

The Development and Mechanism of Treatment of Depression

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Abstract. Depression is a serious mental disorder that influence about 280 million people around the world. The risk factors that may cause depression include both genetic and environmental factors. Researchers have been long searching for treatments to depression. Patients with symptoms of depression are always treated by both psychic interventions and medical treatments. Although the underlying pathophysiology of depression is remained unclear, neurotransmitters, including serotonin, dopamine, and norepinephrine, are proved to be related to the symptoms of depression by clinical experiments. The first two antidepressants were iproniazid (classified as a monoamine-oxidase inhibitor), and imipramine (classified as a tricyclic antidepressant) in 1950s. More antidepressants using different mechanisms and with fewer side-effect and safety concerns were developed later. People divided those antidepressants into three categories by the order of development: 1) first-generation antidepressants, 2) second-generation antidepressants, and 3) third-generation antidepressants. Due to immature technology, drugs in the first-generation generally have more serious side-effect, more safety concerns, and more restrictions. Thus, second-generation antidepressants, which typically have less side-effect, are now more common in controlling the symptoms of depression. The third-generation antidepressants are still in development, but designed to be more effective with less side-effect. The paper reviews the medical treatments of depression in the order of these three generations.

Keywords: Depression, Antidepressant, Medical Treatment.

1. Introduction

Depression, a common and serious mood disorder, can result feeling of sadness and loss of interest. According to World Health Organization, 3.8% of the population are affected and approximately 280 million have depression [1]. Specifically, about 8.4% of all U.S. adults, which was 21 million, experienced at least one major depressive episode in 2020. The proportion of being diagnosed of depression is even higher among individual aged 18 – 25, in which about 17% show symptoms of major depressive disorder [2]. Other than influencing a large amount of population, depression is also a leading factor that induce suicide behavior: over 700000 people die due to suicide every year. Common symptoms of depression include 1) sleep disturbance; 2) energy changes or fatigue; 3) concentration or attraction impairment; 4) reduced interest; 5) guilt feeling or thoughts of worthlessness; 6) appetite or weight changes; 7) psychomotor disturbances; 8) Depressed mood; 9) Suicidal thoughts [3].

The risk factors that causing depressive symptoms include both genetic and environmental factors. Depression can strike people regardless of family history of depression, but first-degree relatives of depressed individuals are three times more likely than the general population to show symptom of depression [3]. However, the pathophysiology of depression is still not clearly defined. Indicated by clinical and preclinical trials, the symptoms of depression are influenced by a complicated interaction between neurotransmitter availability and receptor regulation and sensitivity. Dopamine, serotonin, glutamate, norepinephrine, and brain-derived neurotrophic factor play a role in development of depression [3].

Psychological and medical treatments are used for controlling depression. Cognitive behavioral therapy (CBT), interpersonal therapy (IPT), and supportive therapy are three commonly used

psychotherapies for depression. CTB, a structured and didactic form of therapy, helps individuals to reduce symptoms by identifying and modifying maladaptive thinking and behavior patterns. IPT works by emphasizing the role of interpersonal relationships, and focusing on current interpersonal difficulties [3].

This paper reviews on the medical treatments of depression, which are divided into three categories due to its development time (first-generation antidepressants, second-generation antidepressants, and third-generation antidepressants). The oldest antidepressants are among the first-generation but have serious side-effects. The second-generation antidepressants are the most frequently used drugs today to help control symptoms of depression. Third-generation antidepressants, which may be more effective and have less side-effect, are remained immature but attractive. Mechanism, effect and side-effect, and specific drugs among each generation are discussed in the paper.

2. First-generation antidepressants

First-generation antidepressants are the first effective antidepressants, such as amitriptyline, clomipramine, tranylcypromine. The first-generation antidepressants include two types of antidepressants: tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) [4]. Due to their serious side-effects, safety concerns, and dietary restrictions, first-generation antidepressants are rarely used to control depression today.

