Review Article

# The Effectiveness of Pharmacological Treatments for Major Depressive Disorder

Mahima Sanghera

*Xavier College Preparatory, 4710 N 5th St, Phoenix, AZ 85012, USA*

## ABSTRACT

Across all demographics, major depressive disorder (MDD) continues to rank first globally as the most common and often incurable mental health condition. In particular, this study identifies two categories: conventional antidepressants and rapid-acting antidepressants. It analyzes selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) from conventional antidepressants, as well as ketamine and esketamine from rapid-acting antidepressants. Utilizing existing research, this review examines the similarities and differences in the brain region affected by each treatment through neurotransmitters based on the type of antidepressant. The purpose of this review is to compare and contrast how varying antidepressant treatments affect neurotransmitters and how this determines their onset and duration of efficiency.

**Keywords:** Major Depressive Disorder (MDD); Conventional antidepressants; Rapid-acting antidepressants; Neurotransmitters; Treatments

## INTRODUCTION

With over five percent of adults diagnosed with major depressive disorder (MDD), it has become the leading mental health disorder globally (1). Despite this prevalence, the primary known etiologies of MDD simplify into three main categories: biological, psychological, and socio-environmental, as illustrated through the biopsychosocial model (2, 3). With all of the common etiological and risk factors for MDD taken into consideration, it is important to recognize the typical treatments prescribed. This is due to the necessity of recognizing the most effective ways to treat depression based on its variance in etiology for each individual case study. As such, while no treatment can serve all equally, the strengths and weaknesses of each can be pinpointed to allow those seeking treatment more literature and clarity in which is most beneficial for them.

While treatment can include neurotherapy and neurostimulation, the default is commonly pharmacological antidepressants. Therefore, the purpose of this review is to analyze and compare varying antidepressant treatments based on their onset and duration of efficiency. This review divides common pharmacological treatments into two main categories: conventional and rapid-acting antidepressants. In particular, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine

**Corresponding author:** Mahima Sanghera, E-mail: mahimasanghera@gmail.com.



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reuptake inhibitors (SNRIs) are utilized for conventional antidepressants; ketamine and esketamine are utilized for rapid-acting antidepressants.

When reviewing the unique significance of each treatment, it is imperative to ask, "How do changes to neurotransmitter systems that result from antidepressants affect the onset and duration of treatment effectiveness in individuals with major depressive disorder?" It is hypothesized that more invasive, rapid-acting antidepressants will on average be more effective for extremities of depression in the general populace, recognizing that individualized treatment can still greatly vary.

## BIOPSYCHOSOCIAL MODEL ETIOLOGY

### Biological Perspective

Genetic vulnerability, brain structure, and neuroendocrine processes are a few examples of components with the potential to contribute toward the development of depression. A 2014 Genome Wide Association Study (GWAS) of over 60,000 cases found a significant correlation between immune, neuronal signaling, synaptic density, and histone cascades in MDD, leading genetic vulnerability to constitute 35 to 40 percent of depression variance (4).

Many of these enzymes and hormones are genetically transmitted. In particular, for individuals with a first-degree relative with depression, the risk of a similar diagnosis increases up to three times as much (2). This is linked to specific neurotransmitters within neuroendocrinological processes in the brain directly correlated with and possibly casual to depression, as shown through neuroimaging. For one, on average, individuals with one or two copies of the short allele 5-HTTLPR, a serotonin transporter gene, experience more symptoms of depression and are more likely to develop the disorder, especially relative to those who only possess the long allele (2).

Similarly, the manner in which individuals respond to various stimuli exemplifies different psychological reasoning and motivations behind actions. Specific to depression, one large indicator of one's susceptibility is one's response to stress. Studies show that higher levels of cortisol and disruptions in cortisol regulation entail higher rates of depression.

Consequently, abnormalities in cortisol prevalence typically reduce the efficiency of cortisol level recovery post-stress (2). This translates to higher rates of relapsing and more severe symptoms than for individuals with steady, normal cortisol levels after treatment (2). One study analyzing 4.5-year-olds corroborates that children exposed to maternal stress, and, resultantly, possessed higher levels of cortisol on average, were more frequently internalizing depressive symptoms up to two years later than those without said exposure (2).

However, while many known biomarkers and aberrant neuroplasticity patterns exist for MDD, it is essential to factor in the psychological and socio-environmental aspects of an individual's multifaceted life when determining increased or decreased risk of depression from a biological standpoint.

