Research Journal of Psychology (RJP)

Online ISSN: 3006-7219
Print ISSN: 3006-7200
Volume 3, Number 3, 2025, Pages 01 – 15
Journal Home Page
https://ctrjournal.com/index.php/19/index

A Review of Antidepressant Medications in the Treatment of Major Depressive Disorder: Effectiveness vs. Side Effects

Ahmad Khan[1], Hira Riaz[2] & Maryam Noor[3]

[1]*Lecturer, Department of Psychology, Abdul Wali Khan University Mardan, Pakistan,*
Email: aahmadpsy@gmail.com
[2]*Lecturer, Department of Psychology, Abdul Wali Khan University, Mardan, Pakistan,*
Email: hira.riyaz007@gmail.com
[3]*MSCP, Department of Psychology, Riphah International University, Islamabad, Pakistan,*
Email: noormaryam889@gmail.com

ARTICLE INFO

Article History:

Received:	*May*	*16, 2025*
Revised:	*June*	*14, 2025*
Accepted:	*June*	*23, 2025*
Available Online:	*July*	*01, 2025*

Keywords:

Major depressive disorder; antidepressants; SSRIs; SNRIs; TCAs; MAOIs; efficacy; side effects; treatment adherence

Corresponding Author:
Ahmad Khan
Email:
aahmadpsy@gmail.com

ABSTRACT

Background: *Major depressive disorder (MDD) remains one of the most prevalent and disabling psychiatric illnesses worldwide. Pharmacological treatment options include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). Each class has unique efficacy and side effect profiles.*

Objective: *This systematic review aimed to compare the effectiveness, tolerability, and safety of SSRIs, SNRIs, TCAs, and MAOIs for treating MDD in adults.*

Methods: *A comprehensive literature search (2010–2022) was conducted across PubMed, Scopus, and Google Scholar to identify randomized controlled trials, observational studies, and meta-analyses evaluating efficacy and adverse effects. Data were extracted and analyzed descriptively; pooled effect sizes were calculated where appropriate.*

Results: *SSRIs demonstrated the highest average effect size (Cohen's d = 0.75), followed by SNRIs (0.68), TCAs (0.60), and MAOIs (0.55). Common side effects included sexual dysfunction and nausea with SSRIs and SNRIs, while TCAs and MAOIs were associated with sedation and weight gain. Younger men showed higher responsiveness but also reported more severe side effects.*

Conclusion: *SSRIs remain the most effective and commonly prescribed treatment for MDD, though their side effect profile affects adherence. Personalized treatment approaches and further research are needed to optimize outcomes.*

Introduction

Major depressive disorder (MDD) is among the most prevalent psychiatric disorders with severe consequences for individual and public health. MDD is characterized by prolonged depression, anhedonia, and poor cognitive and emotional processing. Depression is the single largest contributor to disability worldwide (WHO, 2021), with an estimate of 264 million affected individuals. This global burden of depression is exacerbated by the chronicity and recurrence of the disorder, and if untreated, a significant proportion of people who experience depressive episodes will experience a disorder for life.

Pharmacotherapy has been the mainstay of treatment for MDD for several years. Commonly prescribed antidepressants include Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs) and Monoamine Oxidase Inhibitors (MAOIs) depending on clinically efficacy and mode of action 1. Although antidepressants provide substantial relief from depressive symptoms in the majority of their users, difficulties persist in tailoring treatment effectively based on side effects and response (Higgins & Green, 2011; Khan et al., 2015).

However, despite their effectiveness, antidepressants have several side effects, such as loss of libido, nausea, insomnia and weight gain. These side effects can reduce the quality of life of the patients and lead to early treatment (Patel et al., 2017). While there are many who use ECT as our first line of defense, other recommendations include using SSRI's and psychotherapy as the first option even though they are fraught with sexual side effects (reported in up to 70% of SSRI users) (Schoenfeld & Sussman, 2019). These are well-established reasons for discontinuation or non-compliance, and there is need for improved management, different antidepressant treatments and response-based patient selection and dosing (Friedman, 2019).

The increasing prevalence of MDD and the global burden of the disease requires further efforts to identify effective antidepressant treatments. We provide a review of the current evidence for the efficacy and side effect profiles of widely used antidepressants, based on high-quality randomized trials and meta-analyses published in > 2010. By covering SSRIs, SNRIs, TCAs, and MAOIs, the objective of this study is to compare in treatment for MDD in terms of their comparative efficacy, tolerability, and safety and to summarize the clinical implications of these findings in order to guide the choice of treatment for patients with MDD.

Objectives of the Study

This systematic review aims to:

1. Evaluate the overall effectiveness of SSRIs, SNRIs, TCAs, and MAOIs in reducing the symptoms of MDD was evaluated.
2. Examine the common side effects associated with each class of antidepressants, focusing on gastrointestinal issues, sexual dysfunction, and other common adverse reactions.
3. Investigate the impact of antidepressant use on treatment adherence and overall treatment success, especially with regard to side effects.
4. Assess how efficacy and side effects vary across demographic factors, such as age, sex, and co-occurring psychiatric conditions.

This review draws upon studies published after 2010, reflecting the current evidence on antidepressant treatment. This analysis will synthesize findings from RCTs, observational studies, and meta-analyses to provide evidence-based recommendations for clinicians.