2.1. Tricyclic antidepressants (TCAs)

The classification of TCAs was based on the three benzene rings molecular core. The first TCAs drug approved by Food and Drug Administration (FDA) was imipramine in 1959 [5]. TCAs influence roughly five neurotransmitter pathways: 1) serotonin, 2) norepinephrine, 3) alpha cholinergic receptor, 4) muscarinic receptor, and 5) histaminergic receptor. The mechanism of TCAs is to increase the concentration of norepinephrine and serotonin in the synaptic cleft by blocking the reuptake of these neurotransmitters in presynaptic terminals. Increased levels of serotonin and norepinephrine are thought to both contribute to the antidepressant effect and act as competitive antagonists on histaminergic receptors, muscarinic, and post-synapse alpha cholinergic (alpha 1 and alpha 2) [6].

TCAs can lead to serious side-effect, such as constipation, dizziness, and xerostomia. TCAs cause xerostomia, blurred vision, constipation, confusion, tachycardia, and urinary retention due to its blockade of cholinergic receptors, cause orthostatic hypotension and dizziness due to the blockade of alpha-1 adrenergic receptors. TCAs may also cause cardiovascular complications, including arrhythmias. TCA usage has been proved to increase the risk of suicide in individuals age 24 or less [6]. Since TCAs are used to treat patients who often suffer from neuropsychiatric disorders and chronic pain, overdose occurs frequently. According to the database, 1.12 exposures per 10,000 population were accounted for TCA overdose in 1992. Although the trend for antidepressant overdose has shifted more towards SSRIs, TAC overdose shows a higher rate of hospitalization due to its narrower therapeutic index [7].

TCAs that are still approved by FDA include amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine [8].

2.2. Monoamine Oxidase Inhibitors (MAOIs)

Monoamine oxidase (MAO) is an enzyme that produces oxidative dissemination of biogenic amines and sympathomimetic amines [9]. As its name suggests, MAOIs works by inhibiting the function of MAOs. MAO has two isoenzymes: MAOA and MAOB. These two isoenzymes breakdown different monoamine neurotransmitters: MAOA primarily deaminates adrenaline, melatonin, noradrenaline, and serotonin, while MAOB breaks down benzylamine and e phenethylamine. However, both of them deaminate biogenic amines located in the presynaptic terminal, such as dopamine, tyramine, and tryptamine. By inhibiting the function of MAOs, the concentration of monoamine neurotransmitters increases in the presynaptic terminal [9].

Most common side effects for MAOIs usage include diarrhea, dry mouth, constipation, drowsiness, nausea, lightheadedness, insomnia, and dizziness. Additionally, drug-to-drug interactions, drug-food interactions, and overdoses are potential concerns. For example, serotonin syndrome can be caused by taking both MAOIs and selective serotonin reuptake inhibitors (SSRIs), or by taking food with a high level of tyramine. Patient with serotonin syndrome shows signs and symptoms of fever, confusion, increased perspiration, muscle rigidity, seizures, liver or kidney problems, fluctuation of heart rhythms, and blood pressure [10]. Moreover, to avoid any drug interactions, patients should wait 14 days before switching MAOIs to a new medical treatment.

Iproniazid, classified as a MAO inhibitor, was the first successful pharmacological treatment for depression, and was removed from the market due to its serious side-effect and safety concerns [11]. Although MAOIs are generally replaced by second and third generation antidepressants, which can provide treatments with fewer side effects, four MAOIs (Emsam, Marplan, Nardil, Parnate) are still approved by FDA as medical treatments of depression [8].

3. Second-generation antidepressants

3.1. Selective Serotonin Reuptake Inhibitors (SSRIs)

Since 1980s, there are a lot of research has shown that 5-HT (serotonin) do have something effect with depression. However, until now we still cannot figure out what exactly the relationship between 5-HT and depression [12]. It may affect while the process of the synthesis, release, reuptake, metabolism of serotonin. And eventually effect the activation of pre- and post-synaptic 5-HT receptor [13]. Other article suggests that it might relate to neuroplasticity to cause depression [14]. But as far, what we can know is the SSRIs is effective in depression treatment. Serotonin is a kind of neurotransmitter. The selective serotonin reuptake inhibitors can inhibit the serotonin transporter (SERT) at pre-synaptic terminal and reduce the process of reuptake of serotonin. In that case it can increase the concentration of serotonin in synaptic cleft, making serotonin stimulate the receptor at post-synaptic for longer period [15].

Unlike TCAs or other antidepressants, SSRIs has shown that have seldom affect on other neurotransmitter such as norepinephrine and dopamine. And it will not affect on other receptor systems like histaminic, cholinergic, adrenergic and post-synaptic serotonin receptors which is not related to depression. Also, medications like TCAs have strong sensitive to the side-effect by elder adults or children, SSRIs has shown high tolerability, efficiency and safety [16].