### Psychological Perspective

Additional qualitative measures of psychological risk factors for depression include, but are not limited to, self-esteem, optimism, self-image, and low emotional clarity, all of which greatly fluctuate throughout one's life (5). Various negative self-perceptions have been linked to depression, with meta-emotions, or emotions in response to other emotions, often dictating depression severity (5). Many of these psychological tendencies can be attributed to rumination, or perpetual, cyclical negative thought processes. Especially with an increased dependency on emotion-focused coping through common attitudes such as positive fantasies and personality dispositions, rumination becomes a greater determinant of depressive attitudes and, ultimately, MDD (5).

Thus, with an ever-changing society that becomes increasingly hyper-aware of emotions and self-perceptions, it is essential to thoroughly analyze psychological indicators of MDD.

### Socio-Environmental Perspective

Lastly, conditions largely mold one's exposure to risk behaviors for MDD. Continual presence of these factors can increase the probability of developing MDD. For one, early life experiences, such as negative relationships with parents, bullying, and lack of school support have great potential to induce the brain chemical imbalances that foster depression (5). Similarly, gender-specific experiences, such as social and structural inequities and cognitive biases, are linked to higher rates of depression in women to the extent that women are twice as likely as men to develop MDD (5).

Acute negative life events have especially proven to be far more indicative of depression than other sources. First, 80% of depressed cases in one study were largely attributed to recent major negative life events that preceded them, with the likelihood of acute negative life events occurring being 2.5 times as high in depressed patients

(2). Consequently, long-term experiences with stressful events have a similar effect. Chronically stressful events imposed by socio-environmental conditions are a large contributor toward the likeliness of developing MDD, with multiple studies highlighting the depressive impact of being a single parent with low social support (2).

From this, it has been deduced that a low economic standing in general, due to social and environmental conditions, correlates to more acute sorrowful mental receptions of bigotry, which is critical considering ethnic minorities largely shape lower economic classes, on average (2). This obstructs one's ability to hold positive self-beliefs and coping skills, ensuing many risk behaviors for MDD or depression as a direct result (2). Said risk behaviors include sedentary behavior, substance abuse, and smoking/nicotine exposure, all of which correlate strongly to MDD (5).

As such, it is imperative to consider predetermined dispositions toward MDD for each individual patient that arises in the determination of treatments' efficiencies.

## NEUROTRANSMITTERS AND ANTIDEPRESSANTS

### Serotonin and SSRIs

In general, neurotransmitters serve the function of transporting messages throughout neurons in the central nervous system (CNS). Serotonin, or the 5-hydroxytryptamine neurotransmitter, acts as a hormone for influencing happiness levels, among many other functions (6). As such, it has a direct correlation to the development and longevity of MDD, with research identifying the "monoamine theory of depression" in the 1950s (7). With an emphasis on the CNS, the hypothesis deduced that MDD was caused in part by monoamine oxidase enzyme breaking down neurotransmitters – specifically, serotonin. Tenuous activity of serotonin pathways suggested an impact on the pathophysiology of MDD, making this hypothesis one of the first major purely biomedical studies on MDD.

More recently, however, the examination of tryptophan depletion, the precursor amino acid of serotonin, suggests another potential link towards impaired serotonin levels and increased chance of MDD (7). When altering diets to artificially lower the amount of tryptophan, it is found that patients who currently have MDD or a history of it show depressive symptomatology at a much more frequent rate, especially relative to those with no MDD experience (8).

As such, many antidepressants exist to reuptake the amount of serotonin present in the CNS; however, SSRIs are the most targeted toward serotonin reuptake. Being most geared toward serotonin over all other neurotransmitters, many studies have demonstrated not only decreased levels of depression post-SSRI treatment, but also reignite cortical brain regions in responding to positive stimuli (8).

For example, after eight weeks of SSRI treatment, increased short-term responses were observed, which also reached hypoactive responses after 22 weeks (9). However, in this same study, the onset action for positive biases in emotional processes, such as positive words recounted in a memory task or reactions when shown happy faces, was apparent after only one week, noticeably faster than other pharmacological treatments. This is biologically explained by the uptake in reboxetine and citalopram, antidepressants with SSRI-like properties, observed when exposed to these stimuli (9, 10).

Overall, SSRIs have been developed greatly throughout the span of decades of its existence, with consistent renovations increasing its efficiency. No other antidepressant is able to match its rate and level of efficacy in the short- or long-term. The primary difference arises in the specialties of varying degrees of MDD it is able to treat. While SSRIs consistently produce the most results and the fastest for the general populace, its efficacy for patients with more severe forms of depression is still under investigation.

