Comprehensive review of SSRIs and SNRIs, their efficacy, and associated side effects

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Abstract

This paper provides an overview of various antidepressants, which are often used to treat depression. Depression is a prevalent mental disorder characterised by persistent sadness and lack of interest in previously enjoyable and rewarding activities. The World Health Organisation (WHO) estimates that depression affects approximately 3.8% of the population, which is equivalent to approximately 300 million people globally. Depression is caused by biological, genetic, environmental, and psychosocial factors. The conventional treatments include therapeutic and social support for mild depression and pharmacological interventions for moderate to severe instances, primarily involving antidepressants such as SSRIs and SNRIs. SSRIs and SNRIs target neurotransmitters such as serotonin and norepinephrine to alleviate depressive symptoms. However, these antidepressants have potential side effects such as cardiovascular issues, gasastrointestinal problems, insomnia, sexual dysfunction, and increased suicidal thoughts. Despite all these side effects, antidepressants remain a crucial tool to combat depression.

Introduction

Depression is a mental disorder characterised by the World Health Organisation (WHO) by persistent sadness and lack of interest and pleasure in previously rewarding or enjoyable activities. In today's competitive world, it is no surprise that depression has risen in the past decades. WHO estimated that 3.8% of the population and 5% of the adults are depressed, even though the figure could be much higher since not everyone with depression obtains proper psychological diagnostics.(1) In 2021, it is estimated that 5.0 million adolescents aged 12 to 17 in the United States had suffered from depression, which is equivalent to 20.1% of the U.S. population aged 12 to 17.(2) This mental health problem has a significant impact on the society. Depression can lead to problems such as self-harm or even suicide. Globally, there are over 700,000 deaths annually due to suicide, making it the fourth leading cause of death among young adults aged 15-29 years old.(3) Despite being a mental disorder, depression can affect one's physical health, including one's heart, kidney, nervous system, and immune system health. Depression can ultimately result in problems such as experiences of sadness or emptiness, insomnia, memory loss, preoccupation with death,

feelings of clinginess, fatigue, lower interest in sex, weakened immune system, weight fluctuations, constricted blood vessels, weakened immune system, and risk of heart attack. (4)

Depression is caused by a multitude of factors, including biological, genetic, environmental, and psychosocial factors.(5) The risk of developing major depression increases by approximately 3 times for those who have a first-degree relative with depression. On the other hand, having a highly life-threatening event increases the risk of depression from 5 to 16 times within a few months of the event.(6) Neurochemically, depressive symptoms are caused by imbalances in neurochemicals such as serotonin, dopamine, and norepinephrine.(7) Environmental factors such as stress, traumatic events, and childhood difficulties could play a significant role in the development of depression, acting as external influences on mental health.(8)

Psychiatrists distinguish several stages of depression, ranging from mild to moderate to severe depression. In the case of mild depression, one approach is to monitor the symptoms over a period of time to assess if they improve naturally without intervention. This approach doesn't mean that the symptoms are completely ignored and no treatment is applied. It is crucial to stay in touch with therapy, keep in contact with family members and friends, and seek help from support and information centres. On the other hand, in moderate and severe cases, it is very important to get immediate treatment due to the fact that these symptoms are very distressing, can last for a while, and further progress to more severe degrees of depression.(9) Conventional treatments include therapy sessions, engaging with mental health teams, counselling, and sometimes using antidepressants.(10)

The 4 major classes of antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs). All these classes of antidepressants target proteins that interact with neurotransmitters such as serotonin, norepinephrine, and dopamine. They increase the concentration of these neurotransmitters in the brain, positively affecting the mood and effectively reducing the occurrence of depression. However, drugs like antidepressants also have negative side effects, such as cardiovascular side effects, gastrointestinal side effects, and seizures.(11) SSRIs and SNRIs are more popular than TCAs and MAOIs due to several reasons. One of the primary concerns with the TCAs is their adverse effect burden and their potentially lethal toxicity in overdose situations. An overdose with a TCA is significantly more likely to result in death compared to an overdose with an SSRI. An overdose of TCA is 5 times as lethal as an overdose of SSRI.(12) On the other hand, MAOIs are not often used in treating depression due to several dietary restrictions and other safety concerns.(13)

However, the consequences of depression are more severe and threatening than the side effects of antidepressants. Hence, psychoactive substances are the most effective and safe way to combat this mental condition. Therefore, it is crucial to know the different classes of antidepressants, their chemical structures, pharmacokinetics and pharmacodynamics properties, and the mode of action of each class of antidepressants.