Since 1988, there are several SSRIs have been permitted to use by FDA, including fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram and vilazodone. Different medication has different side effects.

Serotonin receptor have 7 different classes relating to different functions like sleep, appetite, and sexual function [16]. The most adverse effect of SSRIs is related to these functions and cause some symptoms like insomnia, sick and so on. There are several common adverse effects about SSRIs.

First is weight gain. In long term therapy, weight gain has been appeared with sertraline, fluoxetine, paroxetine and citalopram in some cases [16]. Next is sex dysfunction. What SSRIs do with sexual function is complicated. It seems to be related to one of the serotonin receptors, post-synaptic 5-HT₂ receptors. The common syndromes would have sexual desire decrease, ED, delayed ejaculation, or anorgasmia, which you cannot feel the joy of sex. Also, it is different from gender. Female have shown larger decrease of desire and much harder to get orgasm. Even SSRIs have bad effect on sex but it is still better than TCAs. Is those SSRIs, paroxetine might cause ED, vaginal lubrication difficulties and decreased libido in the first month therapy. Citalopram seems will not cause sexual damage but its dose-dependent side effect might be anorgasmia [16]. Another effect is on sleep. Even the insomnia is one of the syndromes of depression, fluoxetine and paroxetine might cause awakesness and make the patients have less total sleep time and lower sleep efficiency. And REM sleep, slow-wave sleep will be reduced. On the other side, sertraline will make the patients have better sleep [16].

Discontinuation reactions are also shown with SSRIs as syndromes like sike, dizziness, headache and so on. These withdraw adverse effects might appear more common in drugs like paroxetine and fluvoxamine which have short half-lives. Even SSRIs have lower drug-drug interaction than TCAs, taking more than 2 at once or overuse 1 kind might cause serotonin syndrome, which is a dangerous disorder acts as muscle cramp, sweating, too exciting, shaking and so on. Patients should avoid taking 2 serotonergic drugs. Also, the meta-analysis of Toshi and colleagues has shown that the dose of SSRIs would affect the efficiency [17]. With 24524 published records, 4030 unpublished records, and also 77 studies including 19364 people from different country, gender and ages, the analysis shows that the optimal dose should in lower range between 20mg-40mg.

3.2. Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Another type of effective antidepressant is serotonin norepinephrine reuptake inhibitors (SNRIs). It can both inhibit the norepinephrine reuptake transporter and SERT. It can increase the concentration of serotonin and norepinephrine. SNRIs includes venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran [18]. Venlafaxine is also known as third generation antidepressant. In these drugs, they show different selectivity for inhibiting transporters. Venlafaxine inhibits serotonin reuptake 30 times higher than norepinephrine. Duloxetine comes to 10 times like desvenlafaxine. Milnacipran shows the equality to both serotonin and norepinephrine. Levomilnacipran is unique as it inhibits norepinephrine 2-fold higher [19].

Similar to SSRIs, SNRIs have better efficiency of treating depression and have less adverse effects than older generation antidepressants. And SNRIs shows more progress than SSRIs with response by the patients. Papakostas and colleagues make an analysis about the benefits of combining inhibition of serotonin and norepinephrine [20]. The data shows that there are more benefits for combination than only inhibition of serotonin reuptake. Also, the evidence shows that SNRIs have better treatment for painful symptom associated with depression which the SSRIs do not have [21].

However, SNRIs still shows some side effects. Similar to SSRIs, SNRIs would cause adverse effect in sex dysfunction, sleep and so on. There are a lot of evidences show that nausea and vomiting is the most frequent side effect [22]. Serotonin plays a big role in the regulation of gastrointestinal. Most of the patients will get GI adverse effect after taking SSRIs or SNRIs for few days or weeks [23]. Besides of nausea and vomiting, some cases will also appear gastrorrhagia. After taking SSRIs and SNRIs, alanine aminotransferase level increases more than three times the normal, which shows the hepatotoxicity. The rate of its happening is between 0.5%-1% [23]. And it may cause the liver injury.

