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A Comparative Efficacy of Antidepressants in the Treatment of Major Depressive Disorder: A Systematic Review and Meta-Analysis

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Abstract

Major Depressive Disorder (MDD) affects about 280, 000, 000 people globally, with a higher incidence among females than males. The increasing incidence implicates health burdens and clinical dilemmas regarding the low efficacy of the existing antidepressants. A literature search was performed on electronic databases, PubMed, the Cochrane Library of Randomized Trials, Scopus, and ProQuest, for studies reporting the efficacy of an SNRI (Desvenlafaxine 50 mg/d), a serotonin modulator (Vortioxetine 10-20 mg/d), and an aminoketone antidepressant (Bupropion). Study selection focused on randomized controlled trials (RCTs) and observational studies. All statistical analyses and visualization were performed using the Review Manager (RevMan) software and Python programming. The random effects model, ANOVA test, and Cohen's d were used for statistical analyses. The present meta-analysis involved 17 studies, including 11, 533 participants. The results aligned with previous studies and accounts provided by literature regarding the efficacy of antidepressants used to manage MDD. Five studies, including 2, 377 MDD patients, reported a statistically significant outcome, that Desvenlafaxine 50 mg/d reduced MDD's severity than placebo (OR: 0.52, 95% CI [0.44, 0.62], P < 0.00001, I2 = 0%). Three studies involving 742 MDD patients reported the efficacy of dextromethorphan-bupropion (AXS-50). The reduction of MADRS scores in the treatment group was statistically insignificant, with high variability, favouring the placebo (OR of 1.85 [95% CI: 0.93, 3.70], p = 0.08, I2 = 79%). Additionally, Vortioxetine 10-20 mg/d produced adverse effects, headache, vomiting, nausea, diarrhea, dizziness, nasopharyngitis, somnolence, and suicidal ideation among 6, 669 MDD patients reported by the 9 studies. The finding was statistically significant but with a high variability OR: 15.25, 95% CI [12.55, 18.52], P < 0.00001, I2 = 98%). A preliminary analysis of evidence collected following Desvenlafaxine, AXS-50, and Vortioxetine administration yielded compelling evidence on the efficacy of antidepressants in MDD treatment. Desvenlafaxine and AXS-50 reported reduced severity and symptomatology in MDD, respectively. On the other hand, Vortioxetine implicated adverse effects, which are common with most antidepressants. Despite adverse effects like headache, vomiting, nausea, diarrhea, dizziness, nasopharyngitis, somnolence, and suicidal ideation, antidepressants used to treat MDD yield clinically satisfying outcomes like decreased severity of depression and relief from symptoms. Clinicians should monitor patients to take care of any adverse effects resulting from the treatments.

Keywords: *Antidepressant efficacy, adverse effects, major depressive disorder, MDD symptomatology, severity, improved outcomes.*

1.0 Introduction

MDD is a severe mood disorder characterized by persistent disinterest and sadness, cognitive dysfunction, poor quality of life, and physical dysfunction [1], [2]. The debilitating psychiatric condition affects millions across the globe. The disease is more prevalent among females than males. Today, MDD is known to affect about 280, 000, 000 people across the world. In 2022, the World Health Organization ranked MDD 3rd cause of disease worldwide and estimated that MDD will be the leading cause of health burden by 2030 [3]. Therefore, raft measures must be taken to develop the most effective interventions to prevent MDD exacerbation.

Currently, many therapeutic approaches against MDD include antidepressant administration to modulate mood and reduce symptoms and severity of the disease. The choice of antidepressant indicated to different patients depends on the medication's safety and efficacy profile. The efficacy of antidepressants is crucial as they affect patients' overall well-being and determine clinical outcomes like mood alleviation, reducing symptomatology, and disease severity [4], [5]. Additionally, the choice of antidepressants has focused on medications producing the least adverse reactions. The rationale of this approach regards producing maximum desirable outcomes while limiting adverse effects.

In the last decades, low efficacy and the incidence of adverse effects. There have been concerns of poor patient response, low improvement of mood, and alleviation of symptoms of MDD. Previous studies report that antidepressants implicate undesirable outcomes in the cardiovascular system [6], result in poor sleep, and increase the risk of hyponatremia [7], among other adverse effects like headache, dry mouth, blurred vision, drowsiness, and erectile dysfunction. The adverse effects vary according to the class of the antidepressant.

The increasing health burden and concerns about the efficacy of antidepressants have prompted investigations to determine the clinical outcomes of the medications. The present meta-analysis focuses on the efficacy of antidepressants in managing MDD among adolescents, children, and adults to elucidate the efficacy profile and the potential adverse effects. The comparative study examined the clinical outcomes of three classes of antidepressants. The evidence obtained informed the selected medications' efficacy profiles, making their efficacy and safety profiles clear for clinical consideration.

2.0 Materials and Methods

Eligibility criteria

Studies were included in the present meta-analysis based on the Patient, Intervention, Comparison, Outcome, and Studies (PICOS) protocol [8], [9].

Inclusion criteria

The criteria were as follows:

- Participant (P): Only patients diagnosed with the Diagnostic and Statistical Manual for MENTAL Disorders. The participant group consisted of children, adults, and the aged population.
- Interventions (I): SNRI (Desvenlafaxine 50 mg/d), serotonin modulator (Vortioxetine 10-20 mg/d), and an aminoketone antidepressant (Bupropion)
- Comparison (C): Placebo.

- Outcome (O): MDD symptomatology, severity of depression in MDD, and adverse effects
- Studies: Eligible studies were RCTs and observational studies, reporting the efficacy of Desvenlafaxine 50 mg/d vs. placebo, vortioxetine 10-20 mg/d vs. placebo, and AXS-50 vs. placebo.

Exclusion criteria

Studies were eliminated from the study on the following grounds:

- Cross antidepressant comparisons.
- Study designs, case studies, personal views, and meta-analyses.
- Irrelevant outcomes to the present topic.

Information sources

A systematic literature search was performed in four electronic databases: PubMed, the Cochrane Library of Randomized Trials, Scopus, and ProQuest. The literature search was limited to articles published from January 2, 2005, to October 1, 2023, and reporting the efficacy of antidepressants used to manage MDD.