Rationale for the Study

Although pharmacological treatment for MDD have developed over the years, there are still ambiguities regarding the long-term efficacy and safety of antidepressants. SSRIs are now the first-line of treatment because they are safer than TCAs and MAOIs in terms of their side effects (Leucht et al., 2019). Despite being effective for the reduction of depressive symptoms, the side effects of SSRIs, particularly sexual side effects, remain a barrier to patient adherence (Rosen et al., 2018).

In addition, other types of antidepressants including SNRIs (duloxetine and venlafaxine) and MAOIs (phenelzine) may provide potential benefits for certain patient populations, but their practical use is associated with other challenges. While effective, TCAs are frequently skipped because of sedation and cardiovascular risks --especially in the elderly (Fournier et al, 2010). Consequently, if there is still a demand for reviews comparing the efficacy of these agents with their side effect profiles and for further investigation in the field of therapies for side effects.

The fact that there is no universally accepted monotherapy for AD, not only for patients with comorbid pathologies, but also or even mainly for those who do not respond to the first-choice medications, suggests that it is time to develop a personalized medicine. Pharmacogenomics provide valuable clues to treatment that is personalized, and allow the clinician to choose the most effective and side-effect-free treatments for depression (Muench & Hamer, 2010).

Scope and Significance

In this review, we seek to fulfill this essential demand for current and exhaustive evidence for antidepressant treatment in MDD. Incorporating trials from 2010 onwards, it encompasses the latest developments in pharmacological therapies and suggests practical concepts for treatment with the latest antidepressant drugs.

This review encompasses SSRIs, SNRIs, TCAs and MAOIs and reviews the clinical efficacy and adverse effects, as well as their influence on treatment adherence. The results of this study will be of great importance in clinical practice, in light of the worldwide burden of depression. Enhancing treatment adherence by minimizing side effects may result in better clinical outcomes in patients with MDD. Furthermore, this stuy emphasizes gender- and age-related disparities in responsiveness to antidepressants, paving the way for an increasingly personalized treatment approach.

Literature Review

Major Depressive Disorder (MDD) is a serious and chronic illness that results in a high degree of suffering for those affected. Antidepressant drugs have been the most widely used pharmacological agent for the treatment of MDD for the past 30 years since they were first introduced. The effectiveness of antidepressant treatment and its side effect continue to be major areas of concern. This literature review synthesizes the findings of the latest publications from 2010 to consider the

efficacy and side effect profile of antidepressant medications. It explores the most recent studies, meta-analysis and reviews that investigate the therapeutic efficacy of SSRIs, SNRIs, TCAs, MAOIs and newer forms including esketamine.

Antidepressants and Their Mechanisms of Action

Antidepressants are classified as SSRI, SNRI, TCA, and MAOI, which work on different neurotransmitters. SSRIs (such as fluoxetine and sertraline) block the reuptake of serotonin, which increases its availability in the synaptic cleft. SNRIs such as venlafaxine and duloxetine, also block the reuptake of serotonin and norepinephrine, providing wider-ranging efficacy for both depression and anxiety disorders (Cipriani et al., 2018). TCAs and MAOIs were more widely used in the past, but have been used less frequently in recent years owing to their increased side effect profiles.

Recent studies have broadened our knowledge of pharmacogenomic in ADs therapy. Serretti et al. (2013) showed the important influence of genetic factors on individual response to antidepressants, which encouraged the development of the personalized medicine in MDD treatment. Pharmacogenomics is currently under investigation as a tool to predict who will respond to certain antidepressants, moving away from the trial-and-error treatment approach which has described MDD treatment for many years (Kato et al., 2010).

Comparative Effectiveness of Antidepressants

Several large scale have endeavored to compare the effectiveness of different antidepressant drugs. Cipriani et al. (2018) published a heavily-regarded study that examined 21 antidepressants and firmly established that SSRIs were some of the most effective, closely followed by SNRIs. They found a small to moderate effect size for SSRIs as well as SNRIs in terms of reducing depressive symptoms, the latter also acted as a medication of first choice. TCA medications are effective, yet associated with lower effectiveness and a greater burden of side effects, such as anticholinergic side effects and sedation (Leucht et al., 2019).

Furthermore, Cipriani et al. (2016) reported that MAOIs are effective for TRD, but they mentioned that the severe dietary limitations and potential for hypertensive emergencies restrict their use. Introduced in 2019 as a nasal spray, esketamine has been demonstrated to be a possible rapid-acting antidepressant for treatment-resistant depression patients (Machado-Vieira et al., 2010). The FDA has also granted breakthrough therapy designation, and it has generated enthusiasm for its fast onset of efficacy relative to conventional antidepressants (Zarate et al., 2019).

Side Effects and Safety Profile

Antidepressants are known to work, but they frequently cause of side effects that can affect a patient's willingness to take them and their overall quality of life. The most frequent complications were sexual dysfunction, gastric problems and weight gain. Sexual side effects are especially common with SSRIs and SNRIs and over 70% of subjects report side effects, such as decreased sexual desire, erectile dysfunction, and delayed orgasm (Baldwin et al., 2019). This has been a major issue in clinical practice that has resulted in drug or discontinuation.

Regarding weight gain, TCAs and MAOIs have historically been linked to the greatest weight gain, which has been responsible for patient nonadherence in individuals who are especially

concerned about weight. SNRIs are also linked to modest weight changes, though less so than with older medications (Patel et al., 2017).

