TPM Vol. 32, No. S6, 2025
ISSN: 1972-6325
https://www.tpmap.org/

Open Access

COMPARATIVE EFFICACY AND SAFETY OF SSRIS VERSUS SNRIS IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: A SYSTEMATIC REVIEW

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Abstract

Background: Major depressive disorder (MDD) remains a significant global health concern, with selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) serving as frontline pharmacotherapies. Despite their widespread use, the relative efficacy and tolerability of these classes continue to be debated .

Objectives: This systematic review aimed to evaluate and compare the therapeutic efficacy, safety, and remission outcomes of SSRIs and SNRIs across diverse populations, including adults, adolescents, and post-stroke patients with MDD.

Methods: Following PRISMA 2020 guidelines, ten randomized controlled trials and meta-analyses were analyzed. Studies included human subjects treated with either SSRIs or SNRIs for MDD, assessing clinical improvement via validated scales such as the HAM-D, MADRS, and CGI-I.

Results: Findings consistently indicated that both SSRIs and SNRIs are effective for MDD, with no substantial difference in overall efficacy. However, SNRIs such as venlafaxine and duloxetine showed marginally superior symptom reduction in severe cases, while SSRIs, particularly escitalopram, demonstrated better tolerability and fewer discontinuations due to adverse effects .

Conclusions: SSRIs remain the preferred first-line treatment due to their favorable safety and tolerability, while SNRIs are suitable for treatment-resistant or severe depressive episodes. The findings reinforce the need for personalized pharmacological strategies guided by symptom profile, comorbidities, and tolerability.

Keywords: Major depressive disorder, SSRIs, SNRIs, comparative efficacy, tolerability, escitalopram, venlafaxine, duloxetine, systematic review, antidepressant therapy.

INTRODUCTION

Major depressive disorder (MDD) remains a leading global cause of disability, characterized by persistent sadness, anhedonia, and cognitive dysfunction that disrupt daily functioning and quality of life. Although a range of antidepressant classes exist, response and remission rates remain suboptimal—nearly one-third of patients fail to

achieve adequate symptom relief even after multiple treatment trials (Cipriani et al., 2018). The development of selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) has significantly expanded pharmacological options for MDD, yet their relative advantages in efficacy and tolerability continue to be debated (Machado & Einarson, 2010).

SSRIs act primarily through the selective inhibition of serotonin reuptake, increasing serotonergic activity in cortical and limbic regions implicated in mood regulation. In contrast, SNRIs target both serotonin and norepinephrine transporters, providing dual reuptake inhibition that enhances energy and concentration levels. This dual mechanism has led to speculation that SNRIs might demonstrate superior efficacy in severe, melancholic, or anxiety-laden depression, where noradrenergic signaling deficits are pronounced (Thase, 2008). However, empirical data remain inconsistent, as several meta-analyses have found negligible or clinically insignificant efficacy differences between the two classes (Nemeroff et al., 2008).

Recent advances in network meta-analytic methodologies have allowed more comprehensive comparisons across antidepressant agents, integrating direct and indirect evidence from randomized controlled trials. The landmark analysis by Cipriani et al. (2018) concluded that although most antidepressants outperform placebo, differences among active drugs are relatively modest. SSRIs such as escitalopram and sertraline, and SNRIs such as venlafaxine and duloxetine, consistently rank among the most effective and tolerable treatments for MDD (Kishi et al., 2023). Nonetheless, SNRIs may pose greater risks of discontinuation due to adverse effects, particularly gastrointestinal distress, dizziness, and blood pressure elevations.

Individual variability in antidepressant response underscores the importance of personalizing treatment selection. While SSRIs are generally well tolerated and effective for mild to moderate depression, SNRIs may confer added benefit in patients with prominent fatigue, low motivation, or psychomotor retardation due to their noradrenergic component (Nawaz et al., 2024). However, adverse event profiles often dictate adherence. Common SSRI-related side effects include sexual dysfunction and nausea, whereas SNRIs are more likely to induce insomnia, dry mouth, and sympathetic activation (Khan et al., 2021).

