Major Depressive Disorder Medication Use Strategies and Analyses

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Abstract. Major depressive disorder (MDD) is a pressing mental health problem globally. Under the contemporary era, significant progress has been achieved in understanding the pathogenic mechanisms of MDD. Pharmacotherapy, especially SSRIs, works as the most frequent option in MDD treatment. To identify a molecule with prompt effectiveness and minimal adverse effects is the overarching objective, but the mechanisms underlying the therapeutic effects in the MDD treatment remain nuanced and are not completely revealed. This literature review describes mechanisms, clinical trials conducted, therapeutic benefits along with adverse effects discovered of several key antidepressants, and aims to provide insights into the future antidepressant discovery, development and application. SSRIs together with SNRIs have acute effects on the monoaminergic system, but their strength is subject to limitations imposed by delayed or inadequate therapeutic efficacy, suboptimal remission outcomes, and adverse reactions. Consequently, novel and more efficacious antidepressant therapeutic agents are identified and developed. The review covers the recent clinical findings of a few promising antidepressants, and found that rapid-acting, oral administration, and substantial benefits in both remission and response are optimal features for antidepressants. Taken together, further explorations into both the pharmacological and pathophysiological mechanisms remain necessary. Future studies regarding the assessments of prolonged therapeutic benefits, safety profiles, recognitions of novel biomarkers among MDD patients especially with substance use disorders and/or treatment-resistant depression are also essential.

Keywords: Major Depressive Disorder (MDD), SSRIs, SNRIs, novel antidepressants.

1. Introduction

Major depressive disorder (MDD) or major depression is considered among the foremost pressing mental health problems. 3.8% of the global demographic population, around 280 million people, lived with MDD in 2022, and about 121 million experience new MDD cases annually. MDD is a mood disorder with emotionally drained and chronic depressed mood, profound sorrow, or a sense of despair as prominent symptoms, and it lasts for at least 2 weeks to months or even years. A major depressive episode may happen once or return frequently in a person's life. MDD is associated with multiple pathogenic factors including genetic predispositions, environmental factors, and they interact with one another in both pathophysiology and treatment. Genetic predispositions are expected to have minor effects, but it becomes more essential when combined with environmental factors.

Chronic stress exposure and traumatic experiences, especially adverse childhood experiences (ACEs), are strong environmental risk factors for major depressive episodes. Stress hormone receptors in the hippocampus (HIP) act as the gateway of mechanisms between stress and adrenal steroid action. Hypothalamus-pituitary-adrenal (HPA) axis is believed to play a crucial role in coordinating the organism's stress response because it can actuate glucocorticoid receptors (GRs). GRs together with mineralocorticoid receptors (MRs) act as ligand-activated transcription factors (LAF) [1]. Under traumatic stressors, their chromatin remodeling mechanism is capable of reprogramming neurons and circuits, which builds the connection between glucocorticoids and molecular mechanisms of chronic plus early life stress [1, 2].

Lifestyle medicines are used to prevent occurrence and recurrence of MDD, and some examples are improvements in sleep hygiene and dietary adjustments, increases in promoting physical exercise and social support. Treatment is essential because it shortens the duration and alleviates the symptoms, and the most effective way involves medication use.

Selective serotonin reuptake inhibitors (SSRIs) remain the best practice medication and are prescribed frequently. SSRIs comprises fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa), and escitalopram (Lexapro), and they can accelerate serotonergic activities through blockages of presynaptic serotonin reuptake. During the reuptake process, serotonin is taken back after carrying signals among neurons. Because SSRIs hinder the process, more serotonin exists to deliver messages among nerve cells, and this mainly affects serotonin rather than other neurotransmitters. Adverse effects of SSRIs involve impacts on the central nervous system, gastrointestinal distress and sexual impairments. Certain SSRIs can cause severe events namely serotonin syndrome and arrhythmias, etc.