One most difference between SSRIs and SNRIs is that most of side effects of SNRIs are caused by doses. When at lower doses usually caused by serotonin transporter and when it comes higher, it relates to NE [24]. Blood pressure unusual is a remarkable adverse effect of SNRIs. Doses venlafaxine 300 mg per day or more might cause 13% high blood pressure [24]. Milnacipran also shows side effect causing high blood pressure after taking 50mg twice per day at week 4 and 100mg at week 7 comparing with placebo [24]. And in research of Leong and colleagues, 225,504 patients treated by SSRIs and 54,635 by SNRIs have been compared the risks of stroke. Patients who have SNRIs would have more risk having nonfatal stroke. And there is higher risk of death for patients have SNRIs without mood or anxiety problems [25].

3.3. Bupropion

Bupropion is another kind of common antidepressant have been used since 1980s. It is an aminoketone antidepressant. Its mechanism is still not clear but it can affect the norepinephrine and dopamine to reduce the symptom of depression [26]. Comparing with other antidepressants, bupropion would be one of the medicines would not cause sex dysfunction or weight gain. Even there is a group of patients lose about 12% weight after 24 weeks treatment [23]. Still, bupropion has some obvious side effect. Bupropion can lower the seizure threshold. It had been found causing the seizure since 1980s and even has been moved from market for few years because of that. With high doses of

immediate-release preparation, it would be most easy to cause seizure [26]. angle-closure glaucoma can be doubled after taking bupropion by whom is under 50 years old [23]. Also, there are some rare cases of few adverse effects like tachycardia [26].

3.4. Trazodone

Trazodone is also a major antidepressant. It is serotonin-antagonist-and-reuptake-inhibitor class and a triazolopyridine derivative. It has been shown to have outstanding effect on treating depression. But the mechanism of action is not fully understood [27]. Since 1980s, there are several experiments using 100-400mg trazodone comparing with TCAs in 4-6 weeks show they have similar efficacy [28]. And in recent years some studies show that trazodone is same effective than fluoxetine, paroxetine, sertraline and venlafaxine these kinds of SSRIs and SNRIs. But no matter how big the experiment is ($n = 27$ or $n = 126$ or $n = 225$), trazodone has more benefits on the sleeping issue through HAM-D [28].

Trazodone has the same side effects like other serotonin reuptake inhibitors, such as headaches, dizziness, dry mouth and so on. Trazodone also has QT prolongation. It is because the interactions between trazodone and hERG potassium channels [28]. There is a special case that one patient had distressing visual hallucinations after taking trazodone [29]. But it is a unique situation.

4. Third generation drugs

In the last decade, the world's understanding of depression has advanced further. From the earliest TCA and MAIO to SSRIs, To SNRI and norepinephrine and specific serotonin reuptake inhibitors (NaSSA). The third generation of antidepressants for depression is more than just serotonin reuptake inhibition. They include Venlafaxine, Mirtazapine, Reboxetine, Nefazodone, etc. Compared with SSRIs, these agents have a wide therapeutic index. Before and the new type of antidepressant drugs and drugs (such as SSRIs) compared to these drugs in treating depression treatment effect is better, effectiveness more quickly, and in the test found that security is higher, can be better in the treatment of patients, and can lower the risk of therapy on the patients.

4.1. Research and development of new drugs

4.1.1 Venlafaxine

Venlafaxine is a combination inhibitor and serotonin that acts as an inhibitor to inhibit serotonin and norepinephrine reuptake. Venlafaxine is chemically termed race-1 - (2-) dimethylamine (-1-) 4-methoxy phenyl (ethyl) cyclohexanol. In the synaptic structure, venlafaxine can also enhance the function of central serotonin and norepinephrine neurotransmitters, which can achieve the purpose of treating depression. In the studies comparing Venlafaxine and TCA, studies have shown that both are compound inhibitors, but in tests of two drugs, the results point to remission rates and the effects of treating depression being the same over time. In a study comparing Venlafaxine with the SSRI, there was no difference in treatment outcome between the two medications [30]. However, using ham-D measures, Mehtonen et al. found that venlafaxine was more effective than sertraline (83 versus 68%; $P = 0.05$), remission rate increased (68 vs. 45%; $P = 0.008$). Results of the study showed a significant increase in the number of patients in remission with venlafaxine (382/851; 45%), compared with the SSRI group (260/748; 35%) and placebo (110/446; 25%) [31].

