activated, besides, 5-hydroxytryptamine is released at the axon terminal. At the same time, this rise in 5-hydroxytryptamine takes longer than the climb in 5-hydroxytryptamine in the somatodendritic region of the 5-HT neuron. The process where 5-hydroxytryptamine downregulates 5-HT_{1A} autoreceptors and activates the 5-HT neuron's neuro impulse flow takes a certain amount of time, thus there is such a delay. This delay may explain why antidepressants do not work instantly. This may also give a reason why the mechanisms of antidepressants are linked to increased neural impulse flow from 5-HT neurons. Before the inhibitors begin to operate adequately, the concentration of 5-hydroxytryptamine at the axon terminal increases.

To sum up, SSRI inhibits SERT first, increasing the amount of 5-HT in the somatodendritic region of 5-HT neurons. The somatodendritic 5-HT_{1A} autoreceptors were then desensitized, and the neuro impulse flow was triggered. The release of 5-HT from the axon terminal was subsequently enhanced by this impulse flow. Finally, the desensitization of postsynaptic 5-HT receptor may occur. This desensitization may result in a decrease in the harmful effects of SSRIs as tolerance builds.

5. SSRI's specific application and its effects

SSRIs are commonly utilized in clinical depression treatment. Currently, SSRI drugs that have been approved by FDA for treatment include Citalopram, Escitalopram, Fluoxetine, Paroxetine and Sertraline. Next, the therapeutic applicability and efficacy of these 5 SSRI antidepressants will be briefly discussed.

5.1. Fluoxetine

Fluoxetine is marketed under the brand names Prozac and Sarafem. Fluoxetine for clinical usage is a mixture of R-enantiomers and S-enantiomers. The major metabolite of fluoxetine is called demefluoxetine, which also comprises R- and S-enantiomers. Both R- and S-enantiomers are effective inhibitors of serotonin reabsorption, but they do not have the receptor blocking action of tricyclic antidepressants.

Multiple clinical trials have shown that fluoxetine is useful for the acute and maintenance treatment of major depressive illness in children, and adolescents, and adults. Fluoxetine is the first SSRI drug approved by FDA for adolescents with depression. A large number of randomized controlled trials (RCTs) have confirmed that fluoxetine has good efficacy, safety and tolerability in the treatment of adolescent depression. The Adolescent Depression Study (TADS) [4] is a large RCT, and the results show that fluoxetine or fluoxetine combined with cognitive behavior therapy (CBT) can effectively improve the symptoms of depression in adolescence, but the curative effect gradually diminishes as treatment time is extended; additionally, fluoxetine can reduce adolescent suicide risk of depression.

According to studies [5], fluoxetine can not only improve the mood of depressed adolescents by regulating the function of brain regions associated with adolescent depression, such as the amygdaloid-hippocampus and the dorsal anterior cingulate cortex, but also regulate the level of chemokines related to the onset of depression. Fluoxetine has no anticholinergic impact, no effect on epinephrine and, dopamine and histamine receptors. It does not cause no weight gain and has no evident cardiovascular system reaction. Fluoxetine has little effect on patients' daily lives, and is relatively safe to overuse. It is particularly suitable for geriatric depression and depression accompanied by physical diseases [6].

In general, fluoxetine is more effective than placebo in treating all degrees and subtypes of depression. Furthermore, fluoxetine is appropriate for people of a wide range of ages, from adolescents to the elderly.

5.2. Paroxetine

Paroxetine has no effect on psychomotor function and its effect is significant. It is appropriate for depression consolidation and long-term treatment. Paroxetine is effective at alleviating symptoms of depression, anxiety, movement and behavior retardation, and improving sleep and diet, and takes about two weeks to work. This drug's efficacy is temporary stable. Although the severity of depression gradually decreases as treatment time is extended, its efficacy can still be improved.