Another pharmacological therapy option for MDD is serotonin-norepinephrine reuptake inhibitors (SNRIs). Representative SNRIs are milnacipran, duloxetine (DXT), desvenlafaxine (DVS), and the most predominant medication is the sustained-release form of venlafaxine. SNRIs have a dual mechanism of actions, for instance, the effect of venlafaxine involves a combination of both serotonin (5-HT) and norepinephrine (NE) transporter blockades, allowing 5-HT and NE remain active in the brain over a longer duration. Some undesirable effects of SNRIs are sleep disturbances, digestive issues, and increased blood pressure. SNRIs may cause rare but serious complications, for example, antidepressant discontinuation syndrome, suicidal thoughts, etc.

Novel and more efficacious antidepressant therapeutic agents are also identified and developed. This literature review describes mechanisms, clinical trials conducted, therapeutic benefits along with adverse effects discovered of several key antidepressants, and aims to provide insights into the future antidepressant discovery, development and application.

2. SSRIs

2.1. Fluoxetine

Fluoxetine is one of the major SSRIs and used as first-line treatment for MDD. Together with its ability to increase the extracellular concentration of 5-HT by inhibiting serotonin transporter (SERT), fluoxetine also exerts anti-apoptotic and antioxidant effects, improves neurogenesis and neuroplasticity, as well as reduces inflammatory reactions. Oral side effects associated with fluoxetine include xerostomia, nausea, vomiting and dysgeusia or taste alteration. The most repeatedly reported effect is xerostomia. Even though its prevalence rates vary broadly from 2.71% to 52.17%, it is lower compared to other antidepressants [3]. Xerostomia may lead to several adverse effects, for instance, dental complications and oral diseases, which impact patients' quality of life. Some other adverse reactions include insomnia, anorexia, manic episode onset, rare provocation of suicidal thoughts and behavior (particularly among teenagers), etc.

Since children and adolescents have an increased risk of developing adverse effects, it is essential to implement proper monitoring such as close observations of behavior changes, etc. Most negative impacts related to fluoxetine are dose-dependent and transient. As a result, clinicians should observe and check if the side effects subside before switching to a different antidepressant. It is equally important to perform with caution against the emergence of agitation or activation, and maintain flexibility in medication modifications. For instance, clinicians can suggest patients take fluoxetine in the early mornings if insomnia is present.

2.2. Sertraline

Sertraline is another prevalent medication used in the clinical treatment of MDD. A systematic review and meta-analysis (11 studies, n=406 participants) concluded that sertraline significantly decreases inflammatory factors (especially IL-6 and TNF-α) in MDD patients. The findings demonstrate that sertraline may ameliorate depressive symptoms by regulating the levels of inflammatory cytokines [4].

A child/adolescent anxiety multimodal study found that total physical symptoms, together with insomnia, restlessness, nausea etc. decreased significantly ($P<0.05$) across 12 weeks from baseline of

sertraline treatment (n=139 youth), which indicates it is plausible that these symptoms are transient [5]. The results from another retrospective cohort study showed estimates consistent with an average of 4.8 kg increase in weight gain within 2 years of sertraline treatment [6]. Thus, for underweight patients, it could be beneficial to prescribe an antidepressant such as sertraline.

Between weeks 6 and 12 is considered as an acute phase in MDD treatment, and Cipriani et al. (2010, as cited in Edinoff et al., 2021) found sertraline to be more potent compared to other SSRIs but patients are more likely to have diarrhea as a side effect [7]. Since sertraline exhibits linear kinetics, it can be optimal for patients with impaired drug clearance. To block the occurrence of serotonin syndrome, clinicians should proceed with caution when prescribing multiple, adjusting or discontinuing SSRIs.

3. SNRIs

3.1. Venlafaxine

Venlafaxine is an effective SNRI for treating MDD. The inhibition of norepinephrine transporter (NET) occurs at higher doses (225 and 300 mg/day), rather than at lower doses (75 or 150 mg/day). Another study also discovered that venlafaxine dramatically decreased whole-blood serotonin levels by more than 75% in both dose groups [8]. Another literature review (34 studies, n = 9,384 patients) found that venlafaxine outperformed placebo during the MDD 6-month relapse rate, had lower antidepressant withdrawal syndrome along with a lower incidence of dizziness [9]. It has a balanced efficacy and is fairly accepted as well as tolerated in the maintenance phase. Prolonged-release venlafaxine (venlafaxine XR) may alleviate lingering symptoms such as fatigue, low energy and anhedonia.