Search strategy

A systematic literature search was conducted in electronic databases, PubMed, the Cochrane Library of Randomized Trials, Scopus, and ProQuest, for articles reporting the efficacy of antidepressants used to manage MDD. Keywords specific to SNRIs, serotonin modulators, and aminoketone antidepressants filtered potential studies.

Selection process

Two independent reviewers (LK) and (KO) screened the potential records and settled featuring discrepancies via dialogue. LK and KO systematically screened the records in the following order: title and abstract screening, evaluating the processes of identifying articles reporting the efficacy of antidepressants used to treat MDD.

Data collection process

The independent reviewers focused on title-abstract screening and full-text analysis to identify the most potential studies. Potential studies were extracted and recorded in an Excel sheet. Only studies reporting the efficacy of Desvenlafaxine 50 mg/d, Vortioxetine 10-20 mg/d, and AXS-50 were extracted. Additionally, the independent reviewers focused on studies reporting consistent outcomes: the severity of depression following antidepressant treatment, symptomatology following treatment, and the adverse effects therein.

Data items

The present meta-analysis focused on the efficacy of antidepressants in MDD, including symptomatology, severity of depression, and the adverse effects following treatment. The symptomatology of antidepressant treatment focused on the exhibition of symptoms of MDD after administration of the antidepressants. The incidence of the symptoms after antidepressant administration implied a low efficacy profile of the antidepressants. The severity of depression following treatment would tell the efficacy of the antidepressants in the selected studies. Lastly, the adverse effects of the administered antidepressants would yield evidence of the clinical outcomes of antidepressants in MDD management.

Study risk of bias assessment

The risk-of-bias assessment tool was used to investigate the quality of the randomized-controlled trials [10], [11]. The six domains of the individual studies, including selection, performance, detection, attrition, reporting, and other forms of bias, were assessed to represent the overall quality of the study. In this approach, the risk of bias in the individual studies was represented as low, unclear, or high risk of bias. On the other hand, the Newcastle-Ottawa Scales assessed the quality of evidence of observational studies, focusing on group comparability, selection of study groups, and the ascertainment of outcomes of interests [12].

Effect measures

The present study was based on vital statistical indicators and effect measures: odds ratios (OR), 95% Confidence Interval (CI), heterogeneity, Cohen's d, F-statistic, and the p-values. These effect sizes provided comprehensive information on the presence of heterogeneity, uncertainty, and the statistical significance of the findings of the meta-analysis [13], [14]. The effect sizes OR and 95% CI informed the precision and strength of the association of the variables, whereas heterogeneity reflected between-study variability of results. The variability determined the appropriateness of combining evidence in the meta-analysis. The Cohen's d measures the standardized mean difference, subsequently measuring the effect size of studies bearing different scales. Lastly, the p-values and the F-statistic evaluated the individual study effects and overall significance of the meta-analysis.

Synthesis methods

The Hamilton Depression Rating Scale (HAMD-17) was used to assess the severity of depression symptoms among the participants. MDD consists of 17 items, including physical and emotional symptoms of depression [15]–[17]. To decipher Desvenlafaxine's efficacy, the HAMD-17 tool assessed the physical and emotional symptoms of depression in the treatment group. The weekly measurements were used to judge Venlafaxine's efficacy against control. Higher total scores reflected severe depression and a true converse. HAMD-17 scores at the end of the assessment period were contrasted with the baseline scores to inform Desvenlafaxine's efficacy in MDD.

Apart from HAMD-17, a comparison of symptomatology in MDD was performed using the Montgomery–Åsberg Depression Rating Scale (MADRS) to establish the efficacy of dextromethorphan-bupropion among MDD patients based on scores reported by the included studies. The assessment involved a comparison of the MDD symptomatology over 6 weeks. Higher MADRS implied high symptomatology, whereas lower scores implied reduced symptomatology [18]. The weekly scores reported by the studies indicated the efficacy of the antidepressant, where the increasing number of patients reporting reduced symptomatology implied bupropion's efficacy and improvement in clinical outcomes among MDD patients.

The Review Manager software and Python programming language performed all statistical analysis and visualization. Python programming language was used to perform the ANOVA test to show the p-values of the variables. In contrast, the F-statistic represented the variance ratio within and between groups [19], [20]. The ANOVA test was based on the assumption that insomnia and headache data were normally distributed and the sample independent. Also, it was assumed that between-group variance was equal [21]. The alpha value implying statistical significance was $p \leq 0.05$. Any statistical outcome with a p-value above the alpha level was regarded as statistically insignificant.

$$F - statistic = S_1^2/S_2^2$$

Fisher's statistical method combined p-values from independent studies or tests to yield a single overall test. The collected p-values were transformed using the Chi-Squared statistic, where the Combined P-Value=P($\chi^2 \geq$Combined Chi-Squared Statistic|Degrees of Freedom) [22], [23]. Lastly, Cohen's d was used to measure the degree of the difference between the two groups in the present study [24], [25]. The effect size estimate was used to quantify the differences that imply clinical outcomes to represent the significance of each group.

Reporting bias assessment

Funnel plots and Egger's test were used to assess the risk of publication bias in the present meta-analysis. The funnel plots visually displayed the standard error (SE), representing between-study precision, and the effect size to reveal potential asymmetry. Asymmetry suggested publication bias; small or less precise studies with non-significant or negative results could be missing [26], [27]. Egger's test quantified funnel plot asymmetry and assessed the publication bias statistically.