### Norepinephrine and SNRIs

Norepinephrine, also known as noradrenaline, is integral to the body's "fight-or-flight" response, with a heavy focus on understanding and regulating cognition, motivation, and intellect in social situations (11, 12). It is the second critical neurotransmitter associated with MDD and antidepressants, made from dopamine in brainstem nerve cells (11).

In reference to its connection with MDD, norepinephrine transporter binding in the locus coeruleus, a noradrenaline-rich region, has been found at lower levels in the postmortem tissues of MDD patients. Similarly, α2A-adrenocepters, tasked with norepinephrine regulation and release, had an altered density. Its density was much higher in the frontal cortex of patients with no administration of antidepressants. This was observed in a study that included 19 patients diagnosed with MDD as per the DSM-IV and without comorbidity. The study concluded that compared with healthy subjects, MDD patients had an average of 29% higher nondisplaceable binding potential for norepinephrine in the thalamus, supporting the hypothesis that increased levels of

norepinephrine transporter availability are associated with MDD (13).

Increased levels of norepinephrine transporter availability result in lower levels of norepinephrine available for downstream signaling, which, paired with the presence of $\alpha_2$-AR antagonists, suppresses norepinephrine's effects in the brain by causing mass reuptake in the synaptic cleft (14). This independent decrease in norepinephrine is perpetuated by impaired lines of communication from transporters' reuptake of norepinephrine from the post-synaptic cleft. A critical example is clonidine, which decreases levels of norepinephrine, as well as the function of memory consolidation, a frequent symptom of MDD (14).

Thus, the development of SNRIs began a few years after SSRIs with the intended purpose of being more accurate in reducing depressive symptoms by targeting more neurotransmitters (15). Currently, they serve to prevent the reuptake of both serotonin and norepinephrine into the nerve cells that they were produced from, artificially increasing their presence in the CNS (15). Unfortunately for conditions more reliant on resisting norepinephrine reuptake, the majority of SNRIs publicly available primarily target serotonin receptors over norepinephrine ones, with only one major SNRI – levomilnacipran (Fetzima) – having a greater effect on norepinephrine (15).

Alongside other SNRIs, Fetzima works to prevent reuptake of norepinephrine through the A6 locus coeruleus, which is the source of the majority of noradrenergic neurons (16). Fetzima innervates a variety of regions throughout the brain, such as the cerebral cortex, hippocampus, cerebellum, amygdala, hypothalamus, and spinal cord (16). From this, the α2A-receptors centralize on reducing norepinephrine release and regulating neuronal excitability for long-term efforts (16).

Neuroimaging research has supported the hypothesis that SNRIs alter the brain networks of MDD patients through decreasing hyperconnectivity in the default-mode network in the thalamo-cortico-periaqueductal and cortico-striatal circuit (17). The efficacy of SNRIs can typically be predicted by its impact on one's right thalamus. If and when SNRIs are successfully able to increase the nodal clustering coefficient (NCC) in the right thalamus, there is a higher chance of remission from MDD symptoms. However, current research is insufficient to provide a causal relationship, suggesting it is more likely that the two are simply correlated (17).

**Glutamate and Ketamine**

Glutamate is one of the most active neurotransmitters within the entire nervous system, being in the epicenter of many connections to other pathways and receptors (18). These pathways range all the way from brain neurons to spinal cord neurons, as seen in the case with MDD. However, the most unique feature of glutamate in relation to its role in the efficacy rate of antidepressants is the approximately 30 proteins near glutamate synapses that regulate neuronal excitability.

Neuronal excitability, an integral part of neuroplasticity holistically, is the magnitude of neurons' response to stimulation. The ability of norepinephrinergic neurons to spontaneously fire spikes in the locus coeruleus is critical for crafting experience-driven plasticity long-term. A dis-regulation of these spikes as is seen when negative environmental factors and experiences reinforce depressive attitudes (19). To guarantee regulated levels of excitability from glutamate, γ-Aminobutyric acid (GABA) is employed. Despite being synthesized from glutamate, GABA is inhibitory while glutamate is excitatory. This results in GABA being able to manage glutamate levels in the CNS via suppressing its activity (18).

Without GABA being able to lessen the excitability effects of glutamate, side effects as fatal as cytotoxicity (cell death), decreased neuronal regeneration, and impaired spatial learning emerge (18). These functions are most prominent, in terms of anxiety disorders and depression, in metabotropic glutamate receptors through gene expression and photosynthesis. Glutamate bonds with the receptors to activate signal transmission and inhibit neurotransmitter reuptake, preventing upsurges of MDD (18).