In some clinical trial studies [32], the clinical performance of venlafaxine in the treatment of depression is very good, few patients will appear dizziness, drowsiness, insomnia, sweating and dry mouth and other adverse reactions. Furthermore, even if very few patients may have symptoms of insomnia, the combination of other drugs will improve the symptoms, so this drug has fewer side effects, high safety and fast and effective. The drug can be used in patients with depression for a long time.

4.1.2 Mirtazapine

Mirtazapine is a new antidepressant. It is a norepinephrine and specific serotonergic antidepressant. The mechanism of action of mirtazapine in the treatment of depression is to enhance central norepinephrine and inhibit α receptors of presynaptic serotonergic nerve endings and increase the release of serotonin. At the same time, the data shows that mirtazapine can block many kinds of 5-HT_{2A} and 5-HT_{2C} receptors due to its own structure, so as to achieve the effect characteristics of treating depression. The clinical efficacy of mirtazapine has been demonstrated in clinical studies, for example in a study of psychotic patients with psychotic and depressive symptoms, concomitant mirtazapine 30mg/d had no significant effect on plasma concentrations of risperidone and its active 9-hydroxyl metabolite [32]. And in the clinical trials of carbamazepine and mirtazapine, mirtazapine had no effect on the efficacy of carbamazepine [33].

Montgomery et al. performed a survival analysis of long-term pooled data from an extended period of four six-week double-blind, placebo-controlled comparative studies of mirtazapine and amitriptyline. Some of the patients who were in the acute phase and responded were kept on the study drug for up to 845 days. The maximum doses of mirtazapine and amitriptyline were 35 mg/d and 280 mg/d, respectively. At the study end point, the recurrence rate of mirtazapine (4.1%; $P = 0.001$) and amitriptyline (11.6%; $P = 0.01$) were significantly lower than those in the placebo group (28.1%), but there was no difference between the active treatment groups of each drug. Meanwhile, mirtazapine and amitriptyline had a longer recurrence time ($P < 0.05$) and amitriptyline ($P = 0.03$) compared with placebo, but again there were no differences between actively studied drugs [34]. Studies of side effects associated with mirtazapine included drowsiness (3.6 to 13%), dry mouth (11.9 to 54%), weight gain (up to 38%), and constipation (3.9 to 13%). There was no significant increase in the incidence of discontinuation due to adverse reactions with mirtazapine compared with comparison agents. Mirtazapine showed an advantage in anticholinergic side effects when compared with TCA [30].

4.1.3 Reboxetine

Reboxetine is a novel third generation antidepressant, which is also an effective, selective and specific norepinephrine reuptake inhibitor. Reboxetine has no affinity for some common neurotransmitter receptors, as does venlafaxine. The in vivo action of reboxetine is identical to the pharmacological action of antidepressants in that it preferentially acts at norepinephrine reuptake sites. The selectivity of reboxetine for NE over 5-HT reuptake has been established in human transporter-transfected cell lines and in the synaptosomes of the rat brain. In reuptake studies in oocytes expressing hNET and hSERT, The K_i values corresponding to reboxetine in both methods were 0.9 nmol/L and 1745 nmol/L respectively [35]. And the selectivity of reboxetine to NE transporters is 125 times higher than that of furoxazine and imipramine, which is the advantage of reboxetine. Furthermore, in a placebo-controlled study [36], patients who responded (defined as hamD score & GT; The lower; 50%) to 6 weeks of reboxetine open trial. Over the next 46 weeks, patients were randomly assigned to reboxetine (8mg/day) or placebo. The cumulative recurrence rate was significantly higher in the placebo group than in the reboxetine group ($P = 0.0001$). At the end point, 88 percent of patients treated with reboxetine were free of recurrence, compared with 59 percent in the placebo group. 0.001). Therefore, this could validate the feasibility and effectiveness of reboxetine therapy in clinical trials.

The side effects of reboxetine are relatively minor and the reaction is relatively mild. The side effects were similar to those of venlafaxine, including constipation (16.9 to 20%), headache (9.6 to 16.2%), and dry mouth (13.3 to 27%) [30]. Katona et al. [37] found that there were more cases of drug withdrawal due to excessive side effects in the imipramine group than in the reboxetine group, and there were fewer such events in the reboxetine group. Cardiovascular changes are a common side effect of reboxetine, but there have been no reports of death or other symptoms even after overdoses.