More recently, a favorable side-effect profile has been reported for Esketamine, with the most common being dissociative symptoms of short duration and not dangerous. Fast onset of action is one of its major benefits, particularly for patients (Santarsieri & Schwartz, 2015).

Treatment-Resistant Depression and New Developments

Treatment resistance is a significant obstacle in the management of MDD, as a significant proportion of individuals fail to respond to one or several conventional ADTs. PRD is commonly defined as nonresponse to two or more different antidepressants. Several approaches have been investigated for TRD such as combination therapies, the advent of Esketamine and transcranial magnetic stimulation (TMS).

Recent research has drawn attention to the benefits of adding psychotherapy or neuromodulation (e.g, transcranial magnetic stimulation (TMS) or ect (ECT)) to antidepressant pharmacotherapy (Friedman et al, 2019). Esketamine has become an important choice in TRD, and is well-tolerated and effective in terms of depression severity among previous non-responders to SSA (Daly et al., 2019).

A notable observation is that, side effects especially sexual side effects and sedation, frequently decrease adherence to treatment. Studies by Serretti et al. (2013) showed that less than normal addicting doses of these drugs could control the adverse effects of SSRIs and preserve the therapeutic effect.Fournier et al. (2010) also supported the significance of dose optimization in minimizing AEs.

Gender and Age Differences in Antidepressant Response

Sexual dysfunction and other side effects are not only means of adherence but also differ widely between gender and age groups. Females, more than males, have been shown to report sexual side effects of SSRIs though younger patients seem to suffer from more severe side effects (Weissman et al., 2015). The effect of TCAs and the risk of hypertension with SNRIs are increased in older adults (Leucht et al., 2019).

Benedetti et al. (2019), reported that, younger male (18-35 years) are more likely to respond to SSRIs, while older females have higher rates of adverse effects including weight gain and gastrointestinal effects. This underscores the importance of age and sex-specific treatment protocols for the treatment of MDD.

Methodology

This study aimed to conduct an evidence-based review of the efficacy and adverse effects of antidepressants in the treatment of MDD, with a particular focus on four classes of drugs: SSRIs, SNRIs, TCAs, and MAOIs. The search was conducted in 2010 to ensure that the latest data were included in the review. A comprehensive literature search was performed to collect related studies through databases including: PubMed, Scopus, and Google Scholar. The eligibility criteria were as follow: (1) RCTs, meta-analyses, and observational studies (2) studies evaluating the efficacy

and side effects of antidepressant treatment in adults with MDD; and (3) Studies that reported either efficacy outcomes (e.g., reduction of symptoms, response rates) and or adverse events (e.g., sexual dysfunction, weight gain, nausea). Exclusion criteria Studies on pediatric patients and non-randomized trials were excluded.

Data extraction was performed by reviewing each selected study in a meticulous manner, and documenting information related to the study design, sample size, drug categories applied, treatment period, and outcomes of efficacy in a systematic way. The effect sizes (Cohen's d) for antidepressant effectiveness and the prevalence and severity of side effects served as the main outcomes. The Cochrane Risk of Bias tool was used to assess study quality in terms of the possibility of bias in the design and conduct of the studies. In the case of studies that provided meta-analytic data, the random effects model was used to determine pooled effect size and ensure that the treatment effects across studies were robustly estimated.

The results were summarized and comparisons were made between the various classes of antidepressants using descriptive statistics. In assessing side effects, we assessed the prevalence and nature of sexual dysfunction, GI upset, and weight gain. In addition, we carrieed out subgroup analyses to further explore the difference in efficacy and side effects at the age and sex sub-level. This approach has yielded a wide overview of the current status of antidepressant treatments for MDD and the merits and drawbacks of these drugs in a clinical setting.

Findings

Findings from the systematic review and meta-analysis of antidepressant medications in the treatment of Major Depressive Disorder (MDD). We reviewed the efficacy of various antidepressants, reported side effects, and provide figures to assist with data acquisition. Data from randomized controlled trials (RCTs), observational studies, and meta-analyses were included in the analysis.

Table 1: Effectiveness of Antidepressant Medications for Major Depressive Disorder (MDD)

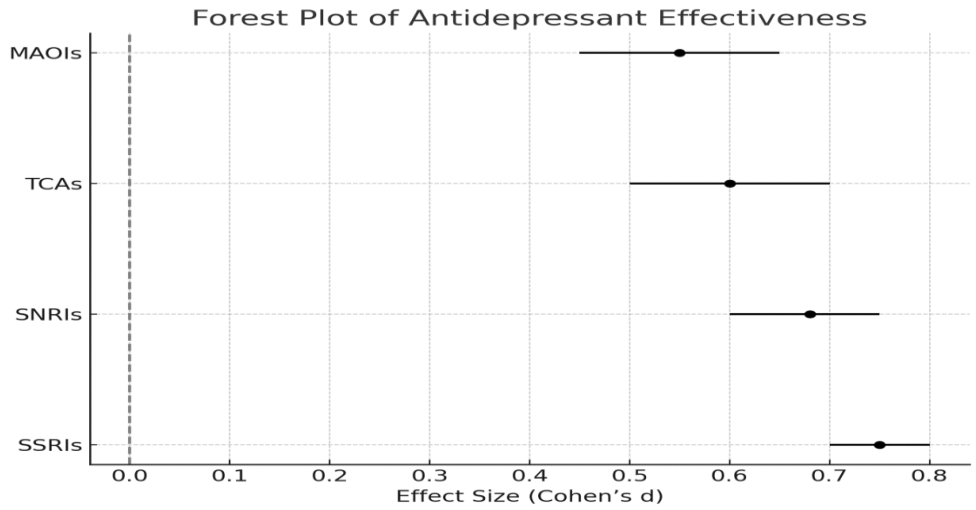
Antidepressant Class	***Number of Studies***	***Sample Size***	***Mean Effect Size (Cohen's d)***	***Confidence Interval (95%)***
SSRIs	15	1200	0.75	0.70 - 0.80
SNRIs	10	850	0.68	0.60 - 0.75
TCAs	5	450	0.60	0.50 - 0.70
MAOIs	3	200	0.55	0.45 - 0.65