SSRI

Chemical Structure

Despite being in the same class, SSRIs have different chemical structures and functional groups.(14) The diversity in the chemical structure results in compounds with substantial pharmacological differences.(15) As shown in Figure 1, antidepressants such as fluvoxamine differ in chemical structure from other SSRIs such as citalopram. This results in different binding affinities to serotonin transporters (SERT).(16)

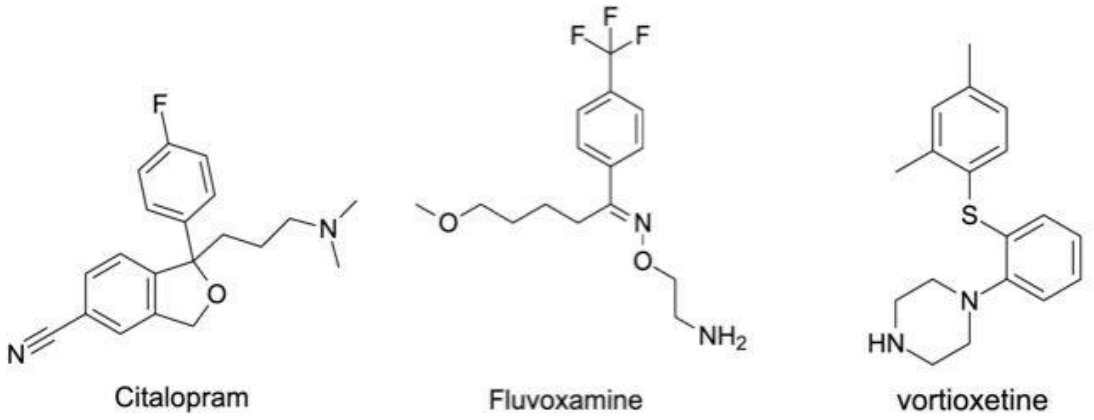

Figure 1 Different structures of SSRIs

The top 3 most prescribed antidepressants include Sertraline, Citalopram, and Fluoxetine, with 17%, 14%, and 11% of total prescriptions, respectively.(17)(18) These antidepressants have a common fragment of a benzene ring and the amino group separated by 4 atoms.

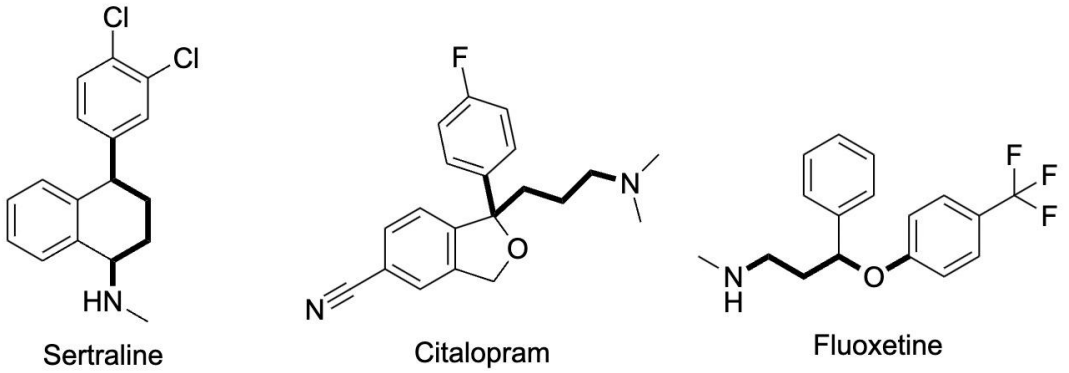

Figure 2 Chemical structures of the 3 most prescribed SSRIs

Mode of action

SSRIs are thought to tackle depression by increasing serotonin levels in the brain. Serotonin, being a neurotransmitter that carries signals between nerve cells in the brain, improves mood. After facilitating signal transmission between the nerve cells, these neurotransmitters are absorbed back into the nerve cells. SSRIs work by preventing the reuptake of these neurotransmitters, increasing the serotonin concentration in the brain.(19)