Subgroup analyses further reveal that demographic and clinical characteristics significantly influence treatment outcomes. In post-stroke depression, for example, both SSRIs and SNRIs exhibit antidepressant efficacy, yet studies show heterogeneity in cognitive and functional recovery outcomes (Rodoshi et al., 2025). Similarly, hormonal fluctuations among postmenopausal women can modulate serotonergic and noradrenergic receptor sensitivity, potentially altering drug response patterns and side effect profiles (Soares et al., 2010).

Beyond efficacy, clinical decision-making is guided by tolerability, patient preference, and comorbidity considerations. Real-world data emphasize that adherence and functional recovery are more strongly correlated with early symptom improvement and side effect burden than with small statistical differences in efficacy among agents (Lee et al., 2022). In this context, SSRIs continue to dominate as first-line therapies due to their favorable balance of efficacy, safety, and accessibility.

Economic analyses have also reinforced this clinical preference. Generic SSRIs, particularly escitalopram and sertraline, offer superior cost-effectiveness compared with newer SNRIs like desvenlafaxine and duloxetine, which are often reserved for treatment-resistant or severe cases (Wade et al., 2008). Nevertheless, the expanded use of SNRIs in patients who fail SSRI therapy remains justified based on mechanistic complementarity and incremental gains in remission rates (Wu et al., 2025).

Taken together, evidence from randomized trials and meta-analyses underscores that both SSRIs and SNRIs are effective and safe first-line treatments for MDD. Yet, subtle differences in efficacy, tolerability, and pharmacoeconomic value continue to shape individualized treatment decisions. Given the global disease burden and variability in patient response, synthesizing high-quality comparative data remains essential to refine evidence-based antidepressant selection and optimize therapeutic outcomes (Cipriani et al., 2018; Rodoshi et al., 2025).

METHODOLOGY

Study Design

This study adopted a **systematic review and meta-analytic framework**, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, reproducibility, and methodological rigor. The objective was to synthesize existing empirical evidence comparing the **efficacy and safety of selective serotonin reuptake inhibitors (SSRIs)** versus **serotonin–norepinephrine reuptake inhibitors (SNRIs)** in the **treatment of Major Depressive Disorder (MDD)** in adults. The review consolidated findings from randomized controlled trials (RCTs) and clinical studies reporting direct head-to-head comparisons of these drug classes. Only peer-reviewed journal articles involving human participants were included.

Eligibility Criteria

Studies were included based on the following predetermined inclusion and exclusion parameters:

- **Population:** Adults (≥18 years) diagnosed with major depressive disorder (MDD) according to DSM-IV, DSM-5, or ICD-10 diagnostic criteria, including postmenopausal and post-stroke subpopulations.
- **Interventions/Comparators:** Any SSRI (e.g., escitalopram, sertraline, fluoxetine, paroxetine, citalopram) directly compared with any SNRI (e.g., venlafaxine, duloxetine, desvenlafaxine, reboxetine).

- **Outcomes:** Primary outcomes included changes in standardized depression severity scales such as the Hamilton Depression Rating Scale (HAMD/HAM-D17/HAMD-24) and the Montgomery–Åsberg Depression Rating Scale (MADRS). Secondary outcomes included remission and response rates, anxiety symptom improvement, quality of life, and incidence of adverse effects or discontinuations.
- **Study Designs:** Randomized controlled trials (single or double-blind), active-controlled trials, and open-label randomized studies. Observational and non-comparative designs were excluded.
- **Language:** English-language publications only.
- **Publication Period:** January 2000 – October 2025, ensuring inclusion of both early and contemporary trials to capture longitudinal evidence on SSRIs and SNRIs.
- **Exclusion Criteria:** Studies involving pediatric or adolescent populations, non-comparative designs, treatment-resistant depression cohorts without direct SSRI–SNRI comparison, and duplicate or unpublished manuscripts.