Certainty assessment

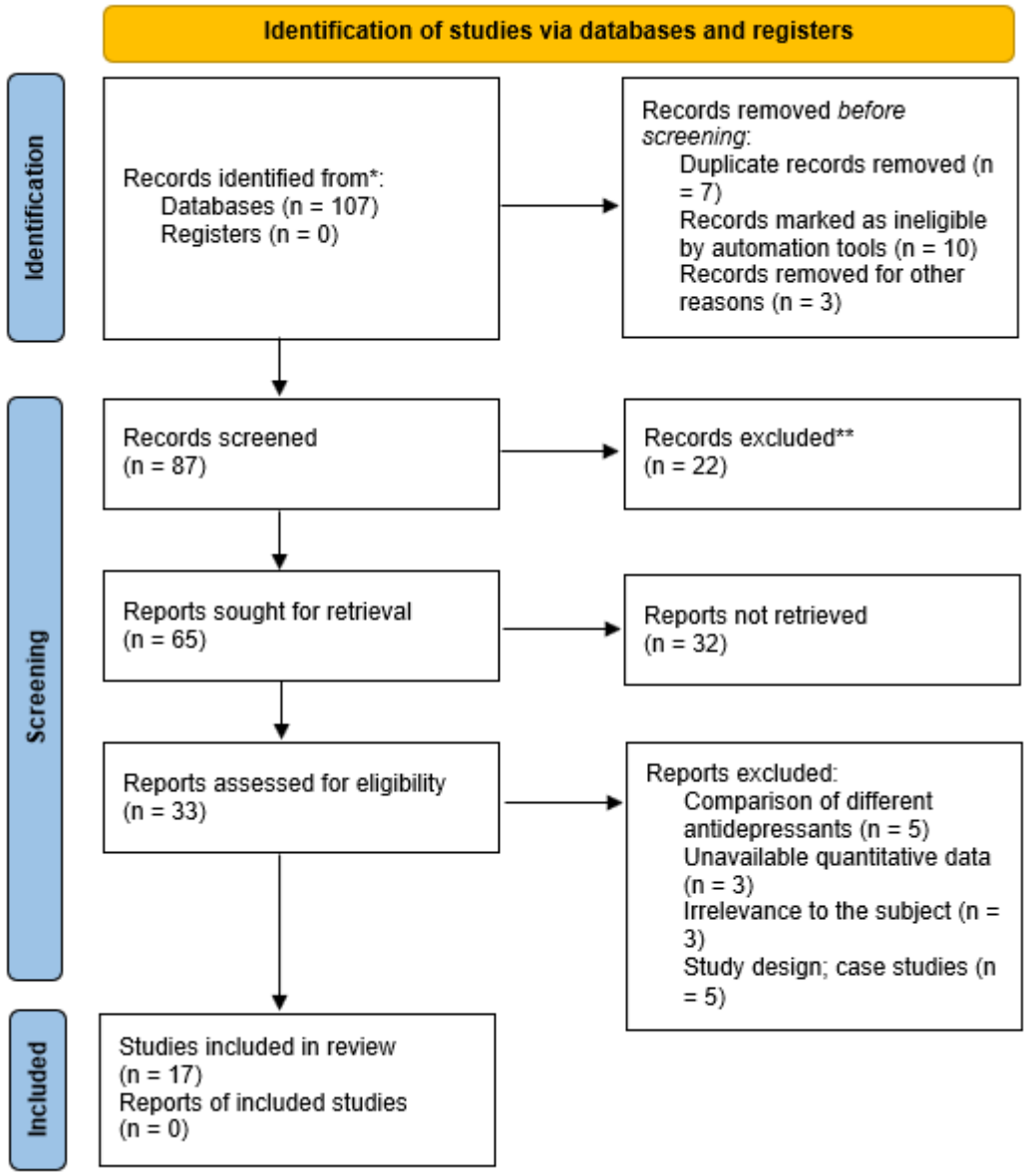
Cochrane's risk-of-bias tool and the NOS were used to assess the quality of evidence of randomized controlled trials and observational studies, respectively. The risk of bias tool focused on randomized trials by assessing selection, performance, detection, attrition, reporting, and other forms of bias [10], [11]. In contrast, the NOS focused on group comparability, the selection of study groups, and the ascertainment of outcomes of interests [12].

3.0 Results

Study selection

In the initial search, 107 studies were identified in the electronic databases. Before screening, 7 duplicate records were removed, and 10 were marked ineligible by automation tools. In contrast, 3 records were removed for other reasons like unclear definitions of objectives, poor methodologies, and insufficient data. Screening the remaining 87 records led to the exclusion of 22 articles, leaving 65 articles for retrieval. Thirty-two articles were not retrieved, leaving 33 records for eligibility assessment. Sixteen articles were eliminated from the study for different reasons: 5 articles were eliminated for antidepressant vs. placebo comparison reasons, 3 articles were eliminated for unavailable data, 3 articles were eliminated due to irrelevance to the topic, whereas 5 articles were eliminated based on study design as they were case studies (**Figure 1**). A total of 17 studies met the inclusion criteria and were included in the meta-analysis.

Figure. 1: A PRISMA flow diagram illustrating literature search and screening



Study characteristics

Seventeen studies, including a total of 11, 533 MDD patients, were included in the present meta-analysis, and they reported different efficacy and safety outcomes of antidepressants. The studies reported different efficacy outcomes against placebo treatment. Five studies reported clinical outcomes of 50 mg/d venlafaxine in MDD, including safety, tolerability, better functions, effectiveness against depression, improved sex functions, and suicidal ideas [28]–[32], 9 studies reported efficacy of Vortioxetine 10-20 mg/d [33]–[41], and 3 studies reported the efficacy of Dextromethorphan-bupropion [42]–[44].

By design, the studies comprised different types of randomized controlled trials and observational studies (**Table 1**). A total of 15 out of the 17 studies were randomized trials, except two studies, which were observational studies [33], [34]. Additionally, the studies were performed in different countries across the world. A total of 13 studies were performed in one country: 10 studies originated from the United States of America [28]–[31], [39]–[44], one

study originated from Canada [32], one study originated from Australia [37], and one originated from China [33]. On the other hand, 4 studies were multinational studies each originating from different regions or countries, including Japan and the United States of America [38], South East [36], Italy and Canada [35], and Canada, Denmark, France, United States, and Japan [34].

Additionally, the studies included different patient profiles including males, females, adolescents, children, perimenopausal, and postmenopausal women. Two studies included the highest number of patients [39], [40], with a total of 1, 111 MDD patients each, whereas one study involved the number of participants, 120 [42].