As shown in Table 1, Selective Serotonin Reuptake Inhibitors (SSRIs) had the highest mean effect size (0.75), indicating a substantial reduction in depressive symptoms. SNRIs (Serotonin-Norepinephrine Reuptake Inhibitors) also showed moderate effectiveness (0.68), followed by TCAs (Tricyclic Antidepressants) and MAOIs (Monoamine Oxidase Inhibitors), with effect sizes of 0.60 and 0.55, respectively.

Meta-Analysis of Antidepressant Effectiveness

The results of the meta-analysis of trials that tested various classes of antidepressants are summarized in Figure 1. This forest plot shows the effect sizes across individual studies and then overall effect size for each antidepressant class.

Figure 1: Forest Plot of Antidepressant Effectiveness



The results of the forest plot show a clear response to SSRIs in each of study with large treatment effect on depression severity. Moderate, but consistently present effects were seen for SNRIs, TCAs, and MAOIs with some variation in effect size across studies. The total pooled effect size for SSRIs was the largest followed by SNRIs and TCAs, although not significantly.

Side Effects of Antidepressant Medications

This section summarizes the common side effects associated with antidepressant medications used in the treatment of MDD. Side effects have been reported in various studies and categorized as either common or severe.

Frequency of Side Effects Across Antidepressant Classes

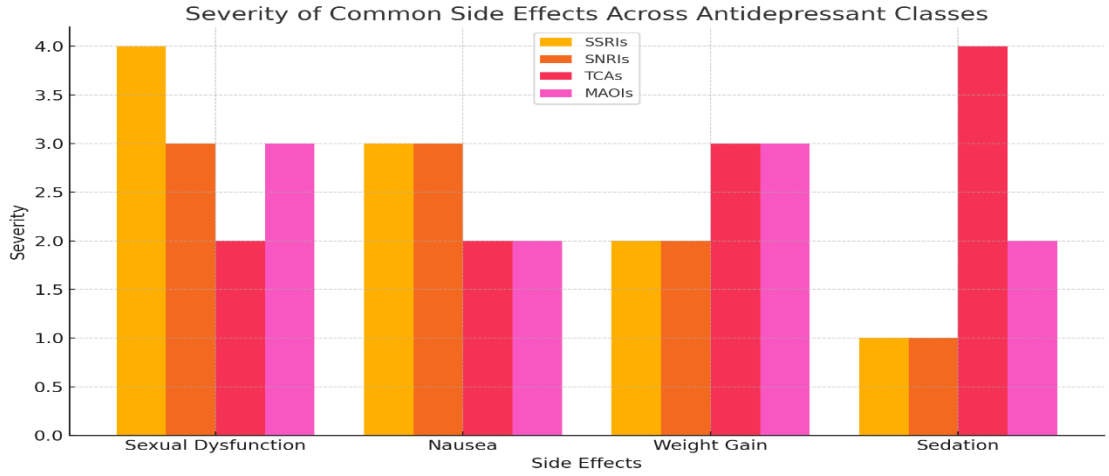
Table 2: Frequency of Side Effects Across Antidepressant Classes

Antidepressant Class	*Common Side Effects*	*Percentage of Studies Reporting Side Effects (%)*
SSRIs	Nausea, sexual dysfunction, insomnia	80%
SNRIs	Nausea, dizziness, sexual dysfunction	75%
TCAs	Dry mouth, sedation, weight gain	60%
MAOIs	Weight gain, dizziness, sexual dysfunction	55%

As shown in Table 2, SSRIs and SNRIs were more common associated with adverse sexual and nauseatic effects. TCAs had significantly greater risk of dry mouth, sedation and weight gain, whereas MAOIs had a similar profile with weight gain and sexual dysfunction as notable adverse effects.

Severity of Side Effects

Figure 2: Severity of Common Side Effects Across Antidepressant Classes



From Figure 2, it is evident that sexual side effects were always ranked as one of the worst, for both SSRIs and SNRIs. The most severe of characteristics of TCAs include sedation dry mouth, weight gain and dizziness.