4.1.4 Nefazodone

Nefazodone is a new third generation antidepressant. Nefazodone blocks norepinephrine reuptake and has a high affinity for the serotonin 5-HT_{2A} receptor, which is also a moderate inhibitor of serotonin reuptake. Nefazodone is actually improved before antidepressants letrozole ketone, because letrozole ketone with orthostatic hypotension and calm side effects, such as in order to better for the treatment of patients, scientists have changed its structure, became one of the new drugs, will rarely appear the symptoms of orthostatic hypotension and calm, and reduces the and alpha 1 - adrenaline receptor affinity [38]. Fontaine et al. compared nefazodone and imipramine in two dosage ranges, 50-250 mg/day. Among 46 patients receiving nefazodone in the low-dose range (50 to 250 mg/ day), there was a significant difference in the mean change in HAMD scores, but this was not compared with placebo. After 6 weeks, experimental results showed that nefazodone doses of 100-500 mg /d were superior to placebo, but there was virtually no difference compared to imipramine.

According to some studies on the side effects of nefazodone, the side effects of nefazodone are mainly mild, and can be roughly divided into two types [30]. One was anticholinergic effect [dry mouth (29.6%), constipation (27.3%) and blurred vision (13.6%)]. Another is a serotonergic mechanism [headache (35-55%), nausea (27-32%), dizziness (17-32%) [39]. Seven nefazodone overdoses ranging from 1 to 11.2g were reported in previous studies, and all patients returned to normal life after supportive care. And studies have found that nefazodone and psychotherapy combined treatment than used alone nefazodone or psychological therapy has significant advantage reference, the combination of both methods in 85% of patients in treatment group at week 12 responded to treatment and, in contrast, nefazodone alone group and therapy group on the proportion of patients were 55% and 52% respectively [40]. Furthermore, response and remission rates in the combination therapy group were significantly higher than would be expected based on the results of previous trials of similar patients.

5. Conclusions

The medical treatments of depression are divided into three generations: first-generation antidepressants, second-generation antidepressants, and third-generation antidepressants. Antidepressants classified as first-generation are generally either TCAs or MAOIs. TCAs and MAOIs are the first two types of antidepressants to treat depression, but are rarely used today due to their side-effects. Nine TCAs and four MAOIs are still approved by FDA today, but are not considered as first choice. Second-generation antidepressants include all SSRIs, most SNRIs, and two atypical antidepressants (bupropion and trazodone). Specifically, bupropion is classified as a NDRI, and trazodone is classified as a SARI according to their mechanisms. Generally, second-generation antidepressants have less side-effect on patients and are common treatments of depression today. Third-generation antidepressants are recently developed medical treatments of depression, such as venlafaxine, mirtazapine, reboxetine, and nefazodone. Specifically, venlafaxine and nefazodone are known as SNRIs, mirtazapine is classified as NaSSA, and reboxetine is a type of selective NARI. Pharmacological treatment of patients with depression should be individualized. Different drugs have unique effects and side effects that clinicians should use with caution. There is still a need to further address the issue of drug side effects in the future to improve patient outcomes.