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Table 1: Characteristics of included studies

Study ID, Year	Country of origin/Region	Study design	Participants					Intervention	Control	Duration of assessment (in weeks)	Main outcomes
			Total (n)	Males	Females	Treatment (n)	Control (n)				
Clayton et al., 2013	United States of America	Phase 4, multicentre, parallel-group, randomized, double-blind, placebo-controlled trial	1066	0	651 perimenopausal and postmenopausal women	217	217	Desvenlafaxine 50mg/d	Placebo	8	Safety, tolerability, and better functions
Kornsten et al., 2014	United States of America	Randomized placebo-controlled study	653	0	426 perimenopausal and postmenopausal women	216	210	Desvenlafaxine 50mg/d	Placebo	8	Effective treatment of depression
Clayton et al., 2015	United States of America	RCT	909	542	369	300	300	Desvenlafaxine 50 mg/d & 100 mg/d	Placebo	8	Comparable outcomes in the two treatment groups. Improved sex function, relief from symptoms of depression and anxiety
Endicott et al., 2014	Canada	Double-blind, placebo-controlled trial	692	93	188	285	142	Desvenlafaxine 50 mg/d & 100 mg/d	Placebo	12	Impaired QOL (46% in treatment, 62% in control)
Khan et al., 2014	United States of America	Phase 4, randomized, double-blind,	480	201	156	357	123	Desvenlafaxine 50 mg/d & 100 mg/d	Placebo	24	Suicidal ideal in the control group

		placebo-controlled study									
Findling et al., 2022	United States of America	Randomizes, placebo-controlled study	1035	54	93	147	154	Vortioxetine 10 mg	Placebo	12	Vomiting, headache, nausea, diarrhea, dizziness & nasopharyngitis were reported as adverse effects
Mahableshwarkar et al., 2015	United States of America	Randomized, double-blind, placebo-controlled parallel, phase 3 study	1, 111 adult males, and non-pregnant women	140	329	157	160	Vortioxetine 10 mg	Placebo	8	≥5% of treated participants reported diarrhea, constipation, dry mouth, vomiting, dizziness, flatulence, headache & nausea
Mahableshwarkar et al., 2015	United States of America	Randomized, double-blind, placebo-controlled parallel, phase 3 study	1, 111 adult males, and non-pregnant women	140	329	157	160	Vortioxetine 10 mg	Placebo	8	≥5% of treated participants reported diarrhea, constipation, dry mouth, vomiting, dizziness, flatulence, headache & nausea
Nishimura et al., 2018	Japan & United States of America	Randomized, double-blind, placebo-controlled parallel, phase 3 study	720	86	64	150	152	Vortioxetine 10 mg	Placebo	8	≥5% of treated participants reported diarrhea, constipation,

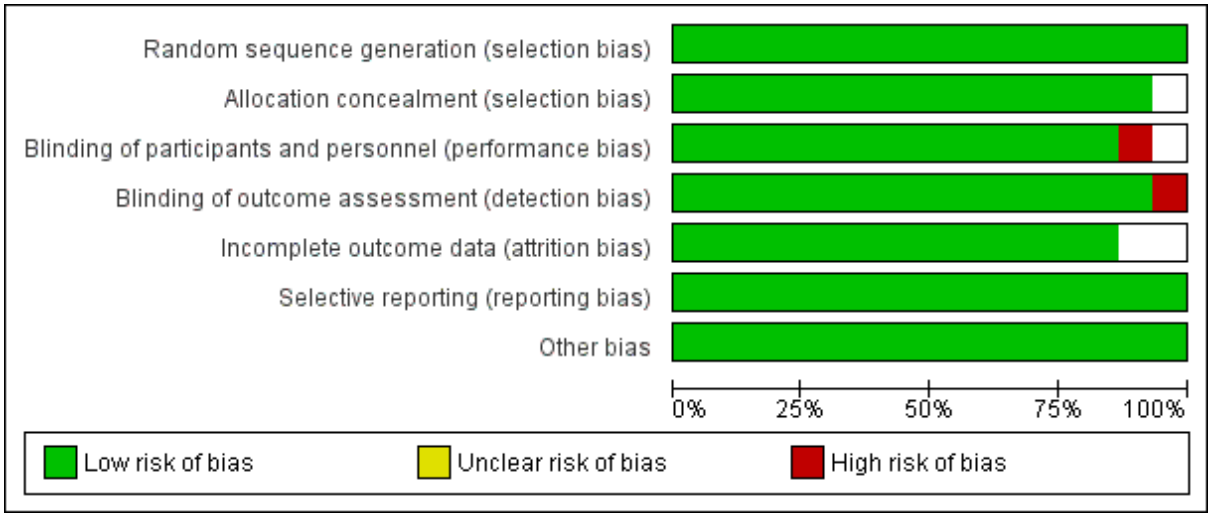
											dry mouth, vomiting, dizziness, flatulence, headache & nausea
Inoue et al., 2018	Australia	Double-blind, placebo-controlled trial	447	85	15	123	124	Vortioxetine 10 mg	Placebo	8 & 52	72 reported diarrhea, constipation, dry mouth, vomiting, dizziness, flatulence, headache & nausea in treatment vs. 59 in control
Ngen et al., 2019	South East	RCT	138	45	86	76	55	Vortioxetine 10 mg	Placebo	12	17 reported diarrhea, constipation, dry mouth, vomiting, dizziness, flatulence, headache & nausea in treatment vs. 30 in control
Di Nicola et al., 2022	Italy & Canada	RCT	113	20	36	56	57	Vortioxetine 10-20 mg/d	Placebo	24	Improved mood, cognition, functioning, safe and tolerable
Mattingly et al., 2022	Canada, Denmark, France, United States of	Observational, prospective cohort study	994	264	473	416	57	Vortioxetine 10-20 mg/d	Placebo	24	Reported outcomes include nausea, headache,

	America & Japan										pruritis, and anxiety in the treatment group
Wang et al., 2022	China	Observational, prospective cohort study	1000	294	565	419	440	Vortioxetine 10-20 mg/d	Placebo	24	Patients reported nausea, dizziness, vomiting, pruritis, headache, decreased appetite & somnolence
Iosifescu et al., 2022	United States of America	RCT	617	106	212	163	164	Dextromethorphan-bupropion 45-105 mg	Placebo	6	Improved symptoms of depression after 1 week of treatment, a significant change at week 6
Tabuteau et al., 2022	United States of America	Randomized, double-blind, multicentre, parallel-group trial	120	25	18	43	54	Dextromethorphan-bupropion 45-105 mg	Placebo	6	Improved symptomatology after week 1, and a significant change at week 6
Jones et al., 2021	United States of America	phase 3, randomized, double-blind, placebo-controlled, multicentre	327			163	164	Dextromethorphan-bupropion 45-105 mg	Placebo	6	Multiple efficacy endpoints, and statistically significant improved symptomatology

Risk of bias in studies

The risk of bias in the 15 studies was summarized as low risk of bias, unclear risk of bias, and high risk of bias across the 6 domains (**Figure 2**). Generally, the studies were found to have a low risk of bias. This suggests an overall low risk of bias across the randomized trials.