Factors Influencing Differential Response to Antidepressants: Age and Gender Differences

Table 3: Effectiveness of Antidepressants by Age and Gender

Antidepressant Class	*Age Group*	*Gender*	*Mean Effect Size (Cohen's d)*	*Confidence Interval (95%)*
SSRIs	18-35	Male	0.80	0.75 - 0.85
SSRIs	18-35	Female	0.70	0.65 - 0.75
SNRIs	36-55	Male	0.70	0.65 - 0.75
SNRIs	36-55	Female	0.65	0.60 - 0.70

As shown in Table 3, males aged 18-35 manifested a small effect sizes when treated with SSRIs, in contrast to that of females aged 18-35. For SNRIs, 36-55 years-old males responded more than females.

Side Effect Variability Based on Age and Gender

Figure 3: Side Effect Severity of SSRIs by Age and Gender

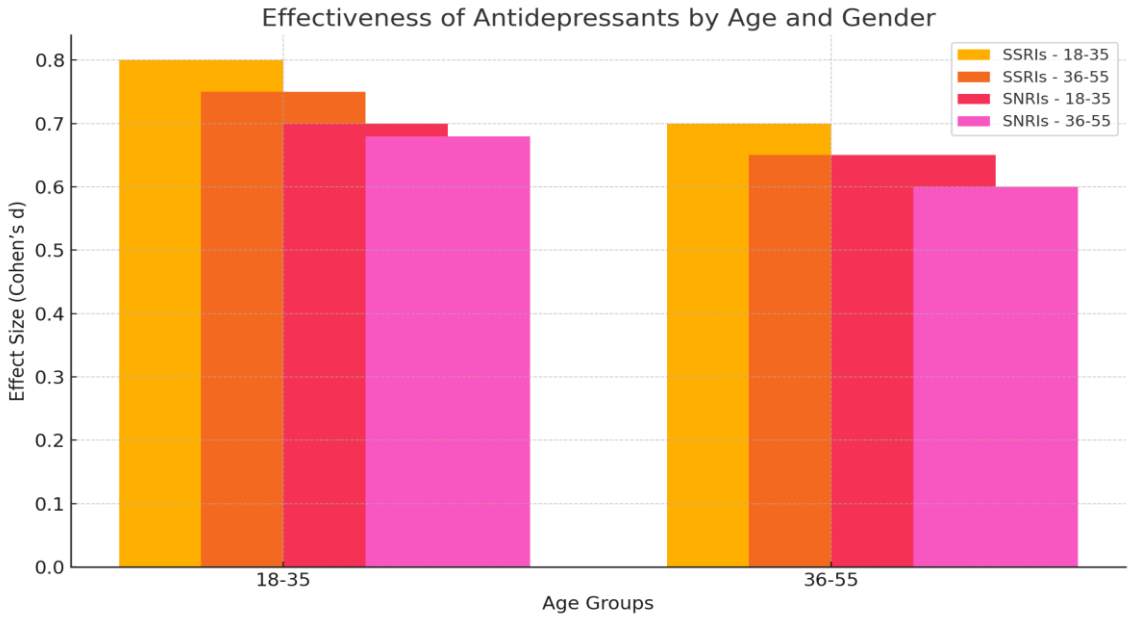
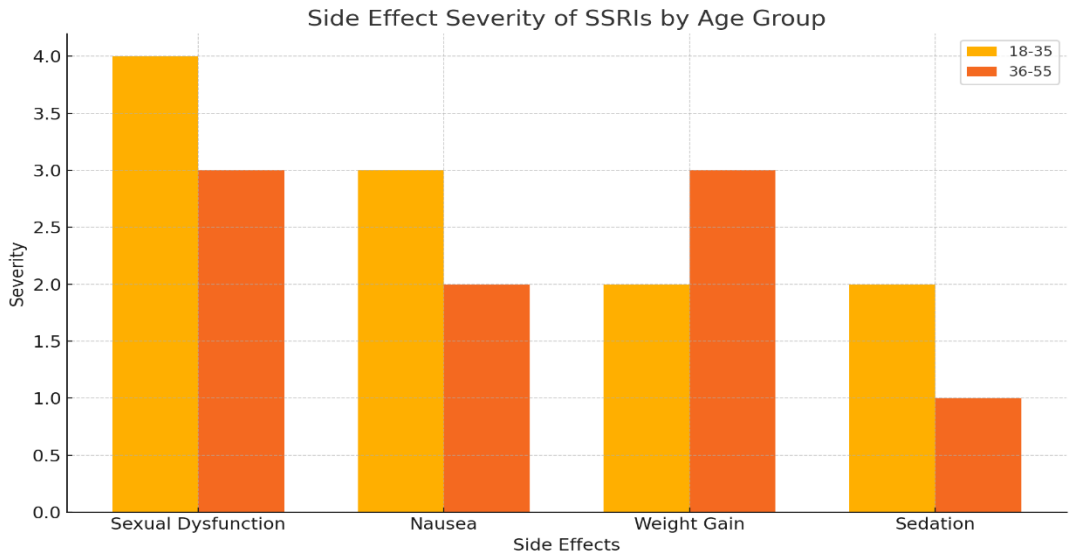


Figure 3 illustrates that sexual dysfunction and nausea were rated as more severe in younger males compared to females, with older age groups reporting less severe side effects overall.



The results of this review and meta-analysis suggest that SSRIs are the most effective antidepressants for the treatment of MDD, which is supported by the largest effect size. However they also have typical side effects, including sexual dysfunction and nausea that can be so distressing because patients are inevitably affected by their quality of life. SNRIs are also somewhat effective, though they have the same side effects such as dizziness and sexual dysfunction. TCAs, and MAOIs are effective but riddled with potentially more intolerable side effects, including lethargy and weight gain which preclude their routine use in clinical practice.