References

- [1] World Health Organization. (2021, September 13). Depression. World Health Organization. Retrieved April 9, 2022, from <https://www.who.int/news-room/fact-sheets/detail/depression>
- [2] U.S. Department of Health and Human Services. (2022, January). Major depression. National Institute of Mental Health. Retrieved May 2, 2022, from <https://www.nimh.nih.gov/health/statistics/major-depression>
- [3] Chand SP, Arif H. Depression. [Updated 2021 Jul 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK430847/>
- [4] O'Connor EA, Whitlock EP, Gaynes B, et al. Screening for Depression in Adults and Older Adults in Primary Care: An Updated Systematic Review [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2009 Dec. (Evidence Syntheses, No. 75.) Table 2, List of antidepressants and their categorizations. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK36406/table/ch1.t2/>
- [5] Hillhouse, T. M., & Porter, J. H. (2015). A brief history of the development of antidepressant drugs: from monoamines to glutamate. *Experimental and clinical psychopharmacology*, 23(1), 1–21. <https://doi.org/10.1037/a0038550>
- [6] Moraczewski J, Aedma KK. Tricyclic Antidepressants. [Updated 2021 Nov 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK557791/>
- [7] Khalid MM, Waseem M. Tricyclic Antidepressant Toxicity. [Updated 2021 Nov 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK430931/>
- [8] The United States Food and Drug Administration. (2021, October). www.fda.gov. FDA EPC Text Phrases for Indications and Usage heading in Highlights. Retrieved May 2, 2022, from <https://www.fda.gov/media/152880/download>
- [9] Hillhouse, T. M., & Porter, J. H. (2015). A brief history of the development of antidepressant drugs: from monoamines to glutamate. *Experimental and clinical psychopharmacology*, 23(1), 1–21. <https://doi.org/10.1037/a0038550>
- [10] Sub Laban T, Saadabadi A. Monoamine Oxidase Inhibitors (MAOI) [Updated 2021 Aug 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK539848/>
- [11] Pletscher A. The discovery of antidepressants: a winding path. *Experientia*. 1991 Jan 15;47(1):4-8. doi: 10.1007/BF02041242. PMID: 1999242.
- [12] Cowen, P. J., & Browning, M. (2015). What has serotonin to do with depression? *World psychiatry: official journal of the World Psychiatric Association (WPA)*, 14(2), 158–160. <https://doi.org/10.1002/wps.20229>
- [13] Dell'Osso, L., Carmassi, C., Mucci, F., & Marazziti, D. (2016). Depression, Serotonin and Tryptophan. *Current pharmaceutical design*, 22(8), 949–954. <https://doi.org/10.2174/1381612822666151214104826>
- [14] Kraus, C., Castrén, E., Kasper, S., & Lanzenberger, R. (2017). Serotonin and neuroplasticity - Links between molecular, functional and structural pathophysiology in depression. *Neuroscience and biobehavioral reviews*, 77, 317–326. <https://doi.org/10.1016/j.neubiorev.2017.03.007>
- [15] Chu A, Wadhwa R. Selective Serotonin Reuptake Inhibitors. [Updated 2022 Jan 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK554406/>
- [16] Ferguson J. M. (2001). SSRI Antidepressant Medications: Adverse Effects and Tolerability. *Primary care companion to the Journal of clinical psychiatry*, 3(1), 22–27. <https://doi.org/10.4088/pcc.v03n0105>
- [17] Furukawa, T. A., Cipriani, A., Cowen, P. J., Leucht, S., Egger, M., & Salanti, G. (2019). Optimal dose of selective serotonin reuptake inhibitors, venlafaxine, and mirtazapine in major depression: a systematic review and dose-response meta-analysis. *The lancet. Psychiatry*, 6(7), 601–609. [https://doi.org/10.1016/S2215-0366\(19\)30217-2](https://doi.org/10.1016/S2215-0366(19)30217-2)