When a patient uses SSRIs, the serotonin released in the synapses interacts with numerous postsynaptic serotonin receptors. Furthermore, molecular studies have located multiple receptor families. Serotonin impacts presynaptic receptors, leading to reduced serotonergic neurons. By inhibiting serotonin reuptake, SSRIs enhance its concentration in synapses, which in turn further suppresses the serotonergic neurons' activity.(20)

SSRI pharmacokinetics/pharmacodynamics

Dosages from SSRIs are typically absorbed effectively through the gastrointestinal tract. However, their systemic availability might be reduced due to first-pass metabolism. When taken orally, peak concentrations in the body are generally reached within 5 to 8 hours.(21) These drugs are extensively dispersed in body tissues and have a high affinity for binding with plasma proteins. Their elimination from the body is predominantly achieved through liver metabolism.(22) Among the SSRIs, fluvoxamine stands out as a potent inhibitor of CYP1A2, affecting the metabolism of drugs like caffeine and clozapine, while citalopram, fluoxetine, and sertraline show less interaction with this enzyme. Fluoxetine also inhibits CYP2C19, which is notable in about 2% of whites who are poor metabolisers due to a lack of this enzyme, impacting the elimination of drugs, including citalopram. CYP2D6, despite constituting only a small portion of liver P450 enzymes, is pivotal in metabolising many drugs, including tricyclic antidepressants and SSRIs like fluvoxamine, fluoxetine, and paroxetine; these SSRIs, particularly fluoxetine and its metabolite norfluoxetine, and paroxetine, are strong inhibitors of CYP2D6. In contrast, CYP3A4, the most abundant human cytochrome P450, is largely unaffected by SSRIs, except for norfluoxetine, indicating minimal interactions between most SSRIs and CYP3A4. This diverse pharmacokinetic profile underscores the importance of considering individual SSRI characteristics in the context of drug-drug interactions and patient-specific metabolism.(23)

Sertraline, when taken orally by healthy individuals, is absorbed at a gradual pace, reaching peak plasma levels (Cmax) of around 20 to 55 μg/L roughly 4 to 8 hours post a single 100mg dose. In the 48 hours following administration, less than 0.2% of the drug is excreted in the urine in its unchanged form. With an elimination half-life of about 26 hours, sertraline is conducive to once-daily dosing. This pharmacokinetic profile underscores its suitability for daily administration in a therapeutic context.(24) The binding rate for sertraline is 98% in blood and binds to human serum albumin with a high affinity via hydrogen bonding and hydrophobic interactions.(25)

Citalopram is absorbed rapidly after oral intake and reaches peak plasma levels in 1-4 hours, has a half-life of between 24 and 48 hours and an average of 35 hours.(26) When

citalopram is administered orally, around 12-23% of the original dose is excreted through the urine unchanged, and about 10 percent is excreted through the faeces in an unchanged state.(26) Citalopram is available in tablet forms of 10mg, 20mg, and 40mg. Typically, the standard dosage for adults is 20mg per day. However, the treatment may begin with a smaller dose and gradually increase up to a maximum of 40mg daily.(27) Citalopram has a distribution volume approximately equal to 12l/kg. Additionally, the binding rate of citalopram and its metabolites, desmethylcitalopram (DCT) and didemethylcitalopram (DDCT), to human plasma proteins is around 80%.(28)

Fluoxetine, when taken orally, is rapidly and completely absorbed, peaking in concentration between 6 to 8 hours. In the liver, fluoxetine undergoes N-demethylation to form an active metabolite, norfluoxetine, along with other minor inactive metabolites. Both fluoxetine and norfluoxetine are conjugated before being excreted. The drug shows a high protein binding rate of 94%. Its volume of distribution is estimated to range from 11 to 88.4l/kg. Regarding excretion, about 2.5% of fluoxetine is excreted unchanged by the kidneys, and 10% is excreted as the norfluoxetine metabolite. After 35 days, approximately 65% of a radiolabeled dose of fluoxetine is recovered in the urine, and 15% is found in faeces. The elimination half-life of fluoxetine is relatively long, ranging from 48 to 72 hours, averaging around 70 hours. The half-life of its metabolite, norfluoxetine, is even longer, spanning 7 to 9 days.(29) The usual dose for adults is 20 mg per day. However, the dosage can be gradually increased to a maximum of 60 mg per day.(30)