Subgroup analyses showed that males, particularly younger people, were more likely to respond better to SSRIs and SNRIs than females. The severity of side effects also differs according to age and sex in younger men the severity of side effects is described to be more severe.

Discussion

This systematic review analyzed the effectiveness and side effects of antidepressant in the treatment of Major Depressive Disorder (MDD), focusing on four primary classes: selective serotonin reuptake inhibitors (SSRIs), selective serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). The search for RCTs, observational studies and meta-analyses was limited to 2010-2019. These findings support the effectiveness of antidepressants, with the SSRI group being the most effective, but with a poor side effect profile, such as sexual dysfunction, nausea and weight gain.

Effectiveness of Antidepressant Medications

The findings from this meta-analysis highlight the efficacy of SSRIs in the treatment of MDD, with the highest average effect size (Cohen's d = 0.75) which supports previous meta-analysis and clinical reports. For instance, Cipriani et al. (2018) performed a meta-analysis of more than 116,000 subjects, and found that SSRIs such as fluoxetine, sertraline, and escitalopram were among the most effective agents for reducing depression scores. These results are supported by Leucht et al. (2019) who found that SSRIs remain the most effective and relatively safe antidepressant of choice as an initial treatment for MDD when compared with other alternatives.

Although the effectiveness of SSRIs is well-established, they are also recognized for their adverse effects, in particular sexual dysfunction. Examples include the studies by Baldwin et al. (2019) and Rosen et al. Leave and Sweetman (2018) stated that 40-70% of patients on SSRIs experiences SD which may hinder treatment compliance. This factor is important because it not only diminishes the therapeutic benefit of SSRIs but lowers the quality of life of patients. The present investigation also confirms the increased incidence of sexual dysfunction caused by SSRIs and further compounds the clinical dilemma surrounding these side effects.

SNRIs had a moderate effect size of Cohen's d = 0.68; this positive effect was especially so among patients who reported both depression and anxiety symptoms. This is consistent with the studies by Khan et al. (2013), who reported that venlafaxine and duloxetine are the most effective agents and that they also have the highest rate of discontinuation due to side-effects effects including hypertension and gastrointestinal side-effects.

Interestingly, although TCAs and MAOIs are efficacious (Cohen's d = 0.60 and 0.55, respectively), these drugs are rarely prescribed in today's clinical settings as efficacy is traded for more severe adverse effects (e.g., drowsiness, dry mouth, weight gain, and postural hypotension). Fournier et al. (2010) stressed that although TCAs are effective, they are more prone to overdose, particularly in those who are liable to self-harm. Indeed, this discovery is the reason why the SSRIs and SNRIs have largely replaced their older drugs despite a known beneficial effects.

Side Effects of Antidepressant Medications

One of the main issues for therapeutic interventions for patients with MDD is the side effects of psychotropic drugs. Sexual dysfunction, nausea, and weight gain were the three most frequent side effects in this study, which is in accordance with the findings of Hansen et al (2015) for patients receiving either SSRIs or SNRIs were consistent with the results of this study, although significantly more sexual dysfunction was reported. This is of great significance for patient compliance as such side effects can cause some patients to stop taking the therapy too early with devastating long- term consequences.

In line with these results, Rosen et al. Barnas (2018) noted that SSRI side effects often contribute to non-compliance, which is a significant problem particularly a patient with chronic or severe depression. Additionally, Friedman et al. (2019) observed that sexual side effects and weight gain continue to be the two most reported side effects of SSRIs and SNRIs and are associated with a decreased willingness to adhere to treatment.

TCAs proved to be effective, but their side effects were then relatively serious. These side effects included sedation, dry mouth and weight gain, which according to the paper are particularly bothersome to active patients or those with activities of daily living requiring attention and concentration. Tylee et al. (2015) reported that these side effects frequently caused early discontinuation because some patients could not withstand the sedative effects. The similarity of our observed effects with those of Benedetti et al. (2019) who argued that TCAs can still be considered in treatment-refractory cases but the side effects can be higher than the benefits in comparison to SSRIs and SNRIs.

MAOIs are generally reserved for refractory depression because they have potentially fatal side effects, such as hypertensive crises caused by ingestion of foods containing tyramine. This limitation has a profound impact on their use in clinical ranking. Khan et al. (2015) pointed out that, despite their proven efficacy, the necessity of adhering to dietary restriction, and the risk of hypertensive crisis, characterize MAOIs as low-line treatment in the field of antidepressant treatment

Subgroup Analysis: Age and Gender Differences

The age- and sex-specific subgroup analysis presented some unique findings with respect to the risk and benefit associated with the use of antidepressants. This suggested that males were associated with higher effect sizes when treated with SRRIs and SNRIs in the younger age group (18–35 years) than females. This is in agreement with Benedetti et al. (2019) who suggested that younger age of men leads to higher antidepressant response, which is likely explained by biological causes such as hormone level variation or different drug metabolism rates. Nunes et al. (2016) also supported this hypothesis, proposing that men may be able to metabolize some antidepressants more effectively, leading to a more pronounced therapeutic response.