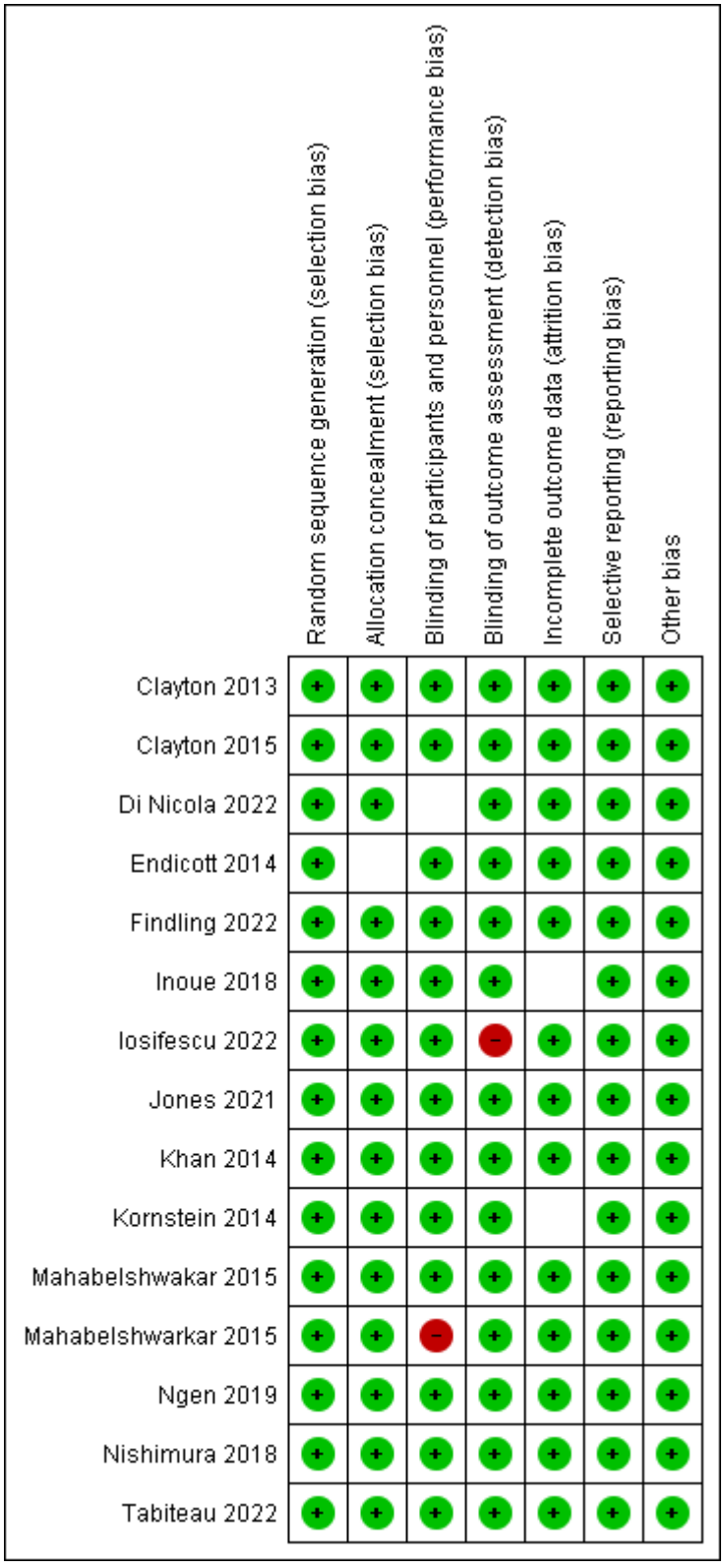
Figure 2: Risk of bias graph



Results of individual studies

Generally, the 15 randomized trials had a considerably low risk of bias (**Figure 3**). Two of the fifteen studies were found to have a high risk of bias [39], [44], whereas four studies were found to have an unclear risk of bias [30], [32], [35], [37]. A total of 9 studies were found with low risk of bias across the 6 domains, suggesting high quality and certainty of evidence.

Figure 3: Risk of bias summary



Efficacy outcomes

The efficacy of Desvenlafaxine was reported in 5 studies, including a total of 2, 377 participants (1, 375 and 992 participants in the treatment and placebo groups, respectively) [28]–[32]. The studies reported that Desvenlafaxine 50 mg/d reduced MDD's symptoms' severity compared to placebo. Unlike the placebo, the OR of the treatment group was < 1. The test for overall effect