SNRI

Chemical Structure

SNRIs display a considerable diversity in their chemical structures. This structural variance significantly contributes to the distinct pharmacokinetic and pharmacodynamic profiles observed within this drug class.(31) The FDA has approved, but not limited to, the following SNRIs to treat depression.(32)

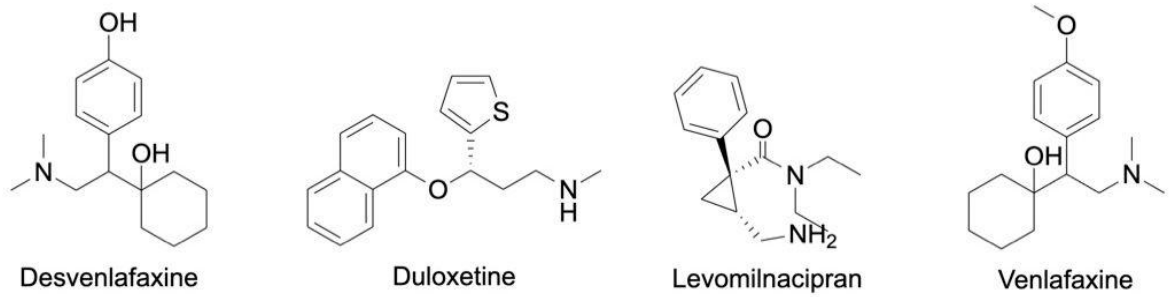

Figure 3 Chemical structure of some FDA-approved SNRIs

Mode of action

SNRIs are among the most commonly prescribed drugs in the United States annually.(33) As the name suggests, the primary mode of action of SNRIs is the inhibition of presynaptic neuronal uptake of serotonin and norepinephrine and prolong the effects of the monoamines in the synaptic cleft within the CNS, leading to increased postsynaptic receptor activation and neuronal activities.(34) Both SSRIs and SNRIs act on neurotransmitters. However, SNRIs act on both serotonin and norepinephrine whereas SSRIs act on serotonin only.

SNRIs Pharmacokinetics / pharmacodynamics

Venlafaxine, a prominent member of the SNRI class, showcases a unique metabolic pathway. It is primarily metabolised in the liver through the cytochrome P450 isoenzymes, specifically 2D6 and 3A3/4. This extensive hepatic metabolism suggests a heightened potential for drug interactions and sensitivity to genetic polymorphisms. As a result, venlafaxine's metabolic profile can significantly influence its efficacy and tolerability in different individuals. Additionally, its active metabolite, desvenlafaxine, also plays a role in its pharmacological effects, contributing to its overall therapeutic impact.(35)

Duloxetine and desvenlafaxine share similarities in their metabolic processing; both are primarily metabolised through the liver's P450 isoenzyme system. Duloxetine particularly involves CYP2D6 and CYP1A2 isoenzymes, whereas desvenlafaxine undergoes partial metabolism through conjugation and predominantly the CYP3A4 isoenzyme. In contrast, Levomilnacipran, another SNRI, is metabolised through demethylation via the CYP3A4 isoenzyme, along with hydroxylation. These metabolic pathways underscore the importance of considering individual patient factors, such as genetic makeup and concurrent medication use, when prescribing these medications, as they can significantly affect the drugs' effectiveness and risk of adverse interactions.(35)

Milnacipran, duloxetine, and venlafaxine, despite being part of the SNRI class, exhibit distinct profiles in terms of their affinity and selectivity towards neurotransmitter reuptake inhibition. Milnacipran stands out for its balanced approach, inhibiting the reuptake of both serotonin (5-HT) and norepinephrine with equal affinity. This contrasts with duloxetine, which shows a preference, being 10 times more selective for serotonin reuptake inhibition compared to norepinephrine. Venlafaxine takes this selectivity further, having a 30-fold higher affinity for serotonin than norepinephrine. This variation in selectivity and affinity among SNRIs underlines their differing pharmacological profiles, influencing their therapeutic applications and side effect profiles.(36)

After oral administration, milnacipran is absorbed rapidly, exhibiting maximum concentrations at 2 to 4 hours with a Cmax of 150 ng/ml after a single 50 mg dose.(37) Milnacipran is a racemic mixture consisting of D-milnacipran and l-milnacipran. D-milnacipran and l-milnacipran have a half-life of between 8-10 hours and 4-6 hours respectively. Dosing is twice a day.(35) Milnacipran reaches a steady state in 2 days.(38) Milnacipran and its inactive metabolites are excreted dominantly via renal excretion, with approximately 50-60% of the original dose excreted in urine as an unchanged drug.(39)