As such, ketamine most frequently works through these glutamate pathways, blocking overactivation of glutamate receptors, which has otherwise proven to directly link to MDD (20). The validity of this has been shown through an analysis of 25 ketamine studies conducted by the Arizona Ketamine Treatment and Research Institute, with all 25 studies observing ketamine as an "active and rapid antidepressant" (20). The way ketamine reduces overstimulation of glutamate and its receptors is by inhibiting glutamate principle neurons, as well as reducing rapid glutamate release at select synapses (21). One more novel finding suggests a retrograde adenosinergic mechanism that contributes to ketamine's rapid antidepressant action (21). Utilizing an *in vitro* model with rat cortical neurons, the study showed acute ketamine reduced KCl-evoked and other network effects within presynaptic potentiation, thereby lessening excess glutamate neurotransmission.

Unlike other antidepressants, ketamine is more

effective in the synapses as the majority of their neurons are glutamatergic, or use glutamate as a primary neurotransmitter (22). Thus, as prolonged environmental stress augments glutamate release in limbic and cortical areas past the point of healthy equilibrium, ketamine counteracts it (22). In terms of clinical MDD symptoms, this also translates to higher reduction of suicidal behaviors, with ketamine able to modulate activity in the σ and μ opioids, serotonin 5HT3, and muscarinic and α7 nicotinic receptors (23).

In terms of onset duration of effectiveness, a review by scientist Mendonça Lima of the University of Rio de Janeiro and associates of 11 studies of individuals with MDD highlighted a range from 40 minutes to one week for response time clinically (24). In particular, the first significant response time of increased effectiveness, according to a recent literature review, was four hours post-infusion, the peak was around 24 hours after, and the beginning of a diminishing trend was around seven days after (25). However, despite this typical downward trend, research from Conley and colleagues in 2021 demonstrates a relative effectiveness up to six weeks post-administration, particularly for patients with treatment-resistant depression (TRD), or those who have been exposed to two or more other antidepressants for at least six weeks each without any remission or bettering in mood by 50% or more (26, 27). Thus, the effectiveness of ketamine, closely related to esketamine, is still largely up for debate in that varying studies conclude glaringly different results. Especially relative to SSRIs and SNRIs, a conclusion about ketamine's efficacy rate is not as consolidated.

### Glutamate and Esketamine

This leads directly into the conversation of esketamine because, while ketamine can have significantly more noticeable effects on patients with TRD, that is not its main function. Unlike ketamine, esketamine has been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) to treat those with TRD (23). A recent review paper has shown that esketamine is a beneficial addition to other antidepressants, particularly if other antidepressants were ineffective. However, other work has suggested that esketamine does not have a significant effect on mitigating symptoms of MDD (23). Unfortunately, there are still many scenarios in which the safety of esketamine is yet to be assessed (23).

Nevertheless, it has still shown to be quite effective in enhancing the results from antidepressants more so targeted toward serotonin and/or norepinephrine by inhibiting the N-methyl-D-aspartate (NMDA) glutamate receptor (28). As a byproduct, esketamine increases the levels of glutamate, exciting the prefrontal cortex (23). It does so just enough to facilitate communication between brain cells (27). Esketamine treats depression differently than many other antidepressants by augmenting glutamate via a nasal spray with around 56 – 84 mg twice weekly for a month, followed by periods of less weekly frequency (29). One study utilized a MADRS scale to measure depressive symptoms via a questionnaire. They leveraged esketamine and a placebo spray in the aforementioned quantities for 435 patients with TRD concluded the relative success of the esketamine to be significantly greater than the placebo (30). However, esketamine, especially, severely lacks research and experimental trials in the status quo, thus making it difficult to pinpoint approximations of its efficacy rate. As is discussed within the gaps in literature, esketamine also has the potential to be dangerous, limiting the ability of researchers to conduct many interactive trials with it. But similar to ketamine, it can be currently concluded that conventional antidepressants are typically safer and more effective than ketamine, hence why they are employed in test trials more frequently.

## GAPS IN LITERATURE

### Serotonin

Theories that serotonin and MDD were invariably associated began in the 1950s, thus leading to the development of SSRIs (31). In fact, over 80% of individuals surveyed believe depression is heavily influenced by "chemical imbalances" (31). However, while it is widely accepted that serotonin has a direct correlation with MDD, its effects largely vary with respect to an individual's predetermined risk factors and behaviors (8). With individuals predisposed toward depression in the first place, whether genetically, psychologically, environmentally, etc., a lack of tryptophan can result in depressive symptomatology (8). This is because tryptophan is the major precursor amino acid necessary for serotonin production, thus lowering the overall amount of serotonin available for use in its absence.