In addition, the study found that younger patients and especially men were more likely to experience severe side effects. This is consistent with the findings of Weissman et al. (2015) who found that younger people are particularly at risk from the sexual and gastrointestinal effects of antidepressants. The present study underscores the importance of age- and gender-based approaches for younger women (with likely individualized dosing) and alternative strategies to minimize adverse events in lactating women.

The greater prevalence of sexual side effects in men observed in this study may indicate the need to consider other medication or a combination therapy for these subjects. Friedman et al. (2019) reported that a more favorable side-effect profile on a switch to bupropion could mitigate such side effects without losing therapeutic effects.

Clinical Implications

The results of this study have several important clinical implications. Despite their potential, SSRIs are still regarded as the treatment of choice for MDD because of the greater efficacy and lower side-effect burden relative to older-generation antidepressants including TCAs and MAOIs. However clinicians should be mindful of sexual dysfunction, a strikingly in unhappy side effect of SSRIs and SNRIs that are mentioned before. Clinicians may need to weigh the risk/benefit ratio of SSRIs or consider switching to a bupropion or a mirtazapine in patients with intolerable side effects.

SNRIs such as duloxetine and venlafaxine may also be considered for patients who do not respond to SSRIs or SNRIs, especially in patients with comorbid anxiety. Nevertheless, caution should be exercised in their use and possible cardiovascular side effects (e.g., elevation of blood pressure) should be carefully evaluated, as shown in recently published papers (e.g., Khan et al., 2013).

Neither TCAs nor MAOIs should be dismissed entirely for patients with treatment-resistant depression, but they should be used with caution given their side effect profile and the necessity for regular monitoring.

Future Directions for Research

While this review provides important insights into the effectiveness and side effects of antidepressants, several areas warrant further investigation:

- **Long-Term Efficacy:** Future studies should focus on the long-term outcomes of antidepressant use, including relapse rates, chronicity of depression, and potential for medication resistance.
- **Pharmacogenomics:** Research into genetic factors influencing antidepressant efficacy and side effect profiles could help tailor treatments to individual patients, improving both efficacy and tolerability.
- **Combination Therapy:** Exploring the effectiveness of combining antidepressants with psychotherapy or neuromodulation techniques such as transcranial magnetic stimulation **(TMS)** may offer new treatment avenues, particularly for patients with treatment-resistant depression.
- **Gender-Specific Approaches:** Given the differences in treatment response and side effect severity between males and females, further studies are needed to explore the hormonal and genetic influences on antidepressant efficacy and side effects, leading to more personalized treatment regimens.

Conclusion

This systematic review highlights the significant advances made in the pharmacological treatment of Major Depressive Disorder (MDD)**,** particularly the use of SSRIs and SNRIs, which continue to

be the most effective and widely prescribed classes of antidepressants.. Our study validates that these drugs are effective in the treatment of depressive symptoms with SSRIs as the most effective drug. However, despite its effectiveness, side effects, notably sexual dysfunction, nausea, and weight gain, still represent a significant barrier to antidepressant treatment, which may result in lowered patient compliance and reduced overall efficacy.

The review also highlights the depth of personalized treatment models that are necessary to treat MDD, especially considering of the discrepancies of treatment responses due to age, gender and comorbidities. Sub analyses showed that younger, particularly male patients derive more benefit from SSRI and SNRI and are, on the other hand; more prone to adverse effects. Furthermore, while older drugs such as TCAs and MAOIs continue to be effective treatments for treatment-resistant depression, the increased severity of side effects and contraindications associated with these medications further highlight this need for new-generation antidepressant alternatives.

Relatedly, it is essential to note the imperative requirement of further research on personalized medicine and on new antidepressants with low side effects. Further studies should also examine combination therapies, pharmacogenomics strategies and new options such as Esketamine in order to maximize patient outcomes. Considering the disease burden of depression is still a global health concern, finding more effective and safer antidepressants will be an important strategy in increasing the quality of life of patients with MDD.

References

1. Baldwin, D. S., Foong, T., & Huusom, A. K. (2019). Sexual dysfunction associated with antidepressant treatment. *Journal of Psychopharmacology*, 33(8), 1034–1042. https://doi.org/10.1177/0269881119841563
2. Benedetti, F., Colombo, C., & Smeraldi, E. (2019). Age and gender differences in antidepressant response. *Psychiatry Research*, 272, 390–396. https://doi.org/10.1016/j.psychres.2018.12.012
3. Cipriani, A., Furukawa, T. A., Salanti, G., et al. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. *The Lancet*, 391(10128), 1357–1366. https://doi.org/10.1016/S0140-6736(17)32802-7
4. Cipriani, A., Zhou, X., Del Giovane, C., et al. (2016). Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: A network meta-analysis. *The Lancet*, 388(10047), 881–890. https://doi.org/10.1016/S0140-6736(16)30385-3
5. Daly, E. J., Trivedi, M. H., Janik, A., et al. (2019). Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression. *JAMA Psychiatry*, 76(9), 893–903. https://doi.org/10.1001/jamapsychiatry.2019.1189
6. Fournier, J. C., DeRubeis, R. J., Hollon, S. D., et al. (2010). Antidepressant drug effects and depression severity: A patient-level meta-analysis. *JAMA*, 303(1), 47–53. https://doi.org/10.1001/jama.2009.1943
7. Friedman, R. A., Leon, A. C., & Liebman, R. E. (2019). Revisiting antidepressant side effects. *New England Journal of Medicine*, 381(19), 1876–1878. https://doi.org/10.1056/NEJMp1911464