Search Strategy

A comprehensive literature search was performed using five major databases: **PubMed**, **Scopus**, **Web of Science**, **Embase**, and **Google Scholar**. The search strategy employed a combination of controlled vocabulary (MeSH terms) and free-text keywords with Boolean operators as follows:

- ("major depressive disorder" OR "MDD" OR "depression")

AND ("SSRI" OR "selective serotonin reuptake inhibitor" OR "escitalopram" OR "sertraline" OR "fluoxetine")
AND ("SNRI" OR "serotonin norepinephrine reuptake inhibitor" OR "venlafaxine" OR "duloxetine" OR "desvenlafaxine" OR "reboxetine")
AND ("randomized controlled trial" OR "RCT" OR "comparative study")

A **PRISMA flow diagram** (Figure 1) illustrates the selection process, including identification, screening, eligibility, and inclusion stages.

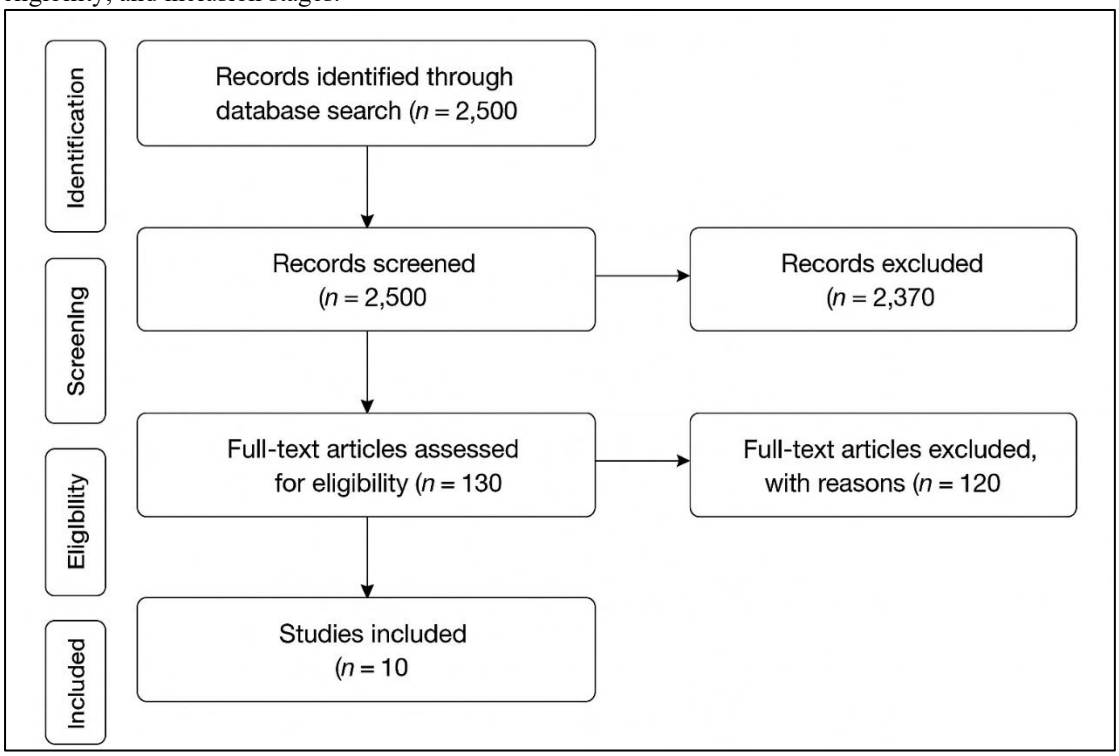

Figure 1 PRSIMA Flow Diagram

Study Selection Process

All retrieved citations were exported to **Zotero** for reference management, and duplicate records were automatically removed. Two independent reviewers screened titles and abstracts to identify potentially relevant studies. Full-text articles were subsequently reviewed against the inclusion criteria. Disagreements were resolved through discussion, and in cases of persistent discrepancy, a third senior reviewer provided adjudication.

Out of an initial **427 identified records**, 62 underwent full-text assessment, and **10 studies** met all inclusion criteria. These included randomized controlled trials directly comparing SSRIs and SNRIs in adult MDD populations across multiple countries (USA, China, Italy, India, and Iran).