Duloxetine has a half-life ranging from 8-17 hours, with an average of 12 hours. The steady-state plasma concentrations are typically reached after 3 days of dosing. Duloxetine is metabolised primarily through the hepatic P-450 isoenzyme system, specifically 2D6 and 1A2 isoenzymes.(35) Duloxetine reaches its peak plasma concentration, which ranges from about 47 ng/mL with a 40 mg twice-daily dosage to 110 ng/mL with an 80 mg twice-daily dosage, approximately 6 hours following administration.(41) The volume of distribution is approximately 1640 litres.(42)

Venlafaxine is absorbed and metabolised in the liver. Approximately 92% of a single oral dose of venlafaxine is absorbed.(43) The half-life of venlafaxine ranges from 3 to 4 hours, while its main metabolite has a longer half-life of approximately 10 hours.(44) Venlafaxine is highly metabolised in humans, with between 1% and 10% excreted of an administered dose.(45) When dosed once per day, venlafaxine reaches peak plasma concentration at 5.5 hours after dose. Venlafaxine undergoes primary metabolism through the cytochrome P-450 2D6 system, resulting in the formation of O-desmethylvenlafaxine, which also actively inhibits the reuptake of serotonin and norepinephrine.(46)

Despite their proven efficacy in treating depression, SSRIs and SNRIs are accompanied by a range of harmful side effects. It is, therefore, important to weigh the benefits and consequences before taking antidepressants. It is also crucial to discuss with healthcare professionals to tailor treatment plans that maximise benefits while minimising adverse effects.

Side effects of SSRIs and SNRIs

SSRIs and SNRIs are widely used antidepressants, but like all medications, they can have negative effects. These side effects can vary in severity and frequency among individuals.

- ### Cardiovascular side effects

An independent review of various scientific sources was performed in 2014 to study the effects of SSRIs on cardiovascular events. 17 studies were relevant and were reviewed. The results suggest that some SSRIs may reduce platelet adhesion and aggregation and control cardiovascular risks, including hypertension, insulin resistance, and body weight. However, chronic use of certain SSRIs can lead to cardiac issues such as arrhythmias, syncope, and atherosclerosis due to pro-inflammatory cytokines.(47) The use of SSRIs has also been linked to vasoconstriction, which can lead to myocardial ischemia, also known as Prinzmetal's angina.(48) In addition to serotonin, SNRIs also inhibit the reuptake of norepinephrine from the synaptic cleft, leading to increased neurotransmission. The

increased levels of norepinephrine and serotonin can increase cardiac sympathetic activity, resulting in a slight rise in heart rate and systemic blood pressure. Excessive sympathetic stimulation may cause tachyarrhythmias and/or hypertensive crisis.(49) Epidemiological studies have reported that patients taking SNRI, particularly venlafaxine, have experienced elevated blood pressure.(50)

- Dry mouth

According to meta-analysis, dry mouth, also known as xerostomia, has been cited as a treatment-emergent side effect in 22% of patients treated with SSRIs.(51) Salivary secretion is regulated by both the sympathetic and parasympathetic nervous systems by the salivary gland receptors.(52) Antidepressants have been proven to reduce salivary flow rate by preventing the effects of acetylcholine on muscarinic M3 receptors, resulting in lowered salivation.(53) Based on a present study, patients who are taking SNRIs are 5 times more likely to experience dry mouth compared to those not taking SNRIs.(54)

- Insomnia

Antidepressants such as SSRIs and SNRIs often lead to a deterioration in sleep quality, primarily due to the activation of serotonergic 5-HT2 receptors and increased noradrenergic and dopaminergic neurotransmission. People taking SSRIs and SNRIs may find it harder to fall asleep, might wake up often during the night, and could have less deep sleep and dream sleep. This is a common issue, with about 17% of people taking SSRIs and 13% of those on SNRIs experiencing sleep problems in clinical trials. The problem is especially noticeable in the first few weeks of treatment, but for some people, it can continue and make their insomnia worse or make them sleepy during the day.(55) SSRI appears to include increased sleep onset latency and/or an increased number of awakenings, resulting in overall poorer sleep efficiency.(56)