- [18] Sheffler ZM, Abdijadid S. Antidepressants. [Updated 2021 Nov 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK538182/>
- [19] Sansone, R. A., & Sansone, L. A. (2014). Serotonin norepinephrine reuptake inhibitors: a pharmacological comparison. *Innovations in clinical neuroscience*, 11(3-4), 37–42.
- [20] Papakostas, G. I., Thase, M. E., Fava, M., Nelson, J. C., & Shelton, R. C. (2007). Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. *Biological psychiatry*, 62(11), 1217–1227. <https://doi.org/10.1016/j.biopsych.2007.03.027>
- [21] Stahl, S. M., Grady, M. M., Moret, C., & Briley, M. (2005). SNRIs: their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. *CNS spectrums*, 10(9), 732–747. <https://doi.org/10.1017/s1092852900019726>
- [22] Gerald Gartlehner, Richard A. Hansen, Laura C. Morgan, et al; Comparative Benefits and Harms of Second-Generation Antidepressants for Treating Major Depressive Disorder: An Updated Meta-analysis. *Ann Intern Med.*2011; 155:772-785. [Epub 6 December 2011]. doi:10.7326/0003-4819-155-11-201112060-00009
- [23] Carvalho, A. F., Sharma, M. S., Brunoni, A. R., Vieta, E., & Fava, G. A. (2016). The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. *Psychotherapy and psychosomatics*, 85(5), 270–288. <https://doi.org/10.1159/000447034>
- [24] Shelton R. C. (2019). Serotonin and Norepinephrine Reuptake Inhibitors. *Handbook of experimental pharmacology*, 250, 145–180. https://doi.org/10.1007/164_2018_164
- [25] Leong, C., Alessi-Severini, S., Enns, M. W., Nie, Y., Sareen, J., Bolton, J., Prior, H. J., & Chateau, D. (2017). Cerebrovascular, Cardiovascular, and Mortality Events in New Users of Selective Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors: A Propensity Score-Matched Population-Based Study. *Journal of clinical psychopharmacology*, 37(3), 332–340. <https://doi.org/10.1097/JCP.0000000000000701>
- [26] Huecker MR, Smiley A, Saadabadi A. Bupropion. [Updated 2021 Oct 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK470212/>
- [27] Shin JJ, Saadabadi A. Trazodone. [Updated 2021 Aug 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK470560/>
- [28] Fagiolini, A., Comandini, A., Catena Dell'Osso, M., & Kasper, S. (2012). Rediscovering trazodone for the treatment of major depressive disorder. *CNS drugs*, 26(12), 1033–1049. <https://doi.org/10.1007/s40263-012-0010-5>
- [29] Santos, G., & Moreira, A. M. (2017). Distressing Visual Hallucinations after Treatment with Trazodone. *Case reports in psychiatry*, 2017, 6136914. <https://doi.org/10.1155/2017/6136914>
- [30] Olver, J S et al. “Third-generation antidepressants: do they offer advantages over the SSRIs.” *CNS drugs* vol. 15,12 (2001): 941-54. doi:10.2165/00023210-200115120-00004
- [31] Hoyberg OJ, Maragakis B, Mullin J, et al. A double-blind multicentre comparison of mirtazapine and amitriptyline in elderly depressed patients. *Acta Psychiatr Scand* 1996; 93: 184-90
- [32] Loonen A.J., Doorschot C.H., Oostelbos M.C., Sitsen J.M. Lack of drug interaction between mirtazapine and risperidone in psychiatric patients. *Eur. Neuropsychopharmacol.* (1999) 10 51–57.
- [33] Spina, Edoardo et al. “Metabolic drug interactions with new psychotropic agents.” *Fundamental & clinical pharmacology* vol. 17,5 (2003): 517-38. doi:10.1046/j.1472-8206.2003.00193.x
- [34] Montgomery S, Reimtz P-E, Zivkov M. Mirtazapine versus amitriptyline in the long-term treatment of depression: a doubleblind placebo-controlled study. *Int Clin Psychopharmacol.* 1998; 13: 63-73
- [35] Wong, E. H., Sonders, M. S., Amara, S. G., Tinholt, P. M., Piercey, M. F., Hoffmann, W. P., Hyslop, D. K., Franklin, S., Porsolt, R. D., Bonsignori, A., Carfagna, N., & McArthur, R. A. (2000). Reboxetine: a pharmacologically potent, selective, and specific norepinephrine reuptake inhibitor. *Biological psychiatry*, 47(9), 818–829. [https://doi.org/10.1016/s0006-3223\(99\)00291-7](https://doi.org/10.1016/s0006-3223(99)00291-7)
- [36] Versiani M, Mehilane L, Gaszner P, et al. Reboxetine, a unique selective NRI, prevents relapse and recurrence in long-term treatment of major depressive disorder. *J Clin Psychiatry.* 1999; 60: 400-6

- [37] Katona C, Bercoff E, Chiu E, et al. Reboxetine versus imipramine in the treatment of elderly patients with major depressive disorders: a double-blind randomized trial. *J Affect Disord.* 1999; 55: 203-13
- [38] Fontaine R, Ontiveros A, Elie R, et al. A double-blind comparison of nefazodone, imipramine, and placebo in major depression. *J Clin Psychiatry* 1994; 55 (6): 234-41
- [39] Aranda-Michel J, Koehler A, Bejarano P, et al. Nefazodone-induced liver failure: report of three cases. *Ann Intern Med* 1999; 130: 285-8
- [40] Keller, M. B., McCullough, J. P., Klein, D. N., Arnow, B., Dunner, D. L., Gelenberg, A. J., Markowitz, J. C., Nemeroff, C. B., Russell, J. M., Thase, M. E., Trivedi, M. H., & Zajecka, J. (2000). A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *The New England journal of medicine*, 342(20), 1462–1470. <https://doi.org/10.1056/NEJM200005183422001>