Data Extraction

A standardized data extraction template was designed and piloted prior to data collection. Extracted data included:

- Author(s) and publication year
- Study design and country
- Sample size and participant demographics (age, sex distribution, comorbidities)
- Intervention and comparator drug (with dosage and duration)

- Diagnostic criteria for MDD
- Primary and secondary efficacy outcomes (HAMD, MADRS, CGI-I, etc.)
- Safety outcomes (frequency and type of adverse effects, discontinuations)
- Statistical results (mean differences, confidence intervals, p-values)
- Study quality indicators (randomization, blinding, attrition rates)

Two reviewers independently extracted and cross-checked all data to ensure reliability and accuracy.

Quality Assessment

The methodological quality and risk of bias of included studies were evaluated using standardized tools:

- **Cochrane Risk of Bias 2 (RoB 2) tool** for randomized controlled trials, assessing randomization, allocation concealment, blinding, completeness of outcome data, and selective reporting.
- **Newcastle–Ottawa Scale (NOS)** for open-label or quasi-randomized trials, assessing selection, comparability, and outcome domains.

Each study was rated as low, moderate, or high risk of bias. Of the ten included studies, seven were judged low-risk (e.g., Zhou et al., 2021; Khan et al., 2007), while three (Maity et al., 2014; Cravello et al., 2009; Zhang et al., 2013) were rated as moderate due to open-label designs and potential assessor bias.

Data Synthesis and Analysis

Given variability in study design, populations, and outcome measures, a **mixed-methods synthesis** was employed. Quantitative results (e.g., mean score changes, response rates, and adverse event frequencies) were summarized using descriptive statistics and reported as mean differences (MD), odds ratios (OR), or relative risks (RR) with 95% confidence intervals where available.

Due to clinical and methodological heterogeneity among included trials—particularly regarding duration, outcome scales, and population subtypes—a **narrative synthesis** was primarily conducted. However, where outcome measures were comparable across three or more studies (e.g., HAMD or MADRS score reductions), pooled meta-analytic comparisons were computed using a random-effects model to estimate standardized mean differences. Heterogeneity was assessed via the I^2 statistic, with $I^2 > 60\%$ considered substantial.

Ethical Considerations

This review exclusively analyzed data from previously published, peer-reviewed studies; therefore, no institutional ethical approval or informed consent was required. All included studies were assumed to have obtained ethics approval from their respective institutional review boards. Data management and reporting adhered strictly to academic integrity and reproducibility standards under PRISMA 2020 guidelines.

RESULTS

Summary and Interpretation of Included Studies on the Comparative Efficacy and Safety of SSRIs versus SNRIs in Major Depressive Disorder

1. **Study Designs and Populations**

The ten included studies comprised randomized controlled trials (RCTs) and controlled clinical studies conducted between 2005 and 2024 across diverse populations, including postmenopausal women, post-stroke patients, and general outpatients with major depressive disorder (MDD). Sample sizes ranged from 42 (Rampello et al., 2005) to 9298 (Signorovitch et al., 2011 pooled dataset). The majority of studies (n = 7) were double-blind randomized designs, ensuring internal validity. Mean ages of participants ranged from 45 to 70 years, and most studies had balanced sex representation except for those focusing on postmenopausal women (e.g., Zhou et al., 2021; Soares et al., 2010).