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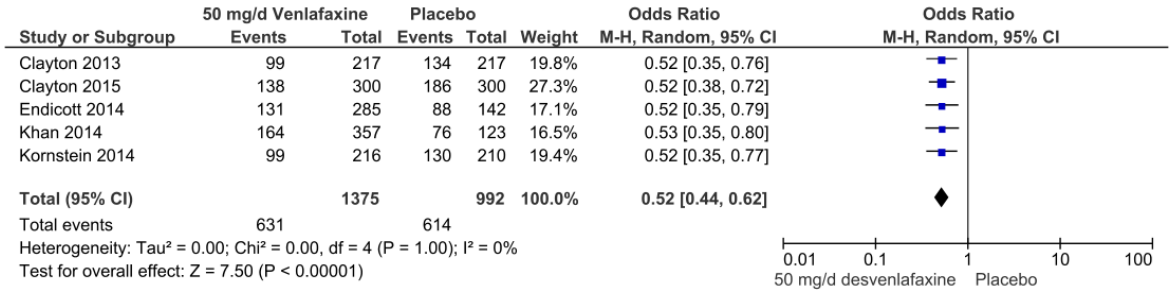
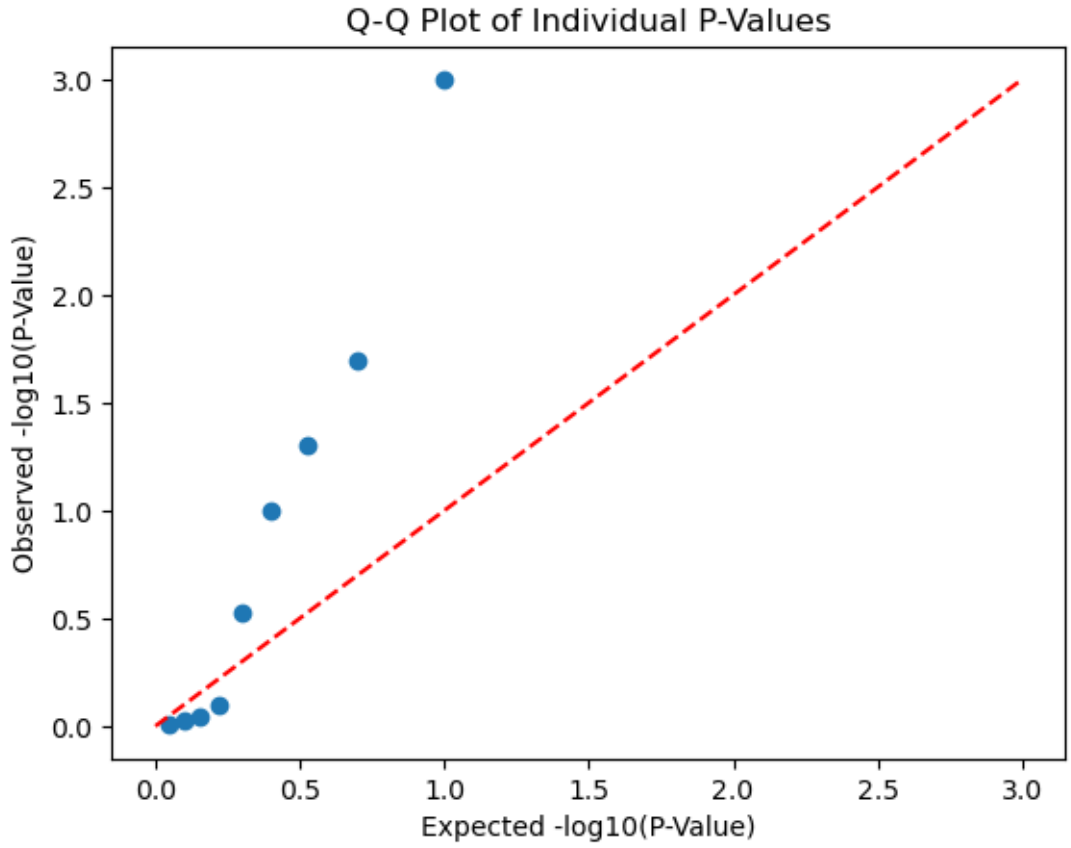
on the outcomes reported by the 5 studies was statistically significant, suggesting that desvenlafaxine 50 mg/d is more effective in the alleviation of MDD's symptoms than placebo (OR: 0.52, 95% CI[0.44, 0.62], P < 0.00001) (**Figure 3**). Additionally, the statistical analysis yielded a low heterogeneity upon assessing the variability of reported evidence across the five studies (I^2 = 0%).

Figure 3: A forest plot of the severity of depression



Four of the five studies reported a statistically significant reduction in HAMD-17 scores [29]–[32], whereas one study reported a statistically insignificant reduction following 50 mg/d Desvenlafaxine treatment [28]. Desvenlafaxine 50 mg/d significantly reduced HAMD-17 scores in the treatment group compared to control (**Figure 4**). The Fisher's method combined p-value of HAMD-17 scores was smaller combined p-value ($p = 1.2729 \times 10^{-7}$). The combined p-value was significantly lower than the alpha value of 0.05.

Figure 4: Distribution of p-values of HAMD-17 scores



Three studies reported the efficacy outcomes of the dextromethorphan-bupropion (AXS-50) combination in MDD [42]–[44]. The investigation included 742 MDD patients (199 patients