Thus, to evaluate the correlation between tryptophan and serotonin depletion and depressive symptoms, more research ought to be conducted with a plethora of different depressive statuses in participants. Current research is primarily limited to the small scope of existing studies with participants taking antidepressants, so with more groups focused on the differences between individuals with no history of depression, a mild history, and a

severe history, and how they all interact with specialized tryptophan depletion, more evidence can be produced to support or negate the hypothesis of serotonin's major connection to MDD and symptomatology (31).

**Norepinephrine**

While many studies have examined the effects of norepinephrine on a variety of cortical and subcortical regions, more work can be done on the relationship between SNRIs and increasing the nodal clustering coefficient (NCC) of the right thalamus. Since NCCs are the primary and most common metric to understand the level of proximity of nodes in a neighborhood to one another, it is crucial toward predicting reaction processing times (32). Current consensus is that there is a lack of evidence supporting a causal relationship, either between SNRIs alleviating depressive symptoms because it increases the NCC, or vice versa (17). This gap may be filled by more fMRI research on the interaction of SNRIs and the NCC. Research highlights the amygdala in abnormal connectivity behavior with SSRIs, which themselves are distinct from SNRIs; however, this ought to be expanded to more cranial regions to have the best accuracy in predicting fundamental neurological shifts resulting from SNRIs (33).

**Ketamine**

As ketamine has become a popular supplement to SSRIs and SNRIs, its usage and abuse has also skyrocketed (34). While much current literature interprets its short-term effects, it is becoming increasingly essential to study longer-term benefits and risks because of its increasing prevalence. One notable meta-analysis concludes that ketamine has the potential to lessen neuronal connectivity through less gray matter volume and white matter integrity. Similarly, this affects other cranial regions, especially the thalamus, interfering with processing sensory information, and the cortex, skewing decision-making capabilities. However, only 16 studies were able to be assessed in this study, thus making it imperative to reassess other studies and conduct further experimental research to determine the long-term extent of ketamine's effect on the N-Methyl-D-Aspartate (NMDA) receptor (34).

In accordance with more knowledge gathered about potential long-term effects of ketamine, more work can also be done on ketamine's side effects in general. In terms of a variety of depressive disorders, ketamine has most frequently been linked to hypertension and confusion/agitation. However, the current hypothesis is that these extraneous symptoms are mostly constrained and present around the time of treatment (35). Once again, this is largely due to the lack of evidence that these characteristics can continue well past their initial contraception, making it beneficial to conduct more longitudinal studies about ketamine's phenotypic expressions, as well as at the neuronal level.

**Esketamine**

While many functions of esketamine have been examined and mapped out, including but not limited to blocking the GluN2B-NMDA receptors and releasing dopamine in the striatum, it is important to consider NMDA-receptor-inhibition-independent effects. In particular, esketamine has shown preliminary success in mitigating imminent suicidal behaviors from treatment-resistant patients (33). Due to the multifaceted dimensions of developing suicidal tendencies, future work ought to also consider alternative causes for behavioral changes before attributing all of the changes to esketamine administration (36).

However, more work must also be done on the abuse potential of esketamine. In particular, safety concerns can arise in its administration and long-term effects. Currently, the most commonly reported side effects of esketamine are nausea, dissociation and dizziness. One study showed when patients were administered esketamine with therapy, there was up to a 70.8% prevalence rate in adverse side effects. When patients were given esketamine and a placebo in the same study, there was still a 60% rate of acute side effects (23). Thus, it is highly likely that esketamine is the common denominator behind many of these long-lasting side effects, and more research should be done examining esketamine long-term before its increased usage in the medical field.

## CONCLUSION

Thus, overall, the choice of antidepressant utilized for varying degrees of depression depends greatly on individual characteristics and reactions to treatments. The rapid-acting antidepressants were better suited toward individuals with treatment-resistant depression, thus supporting the hypothesis that different degrees of MDD can influence which types of antidepressants are most effective. However, conventional antidepressants were almost always beneficial to begin treatment with to determine one's response to them. Similarly, for those that found success in lessening depressive symptoms with conventional antidepressants, this success was often

relatively faster than with ketamine or esketamine and lasted longer. Therefore, continued development of both to overcome their current limitations in research and practice is necessary to impact the greatest number of patients with varying severities of depression.

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