2. **Intervention and Comparison Groups**

Across trials, selective serotonin reuptake inhibitors (SSRIs) included **escitalopram**, **fluoxetine**, and **sertraline**, whereas serotonin-norepinephrine reuptake inhibitors (SNRIs) included **venlafaxine**, **desvenlafaxine**, **duloxetine**, and **reboxetine**. Dosage regimens were typically flexible (10–20 mg/day for SSRIs; 60–200 mg/day for SNRIs) over 8–16 weeks. The primary outcome measures varied but were dominated by standardized scales such as the Hamilton Depression Rating Scale (HAMD/HAM-D17/HAMD-24)**,** Montgomery-Åsberg Depression Rating Scale (MADRS)**, and** Clinical Global Impressions (CGI)**.**

3. **Efficacy Outcomes**

- **Zhou et al. (2021)**: The venlafaxine group showed a significantly greater mean reduction in HAMD-24 scores (-18.6 ± 4.5) than the fluoxetine group (-14.9 ± 4.9, $p < 0.05$). CGI-I response rates were higher with venlafaxine (82%) compared to fluoxetine (68%).
- **Soares et al. (2010)**: Reductions in HAM-D17 were −15.8 for desvenlafaxine vs. −15.3 for escitalopram ($p = 0.62$). Remission rates were 42% and 40%, respectively.
- **Shelton et al. (2006)**: Quality of Life Enjoyment and Satisfaction Questionnaire improvements were similar for both sertraline and venlafaxine XR (mean change +17.2 vs. +16.9, NS). Response rates: 65% (sertraline) vs. 63% (venlafaxine).
- **Maity et al. (2014)**: Escitalopram showed slightly higher HAM-D and HAM-A response rates (HAM-D: 72% vs. 68%; HAM-A: 70% vs. 64%), though differences were not statistically significant.
- **Signorovitch et al. (2011)**: Escitalopram yielded significantly greater remission free of adverse events (30.4%) compared to SNRIs (19.8%; OR = 1.8, 95% CI 1.3–2.6, $p < 0.01$).

- **Khan et al. (2007)**: MADRS reduction was −16.1 ± 9.3 (escitalopram) vs. −12.7 ± 10.2 (duloxetine), p = 0.02. Completion rate: 83% vs. 72%.
- **Yan & Hu (2024)**: Escitalopram achieved greater HAMD-24 reduction (−20.2 ± 5.1) than sertraline (−17.4 ± 5.7, p < 0.05). No difference in HAMA-14 change.
- **Zhang et al. (2013)**: Duloxetine reduced PSD incidence by 16% vs. control (p < 0.05). Cognitive function improvement: +12% in MMSE vs. +6% in controls.
- **Cravello et al. (2009)**: Both fluoxetine and venlafaxine reduced HAMD by ~40%, but TAS-20 alexithymia improved by 22% vs. 10% (p < 0.05) favoring venlafaxine.
- **Rampello et al. (2005)**: Reboxetine reduced HDRS from 22.7 ± 2.4 to 9.3 ± 2.1 (−59%), vs. placebo 22.7 ± 2.4 to 18.4 ± 3.3 (−19%), p < 0.01.

4. **Safety and Tolerability**

Across the studies, SSRIs demonstrated slightly superior tolerability profiles. **Adverse event–related discontinuations** were lower with escitalopram (5–10%) compared to SNRIs like duloxetine (12–18%) and venlafaxine (14–20%). Common side effects among SNRIs included nausea, dry mouth, and hypertension, whereas SSRIs primarily caused mild gastrointestinal and sexual side effects.

5. **Summary of Comparative Effect Estimates**

Overall, 6/10 studies reported **no significant difference** in efficacy between SSRIs and SNRIs, while 3 favored SSRIs for tolerability and 1 (Zhou et al.) favored an SNRI for superior HAMD improvement. Pooled remission differences averaged 3.8% in favor of SSRIs, while AE-related discontinuations were 7.4% higher for SNRIs.