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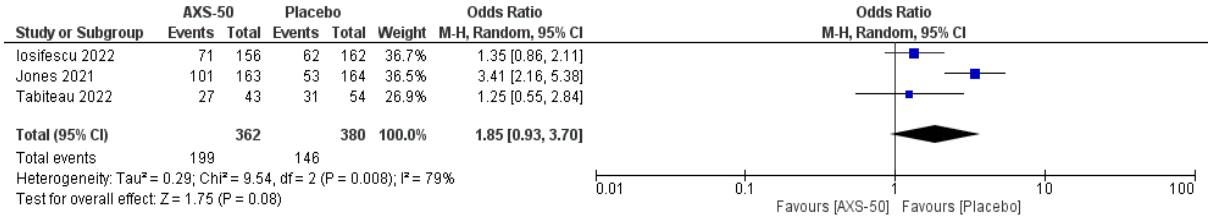
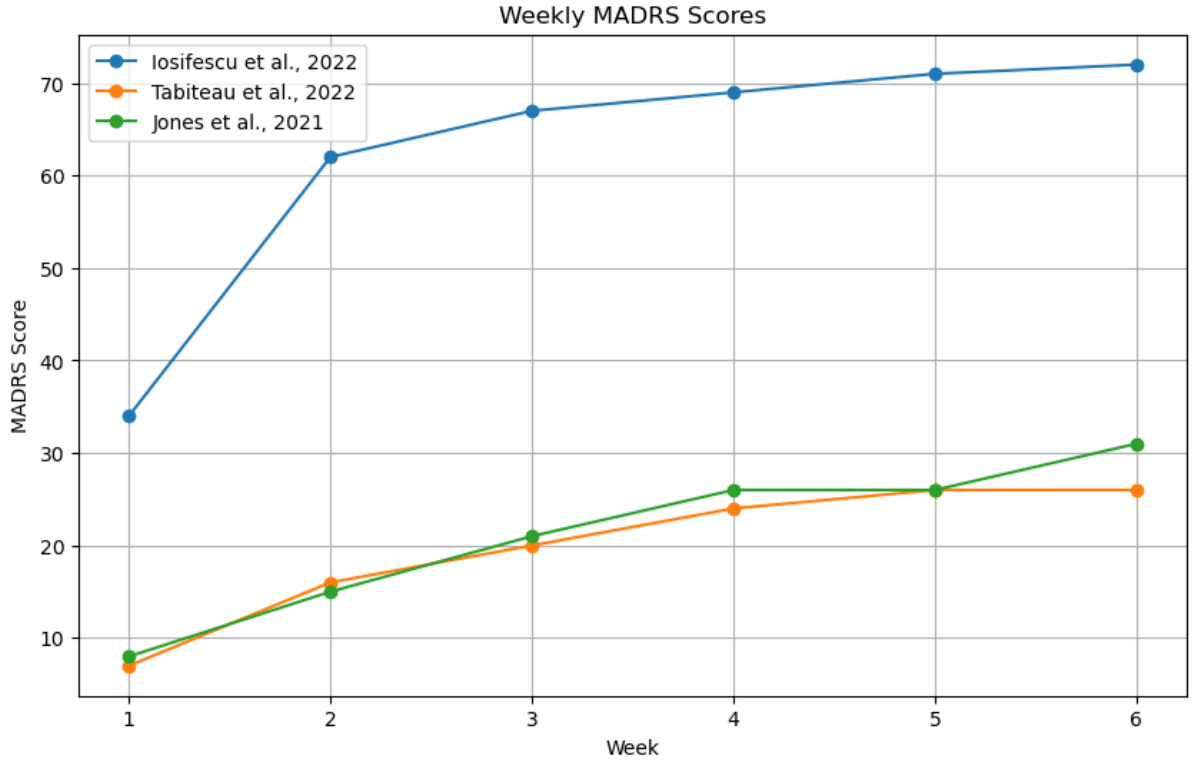
receiving dextromethorphan-bupropion treatment against 146 receiving placebo). Dextromethorphan-bupropion significantly reduced MADRS scores in the treatment group (**Figure 5**). The random effects model produced an effect size estimate OR of 1.85 [95% CI: 0.93, 3.70], whereas the overall test effect was statistically insignificant (P = 0.08), favoring the placebo. These outcomes suggest that AXS-50 reduces MDD's symptomatology significantly. The random effects model yielded a high heterogeneity (I^2 = 79%).

Figure 5: A forest plot of MADRS scores in MDD



Improvement of MDD's symptomatology was observed as early as week 2 in the treatment group. A weekly increase in the number of MDD patients reporting a decrease in MADRS scores was consistent across the three studies (**Figure 6**). Statistical analysis revealed a medium variance between the number of patients reporting a weekly decrease in MADRS scores (Cohen's d: 3.7273). Nonetheless, there was a significant difference in MADRS scores across the three groups (F-statistic: 31.8046, p = 4.023 * 10^{-6}).

Figure 6: Weekly MADRS scores.



Safety outcomes

Nine studies were evaluated for the safety outcomes of antidepressants in MDD. A total of 6, 669 participants receiving Vortioxetine 10-20 mg/d reported adverse outcomes including, headache, vomiting, nausea, diarrhea, dizziness, nasopharyngitis, somnolence, and suicidal ideation [33]–[41]. However, only nausea and headache were the consistent adverse effects consistent across the 9 studies (**Supplementary Table 1**). A random effects model yielded

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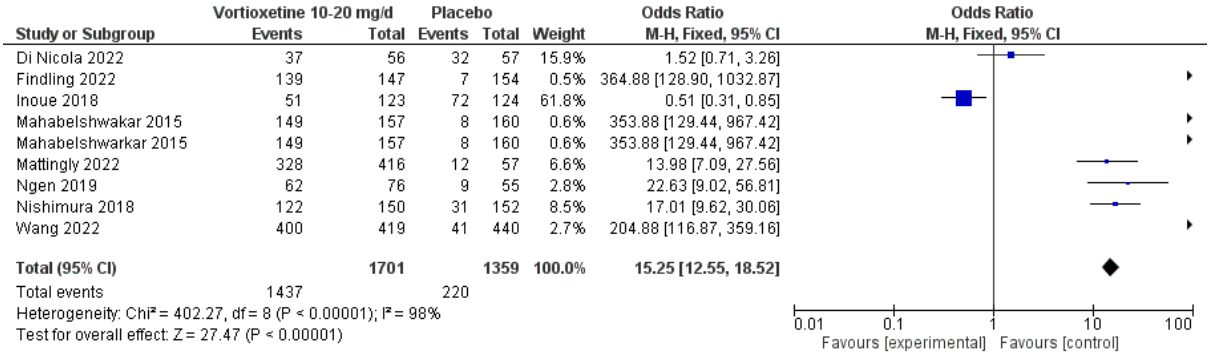
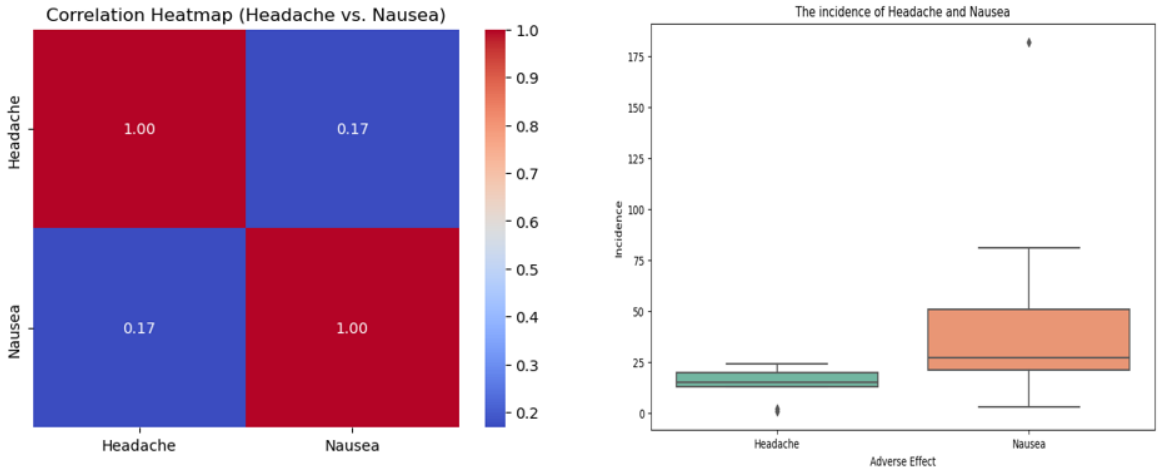
statistically significant outcomes on the incidence of adverse effects of Vortioxetine 10-20 mg/d (OR: 15.25, 95% CI [12.55, 18.52], P < 0.00001), and a high variability (I^2 = 98%) (**Figure 7**).