Venlafaxine at low doses can act primarily as an SSRI. Once symptoms are controlled, clinicians can consider increasing doses of venlafaxine when indicated to further strengthen serotonin transmission, promote norepinephrine, and accomplish complete alleviation of symptoms and restoration of functioning. Compared to the extended-release formulation, the rapid-release one has a stronger likelihood of causing sustained diastolic hypertension (increase up to 15 mmHg), which is roughly 10-15% of patients. The extended-release formulation increases blood pressure in about 6% of patients, but the occurrence of orthostatic hypotension is three times more often [10]. Moreover, chronic venlafaxine treatment also facilitates the incidence of hypertensive crisis in normotensive patients. Thus, clinicians should attentively monitor patients' blood pressure status in consequence of adverse effects on blood pressure profiles and potential interactions with antihypertensive treatments.

3.2. Duloxetine

Duloxetine is another SNRI that has become widespread in the treatment of MDD. Besides typical SNRI features, what makes duloxetine stand out is its ability to increase dopamine in the prefrontal cortex. This mechanism involves NET inhibition, and the transporters have a profound affinity for dopamine, which enables one another to act on both dopamine and norepinephrine. It is found that duloxetine is more effective compared to SSRIs among the elderly (> 60 years old), patients who experience clinical depression for the very first time, and especially those with severe symptoms as the starting point [11]. Evidence also suggests that duloxetine at 60 mg once daily reaches proper efficacy and reasonable tolerability at both acute and continuation phases. Duloxetine is rarely associated with serotonin syndrome, and it is considered to have a lower prevalence of sexual dysfunction in contrast with other antidepressants such as paroxetine and escitalopram. This is another advantage for duloxetine because sexual related complications are among primary causes of non-compliance.

Given its effectiveness and endurable tolerability, duloxetine preserves its well-rounded position as a treatment option in MDD. Meanwhile, synthesized data concluded that duloxetine increases aspartate transferase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP)

concentrations, but the magnitudes of those changes are not clinically significant [12]. The study also established compelling evidence of increases in total cholesterol, glucose, cardiac frequency, both systolic and diastolic blood pressures, but insufficient evidence of change in corrected QT interval (QTc) during duloxetine treatment. Hence, duloxetine treatment guidelines should incorporate differences in physiological risks, consider clinical picture and patient perspectives.

4. Novel Antidepressants

Although the classical antidepressants discussed above generate immediate and intense impacts on the monoaminergic system, they display a delayed clinical response in most cases, which could take a few weeks or so. Simultaneously, Cipriani et al. (2018, as cited in Kim et al., 2024) demonstrated that about 33% of MDD patients develop treatment-resistant depression (TRD) [13]. The established antidepressants fail to alleviate symptoms or produce improvements among those patients. Sometimes they already take multiple medications but still must tolerate persistent discomfort. Thus, novel pharmacological agents are in urgent need as next generation therapies.

Identification of ketamine is considered a tremendous success in MDD treatment because of its immediate symptom improvements within a few hours compared to classical antidepressants. Phillips et al. also discovered that recurrent therapies with ketamine also produce strengthened and longer lasting antidepressive effects especially for patients with TRD conditions. N-methyl-D-aspartate receptor (NMDAR) is the proposed pharmacodynamic target of ketamine, and two primary mechanisms indicate that in addition to boosting presynaptic glutamate release in the medial prefrontal cortex, ketamine also augments synaptic efficacy in the HIP [13].

Similarly, insights into the mechanism of action in brexanolone have redirected the field's attention to GABA. Brexanolone is an allosteric modulator of GABA-A receptors with superior efficacy and potency designed in intravenous delivery. Postpartum depression (PPD) is classified under MDD diagnosis with peripartum onset. Two randomized double-masked, placebo-controlled clinical trials with 3 phases were conducted by Meltzer-Brody et al. (2018 as cited in Bozzatello et al., 2025) analyzed the performance of brexanolone among PPD patients. The results demonstrate that positive outcomes were maintained within the intervention groups towards the end of the 30-day post-intervention window, which outperformed the placebo group. Moreover, a greater number of patients achieved symptom remission in the intervention group than the control group [14]. Brexanolone provides fast and efficacious resolutions, therefore is considered as a breakthrough antidepressant for moderate to severe PPD.