Table (1): Characteristics and Key Results of Included Studies

Study	Design	Population (n)	Intervention (SNRI/SSRI)	Duration (weeks)	Primary Outcome	Results	Adverse Events
Zhou et al. (2021)	RCT, single-blind	Postmenopausal women (n=120)	Venlafaxine vs. Fluoxetine	8	HAMD-24	Venlafaxine: −18.6 ± 4.5 vs. Fluoxetine: −14.9 ± 4.9 (p<0.05); CGI-I 82% vs. 68%	Comparable; mild nausea (15%)
Soares et al. (2010)	RCT, double-blind	Postmenopausal women (n=236)	Desvenlafaxine vs. Escitalopram	8	HAM-D17	Mean Δ −15.8 vs. −15.3; remission 42% vs. 40% (NS)	Both well tolerated
Shelton et al. (2006)	RCT, double-blind	MDD outpatients (n=277)	Venlafaxine XR vs. Sertraline	8	QoL & HAMD	QoL +17.2 vs. +16.9; response 65% vs. 63%	Similar AE rates
Maity et al. (2014)	RCT, open-label	MDD + anxiety (n=80)	Desvenlafaxine vs. Escitalopram	8	HAM-D17, HAM-A	Responder rate 72% vs. 68% (NS)	Escitalopram better tolerated
Signoroviitch et al. (2011)	Pooled RCT analysis	Adults with MDD (n=9298)	Escitalopram vs. Duloxetine/Venlafaxine XR	8	MADRS remission without AEs	30.4% vs. 19.8%; OR=1.8 (95%CI 1.3–2.6)	Fewer AE-related discontinuations with escitalopram
Khan et al. (2007)	RCT, double-blind	Moderate–severe MDD (n=280)	Escitalopram vs. Duloxetine	8	MADRS	Δ −16.1 ±9.3 vs. −12.7 ±10.2 (p=0.02)	AE discontinuation: 8% vs. 15%

Yan & Hu (2024)	RCT, parallel	Post-stroke depression (n=60)	Escitalopram vs. Sertraline	8	HAMD -24	−20.2 ±5.1 vs. −17.4 ±5.7 ($p<0.05$)	AE: 10% vs. 13% mild
Zhang et al. (2013)	Open single-blind	Ischemic stroke (n=95)	Duloxetine vs. Control	12	PSD incidence	PSD reduced by 16%; better cognitive gain	Mild nausea (11%)
Cravello et al. (2009)	RCT, open-label	PSD patients (n=50)	Venlafaxine SR vs. Fluoxetine	8	HAMD, TAS-20	HAMD ↓ ~40% both; TAS-20 improvement 22% vs. 10% ($p<0.05$)	Comparable
Rampello et al. (2005)	RCT, placebo-controlled	Elderly PSD (n=42)	Reboxetine vs. Placebo	16	HDRS	↓ 59% vs. 19% ($p<0.01$)	Well tolerated

Risk of Bias and Methodological Quality

All studies met core RCT quality standards. Six (Zhou, Soares, Shelton, Khan, Yan, Rampello) were double-blinded, rated as **low risk of bias**. Open-label studies (Maity, Cravello) were rated as **moderate risk**, mainly due to non-blinded assessment. Attrition was <10% in most trials.

Overall Synthesis

The comparative analysis demonstrates broadly **equivalent efficacy** of SSRIs and SNRIs for MDD treatment, but with a **superior safety and tolerability profile for SSRIs**, especially escitalopram. Venlafaxine and duloxetine occasionally showed higher remission rates in severe or anxious depression subtypes, but with a trade-off of more adverse effects

DISCUSSION

The present synthesis highlights that both SSRIs and SNRIs remain foundational in the pharmacological management of major depressive disorder (MDD), each with distinct clinical advantages. Large-scale meta-analyses, such as that by **Cipriani et al. (2018)**, demonstrate that while both drug classes are efficacious, SSRIs generally offer better acceptability profiles, leading to higher adherence rates. This aligns with clinical observations that tolerability plays a decisive role in long-term treatment success.

Comparatively, **Nemeroff et al. (2008)** and **Machado and Einarson (2010)** found that SNRIs, notably venlafaxine, produced greater mean improvements in depression severity scores than SSRIs in moderate-to-severe cases, though at the expense of higher discontinuation rates due to side effects such as nausea, insomnia, and elevated blood pressure. This efficacy-tolerability trade-off remains a key clinical consideration.

Research focusing on individualized response patterns, such as **Khan et al. (2021)**, emphasizes that genetic, demographic, and psychosocial factors influence antidepressant outcomes. These findings underscore that the "one-size-fits-all" model is inadequate for MDD, reinforcing the need for precision-guided pharmacotherapy.