Paroxetine is safe to use, well tolerated, and convenient to take. It is especially suitable for patients who are unable to tolerate tricyclic antidepressants. [7]

However, in 2004, the FDA issued a boxed warning for all SSRIs, urging clinicians to use them with caution, due to concerns that paroxetine and other SSRIs could increase the risk of suicide in depressed adolescents. [8]

5.3. Citalopram and Escitalopram

Citalopram is a racemate that contains symmetric S-enantiomers (S-citalopram, escitalopram) and R-enantiomers (r-citalopram). S- enantiomer plays a major role in the treatment of depression, whereas R- enantiomer is inactive and may even inhibit the efficacy of S- enantiomer. According to this theory, escitalopram outperforms citalopram. However, some researchers [9] studied the adult population and discovered that escitalopram and citalopram have comparable clinical efficacy and that their adverse reactions are similar and mild, but escitalopram appears to be more effective for major depression.

5.4. Sertraline

Sertraline is marketed under the trade name Zoloft. Sertraline was the most frequently prescribed psychiatric medication in the US in 2016. HETRICK. S. E et al. [10] conducted a large-scale meta-

analysis that recognized the efficacy and safety of sertraline in adolescents and concluded that sertraline could be used as the first-line treatment for adolescents with depression.

Sertraline and fluoxetine have similar degrees of symptom improvement in adolescent depression patients, but sertraline has fewer adverse reactions and a stronger effect on improving sleep quality [11]. The adverse reactions of sertraline are mainly gastrointestinal reactions, but the symptoms are generally mild. Moreover, sertraline administration had no significant effect on some routine physical examinations. There is less interaction with other concomitant medications, sertraline may be more suitable for older patients with depression or those with other medical issues that necessitate other medications at the same time.

6. Conclusion and discussion

To summarize, SSRI antidepressants have significant benefits in the treatment of depression. SSRIs are typically the first line of treatment for depression. In 1988, Eli Lilly and Company introduced fluoxetine, the first selective 5-hydroxytryptamine reuptake inhibitor, which became a milestone in antidepressant treatment. Although their clinical effectiveness is roughly equivalent to that of tricyclic antidepressants (TCAs), SSRIs considerably reduce the risk of harm from overdose and have superior tolerance. SSRIs, in particular, seldom produce anticholinergic effects and are generally cardiotoxic free. These merits could have a meaningful impact on treatment adherence and cost-effectiveness, especially in long-term treatment.

Furthermore, there is evidence that SSRIs are more effective than TCAs for anxiety-related depressive disorder. SSRIs are safer and produce fewer unwanted side effects than other antidepressants. SSRIs have been shown to be useful for social phobia, obsessive-compulsive disorder and panic disorder, and in addition to depression.

However, despite its high efficacy and safety, SSRIs still have certain risks and inevitable side effects. As a result, it is critical to focus on the rational use of such drugs. Common SSRI side effects include vomiting, nausea, loss of appetite, and other symptoms that have been well recorded in clinical trials. Some SSRI patients may lose weight due to gut reactions, and the incidence of gastrointestinal adverse events is higher with SSRIs than with SNRI antidepressants. Additionally, sexual dysfunction is also a common adverse effect, and it occurs far more frequently than that of SNRI. Withdrawal is another common side effect of SSRIs. The primary reason for withdrawal is that long-term SSRI use reduces the sensitivity of serotonin receptors in the brain. When an SSRI is abruptly discontinued, the concentration of serotonin in the synaptic cleft decreases and neural information transmission efficiency decreases, resulting in dizziness, excessive sleep, increased nerve sensitivity, and other symptoms. If a pregnant woman takes an SSRI, her newborn may experience withdrawal symptoms.

Drug interactions are another issue to consider. The combination of SSRIs and monoamine oxidase inhibitors (MAOIs), as well as other drugs that enhance serotonin neurologic function, such as amitriptyline, can result in serotonin syndrome. Furthermore, drinking alcohol while taking SSRIs increases the risk of psychomotor skill damage.

SSRIs have shown an increasingly broad and effective application prospect in the treatment of various types of depression, as well as diverse mental and psychological disorders and psychosomatic diseases. So far, SSRIs have given hope to countless patients suffering from depression, but there are still flaws and challenges to overcome. Only by understanding the benefits and drawbacks of each treatment will we be able to effectively treat patients and solve the depression problem. It is expected that SSRI drugs will continue to develop, make new breakthroughs, or be combined with other treatment methods in the future to provide more beneficial, perfect, and personalized treatment for depression patients.

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