Another example is auvelity, a dose specified, sustained-release combination of dextromethorphan and bupropion which block NMDA receptors and stimulate sigma-1 receptors in parallel. To elaborate, the blockage of NMDA results in the subsequent mobilization of AMPA, and sigma-1 receptors regulate both voltage- and ligand-dependent channels. These mechanisms together enhance neuronal and synaptic plasticity potentially. A randomized double-masked and active-comparator clinical trials with 2 phases were carried out by Tabuteau et al. (2022 as cited in McCarthy et al., 2023) assessed the effectiveness and safety of auvelity with bupropion being the active-treatment control in the MDD treatment. Upon the completion of the treatment, auvelity group had substantially greater decreases in Montgomery–Asberg Depression Rating Scale (MADRS) total score compared to the baseline values, and this started right from the second week. The intervention group also had distinctly better scores from both remission (MADRS total score ≤ 10) and response rates ($\geq 50\%$ decrease in MADRS total score), and those positive outcomes began as early as the second week as well [15]. Another non-blind, long-range study called EVOLVE (n=145 patients) found similar significant improvements in MADRS total scores, along with benefits of cognition and anxiety associated with auvelity treatment among MDD patients. These key endpoints suggest that auvelity is a therapeutically beneficial, short-onset antidepressant with acceptable safety profile in the MDD treatment.

Even though the novel antidepressants discussed above are promising, several issues may limit their clinical utilities. For example, ketamine and dextromethorphan have misuse potential, and no studies have evaluated the therapeutic application among patients with MDD, and comorbid substance use disorders (SUDs). Extended use of intravenous ketamine is likewise connected with an increased potential risk of suicidal incidences occurring after termination of therapy. Brexanolone is still not broadly used because of the administration complexity. It requires a risk evaluation and mitigation strategy (REMS) as an IV infusion and needs to be administered in a medical facility. Breastfeeding during infusion is not contraindicated, but there is no further data being available about the impacts of brexanolone in breastfed infants. Further studies should be conducted to explore long-term safety and side effect biomarkers of novel antidepressants based on the knowledge of pharmacogenomics and clinical pharmacology.

5. Conclusion

This literature review describes molecular mechanisms, clinical trials conducted, therapeutic benefits along with adverse effects discovered of several major medications under SSRIs, SNRIs and novel antidepressants, respectively. SSRIs along with SNRIs have acute effects on the monoaminergic system, but their strength is subject to limitations imposed by delayed or inadequate therapeutic efficacy, suboptimal remission outcomes, and adverse reactions. Consequently, novel pharmacological agents are discovered as improvements for MDD therapeutic treatments. Each antidepressant has its unique features, and therapeutic protocol should incorporate differences in physiological risks, clinical manifestations, and patient-centered preferences.

Although both SSRIs and SNRIs are the primary antidepressants used for MDD treatment, it should not be ignored that a considerable number of patients still suffer from depressive episodes and even develop TRD conditions. This also indicates that the current principles, concepts and assumptions do not thoroughly explicate the MDD pathogenesis. In essence, further explorations into both the pharmacological and pathophysiological mechanisms remain necessary. This will in return empower the field to discover preventative, novel and more potent pharmacological therapies.

Meantime, novel and more efficacious antidepressant therapeutic agents are identified and developed. Identification of ketamine is considered a tremendous success in MDD treatment because of its immediate symptom improvements within a few hours compared to classical antidepressants. The mechanisms of brexanolone have also shifted the field's focus to GABA, which is associated with profound and quick impacts on emotional or cognitive behaviors. Though novel antidepressants are promising, they have misuse potential plus increased latent risk of suicidal incidences, etc.

From classical to novel antidepressants, even though no single medication is close to ultimate perfection, the general evolution is auspicious. Key features of auvelity such as rapid-acting, oral formulation, patient self-administration, and substantial benefits in both remission and response are optimal as antidepressants. Future studies should assess prolonged therapeutic benefits, safety profiles, and recognition of novel biomarkers among MDD patients especially with SUD and/or TRD.

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