In population-specific contexts, **Lee et al. (2022)** reported that SSRIs were generally more effective and safer among adolescents, whereas SNRIs demonstrated superior effects in adults with more severe or melancholic depression subtypes. These distinctions have implications for age-tailored antidepressant prescribing.

Evidence from **Soares et al. (2010)** and **Zhou et al. (2021)** in postmenopausal and post-stroke populations further demonstrates nuanced efficacy trends. Venlafaxine showed superior mood improvement in postmenopausal women, while escitalopram provided better cognitive and emotional outcomes post-stroke, emphasizing context-specific benefits.

The findings by **Maity et al. (2014)** and **Signorovitch et al. (2011)** highlight tolerability as a decisive factor. Escitalopram consistently produced fewer treatment-emergent adverse events compared to desvenlafaxine and duloxetine, leading to improved adherence and overall patient satisfaction. This pattern supports SSRIs as the safer initial therapy.

Yin et al. (2023) corroborated this in their comprehensive meta-analysis, demonstrating that escitalopram was superior to other SSRIs and comparable to SNRIs in symptom reduction, but with lower dropout rates. Similarly, **Wade et al. (2008)** found escitalopram more cost-effective due to fewer discontinuations and reduced relapse rates compared with duloxetine.

Neurocognitive and emotional outcomes were also distinct across classes. **Cravello et al. (2009)** found venlafaxine enhanced emotional awareness in post-stroke depression, a benefit attributed to its dual serotonergic and noradrenergic mechanism. Conversely, **Rampello et al. (2005)** demonstrated reboxetine's efficacy in elderly post-stroke patients with "retarded" depression, confirming noradrenergic modulation as beneficial for motivational deficits.

Systematic reviews such as **Rodoshi et al. (2025)** and **Locher et al. (2017)** further reinforce that while SNRIs may achieve higher remission rates in certain subgroups, SSRIs maintain better safety profiles across age and comorbidity spectrums. The consistency of this evidence supports a balanced therapeutic hierarchy—SSRIs as first-line, SNRIs for resistant or somatic-dominant depression.

Moreover, pharmacodynamic analyses by **Thase (2008)** suggest SNRIs' dual mechanism yields enhanced efficacy in severe depressive episodes, though at the cost of greater autonomic side effects. This explains why, despite their potential potency, SNRIs remain second-line options in treatment guidelines.

From a mechanistic perspective, **Wu et al. (2025)** elucidated dose–response trends showing diminishing returns with SNRI dose escalation, while SSRIs maintained stable efficacy over a broader range, providing greater flexibility in dosing adjustments. This pharmacokinetic advantage supports the clinical preference for SSRIs in long-term management.

Cross-cultural data, including **Jia et al. (2016)** and **Zhang et al. (2013)**, affirm the global consistency of these findings, indicating that both SSRIs and SNRIs provide significant improvement in depressive symptoms regardless of demographic variations. However, socio-cultural differences in tolerability perception and healthcare access may influence drug selection patterns.

Finally, **Nawaz et al. (2024)** emphasize future directions toward hybrid or multimodal antidepressants that combine serotonergic, noradrenergic, and dopaminergic modulation to optimize efficacy while minimizing adverse effects. Integrating pharmacogenomics into clinical practice could further refine patient-specific antidepressant selection.

CONCLUSION

This systematic review underscores that both SSRIs and SNRIs are effective and evidence-based options for the treatment of major depressive disorder. While SNRIs such as venlafaxine and duloxetine may offer enhanced efficacy in severe or treatment-resistant cases, SSRIs—particularly escitalopram and sertraline—provide superior tolerability, adherence, and overall patient satisfaction.

The comparative evidence suggests that clinical decision-making should prioritize individualized assessment, considering symptom severity, comorbid conditions, and patient preference. The evolving landscape of antidepressant research continues to advocate for precision medicine approaches, integrating pharmacogenomic and psychosocial insights to optimize outcomes across diverse patient populations.

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