- Gastrointestinal side effects

Gastrointestinal side effects are effects that affect human's gastrointestinal system. It includes symptoms such as nausea, vomiting, diarrhoea, and constipation.(57) SSRIs and SNRIs work by stimulating the production of serotonin. When levels of serotonin increase, the movement of food along the digestive tract increases, resulting in symptoms such as diarrhoea.(58) Symptoms such as nausea and stomach upset are present in 17% to 26% of patients taking antidepressants. A study of 84 trials found that 16% of patients taking SSRIs experienced diarrhoea. Lastly, between 11% and 12.5% of patients experience constipation.(59)

- Sexual Dysfunction

The disruption in sexual function caused by SSRIs is complex and may involve nitric oxide. This impact is likely due to the activation of postsynaptic 5-HT2 receptors, which are located

in the spinal cord.(60) Another study suggests that the increase in serotonin may affect other hormones and neurotransmitters such as dopamine and testosterone.(61) This results in side effects in sexual dysfunction as testosterone affects sexual arousal and dopamine affects orgasm.(62) The most common side effects are delayed ejaculation and other types of side effects include lowered sexual desire, reduced sexual satisfaction, impotence and anorgasmia.(63) Even though these are some common side effects of depression itself, it can also be attributed to antidepressants.(64) A study shows that the approximate prevalence of sexual dysfunction is between 25%-73% and 58%-70% for SSRIs and SNRIs respectively.(65)

- Serotonin syndrome

Serotonin syndrome, or serotonin toxicity, is a potentially lethal drug-induced condition caused by excessive serotonin in the synapses of the brain.(66) In most cases, serotonin toxicity involves 2 drugs used simultaneously to increase serotonin in various ways or an overdose of 1 drug causing an increase in serotonin levels. The most common culprits include SSRIs, SNRIs, and MAOIs.(67) Serotonin syndrome ultimately leads to other side effects such as insomnia, rapid heart rate and high blood pressure, agitation, diarrhoea, fever, and irregular heartbeat.(68)

- Suicidal feeling

Despite being used to treat depressants, antidepressants such as SSRIs could ironically increase suicidal ideations, suicide attempts, and fatal suicides. In a study, among the 219635 adults hospitalised taking antidepressant drugs under surveillance, 83 cases of suicidal adverse drug reactions happened. Even though the probability is extremely low at 0.04%, it is still important to note that antidepressants could result in suicidal feelings.(69)

- Effects on neurodevelopment

In the years 2004-2005, 8% of pregnant women were prescribed antidepressants.(70) Studies have suggested that exposure to SSRIs, particularly during the first trimester of pregnancy, causes the risk of autism spectrum disorders to increase.(71) Furthermore, the use of antidepressants by pregnant women is also associated with an increased probability of developing attention-deficit/hyperactivity disorder (ADHD) in children.(72)

Conclusion

In this time and age, depression is a widespread issue, affecting a significant portion of the population across different age groups. Depression can be characterised by persistent sadness and loss of interest in previously enjoyable activities. It is caused by various factors such as biological, genetic, environmental, and psychosocial factors, with varying severity. Even though there are many different treatments such as therapy, interactions with family and friends, and help from support and information centres, the primary treatment method is the use of antidepressants, particularly SSRIs and SNRIs. These antidepressants work by altering the levels of neurotransmitters in the brain to improve mood. Despite their efficacy, these drugs have unintended side effects such as cardiovascular issues, gastrointestinal effects, insomnia, sexual dysfunction, and, in rare cases, increased suicidal thoughts. Additionally, the use of antidepressants during pregnancy raises concerns regarding neurodevelopmental effects on the fetus. Such concerns include the risk of autism spectrum disorders and ADHD. It is, therefore, essential to weigh the benefits and consequences of antidepressants and to tailor treatments to individual needs, with consultation with healthcare professionals to optimise treatment outcomes while reducing the negative effects. I believe that further research could be done on the long-term effects of antidepressants to allow users to fully understand the potential risks and benefits of antidepressants and make more informed decisions when choosing to consume antidepressants. Furthermore, given the advancement in science and technology in recent years, I believe that the neurodevelopmental effects of drugs could be better understood through more sophisticated research techniques.

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