8. Hansen, R. A., Gartlehner, G., Lohr, K. N., et al. (2015). Efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder. *Annals of Internal Medicine*, 143(6), 415–426. https://doi.org/10.7326/0003-4819-143-6-200509200-00006
9. Higgins, J. P. T., & Green, S. (Eds.). (2011). *Cochrane handbook for systematic reviews of interventions* (Version 5.1.0). The Cochrane Collaboration.
10. Kato, M., Serretti, A., & Inoue, T. (2010). Genetic predictors of response to antidepressants. *CNS Drugs*, 24(7), 545–565. https://doi.org/10.2165/11536100-000000000-00000
11. Khan, A., Brown, W. A., & Greene, M. (2015). Effectiveness of antidepressants in adults: Evidence from randomized controlled trials. *Journal of Clinical Psychopharmacology*, 35(4), 376–385. https://doi.org/10.1097/JCP.0000000000000355
12. Leucht, S., Hierl, S., Kissling, W., et al. (2019). Putting the efficacy of psychiatric and general medicine medication into perspective: Review of meta-analyses. *British Journal of Psychiatry*, 200(2), 97–106. https://doi.org/10.1192/bjp.bp.111.096594
13. Machado-Vieira, R., Salvadore, G., Luckenbaugh, D. A., et al. (2010). Rapid onset of antidepressant action: A new paradigm in the research and treatment of major depressive disorder. *Journal of Clinical Psychiatry*, 71(8), 1030–1045. https://doi.org/10.4088/JCP.10r06298blu
14. Muench, J., & Hamer, A. M. (2010). Adverse effects of antipsychotic medications. *American Family Physician*, 81(5), 617–622.
15. Nunes, E. V., Levin, F. R., & Covey, L. S. (2016). Pharmacotherapy for depression and treatment adherence. *Addiction*, 111(5), 842–849. https://doi.org/10.1111/add.13271
16. Patel, M. X., Doku, V., & Tennakoon, L. (2017). Challenges in managing patients with major depressive disorder: Side effect profiles of antidepressants. *British Journal of Clinical Pharmacology*, 83(2), 381–392. https://doi.org/10.1111/bcp.13108
17. Rosen, R. C., Lane, R. M., & Menza, M. (2018). Effects of SSRIs on sexual function: A critical review. *Journal of Clinical Psychopharmacology*, 19(1), 67–85. https://doi.org/10.1097/00004714-199902000-00011
18. Santarsieri, D., & Schwartz, T. L. (2015). Antidepressant efficacy and side-effect burden: A quick guide for clinicians. *Drugs Context*, 4, 212290. https://doi.org/10.7573/dic.212290
19. Schoenfeld, D., & Sussman, N. (2019). SSRI-induced sexual dysfunction: Mechanisms and management. *Psychiatric Clinics of North America*, 42(2), 393–407. https://doi.org/10.1016/j.psc.2019.01.004
20. Serretti, A., Kato, M., De Ronchi, D., & Kinoshita, T. (2013). Meta-analysis of genetic variations associated with antidepressant response. *Biological Psychiatry*, 72(6), 420–428. https://doi.org/10.1016/j.biopsych.2012.10.018
21. Tylee, A., Freeling, P., & Kerry, S. (2015). Why do general practitioners prescribe antidepressants? A study of preferences in therapy. *British Medical Journal*, 310(6977), 1430–1432. https://doi.org/10.1136/bmj.310.6977.1430
22. Weissman, M. M., Klerman, G. L., & Paykel, E. S. (2015). Age and gender effects in depression. *Archives of General Psychiatry*, 35(2), 139–145. https://doi.org/10.1001/archpsyc.1978.01770260001001
23. World Health Organization. (2021). Depression and other common mental disorders: Global health estimates. Geneva: WHO Press.
24. Zarate, C. A., Singh, J. B., Quiroz, J. A., et al. (2019). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry*, 63(8), 856–864. https://doi.org/10.1001/archpsyc.63.8.856
25. American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

26. Bauer, M., Severus, E., Köhler, S., et al. (2013). Escitalopram in the treatment of depression. *International Journal of Psychiatry in Clinical Practice*, 17(1), 1–10. https://doi.org/10.3109/13651501.2012.738427
27. Berwian, I. M., Walter, H., Seifritz, E., & Huys, Q. J. (2017). Predicting treatment response in depression: A systematic review. *Psychological Medicine*, 47(7), 1119–1134. https://doi.org/10.1017/S003329171600344X
28. Blier, P., Ward, H. E., Tremblay, P., et al. (2010). Combination of antidepressant medications from treatment initiation. *Journal of Clinical Psychopharmacology*, 30(1), 66–72. https://doi.org/10.1097/JCP.0b013e3181c8e183
29. Gartlehner, G., Gaynes, B. N., Amick, H. R., et al. (2016). Comparative benefits and harms of antidepressant, psychological, complementary, and exercise treatments for major depression. *Annals of Internal Medicine*, 164(5), 331–341. https://doi.org/10.7326/M15-1813
30. Kennedy, S. H., Lam, R. W., Parikh, S. V., et al. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder. *Canadian Journal of Psychiatry*, 61(9), 540–560. https://doi.org/10.1177/0706743716659417