Figure 7: A funnel plot of adverse effects of vortioxetine in MDD



Variability of the incidence of nausea and vomiting and outliers was notable. Data variability was consistent between the two groups and within the group. As for the outlier, the highest incidence of nausea, with a total of 182 MDD patients [33], and the incidence of one headache[36], implied outliers (Figure 8).

Figure 8: Incidence of nausea and headache



a) A correlation heatmap for adverse effects

b) Distribution of headache and nausea

The incidence of headache and nausea did not vary significantly. The ANOVA testing between-group and within-group variability produced an F-statistic of 3.6084 and a p-value of 0.0757 for headache and nausea in the treatment group (**Table 2**).

https://doi.org/10.53819/81018102t4218

Table 2: ANOVA test results

ANOVA results		
	Headache	Nausea
F-statistic	3.6084	3.6084
P-value	0.0757	0.0757

Results of syntheses

The comprehensive meta-analysis on the efficacy of Desvenlafaxine 50 mg/d in the treatment of MDD across the five studies justifies the rationale of SNRIs' rationale for indication in MDD. Out of 2, 377 participants 1, 375 received Desvenlafaxine 50 mg/d; the outcomes were contrasted with 992 placebo participants. The severity of depression was recorded in the treatment group for up to 24 weeks.

A preliminary analysis revealed a consistent result demonstrating that Desvenlafaxine 50 mg/d significantly reduced the severity of MDD's symptoms in the treatment group than in comparison. The test effect size estimate odds ratio for the treatment group, <1, supported our findings, and asserted Desvenlafaxine's importance in MDD management. The statistical test for Desvenlafaxine's overall effect on MDD symptoms across the five studies was highly significant (OR: 0.52, 95% CI [0.44, 0.62], P < 0.00001). This outcome does not only indicate that Desvenlafaxine 50 mg/d effectively reduced MDD's severity but also substantiates the importance of other SNRIs.

The present meta-analysis focused on the effect on the severity of expression in MDD by assessing reported HAMD-17 scores across the five studies. Four out of the five studies reported a statistically significant decrease in HAMD-17 scores in the treatment group, asserting the efficacy of Desvenlafaxine 50 mg/d.

To decipher the combined robustness of evidence reported by the five studies, Fisher's method yielded a very small p-value ($p = 1.2729 * 10^{-7}$), which is tremendously less than the conventional alpha value. This finding supports the efficacy of Desvenlafaxine 50 mg/d in the management of MDD. Particularly, the present meta-analysis asserts Desvenlafaxine 50 mg/d's efficacy in reducing the severity of depression in MDD. The findings of the present meta-analysis were backed by low heterogeneity ($I^2 = 0\%$), indicating a high degree of agreement and consistency between the five studies.

A total of 6, 669 participants receiving Vortioxetine 10-20 mg/d reported adverse outcomes, including headache, vomiting, nausea, diarrhea, dizziness, nasopharyngitis, somnolence, and suicidal ideation. An examination of between-group and within-group variability of the incidence of headache and nausea in the treatment group was performed on 9 studies, involving 6, 669 MDD patients treated with 10-20 mg/d Vortioxetine. They found adverse outcomes, including headache, vomiting, nausea, diarrhea, dizziness, nasopharyngitis, somnolence, and suicidal ideation. Only nausea and headache were consistent across the 9 studies. However, the incidence of nausea and vomiting varied across the 9 studies. In both cases, the statistical analyses yielded a p-value greater than the alpha level ($p = 0.0757$), suggesting insignificant differences in the incidence of insomnia and headache in the 9 studies. A preliminary analysis of the data revealed substantial variability in the incidence of nausea and headache across the 9 studies. Study methodology, population, and other factors could influence or account for the high variability. The incidence of one headache and a total of 182 nausea represented the outliers in this study. These outliers could have been triggered by factors like study design, population, or assessment measures adopted in the respective studies.

The investigation on the efficacy of antidepressants included AXS-50, where three studies reported evidence. Out of the 744 MDD participants, 199 received AXS-50 treatment, whereas 146 received a placebo. A consistent drop In MADRS scores across the three studies was accompanied by statistically insignificant outcomes favoring the placebo group (OR: 1.85, 95% CI [0.93, 3.70], P = 0.08), and a high heterogeneity (I^2 = 79%). Even though the weekly difference in MADRS scores was slight (Cohen's d: 3.7273), the overall difference among the three groups was significant (F-statistic: 31.8046, p = 4.023 * 10^{-6}).

A meta-analysis of three studies revealed that antidepressants improve MDD symptomatology continuously [42]–[44]. The efficacy of AXS-50 emerged in 199 MDD patients over 6 weeks of treatment. The number of patients reporting decreased symptomatology through the MDRS scores increased as early as the second week of treatment. The meta-analysis found a profound increase in patients reporting a decline in MADRS scores across the three studies, with statistically insignificant outcomes favoring the placebo group (OR: 1.85 [95% CI: 0.93, 3.70], p = 0.08). However, a high heterogeneity characterized the evidence reported by the three studies (I^2 = 79%).

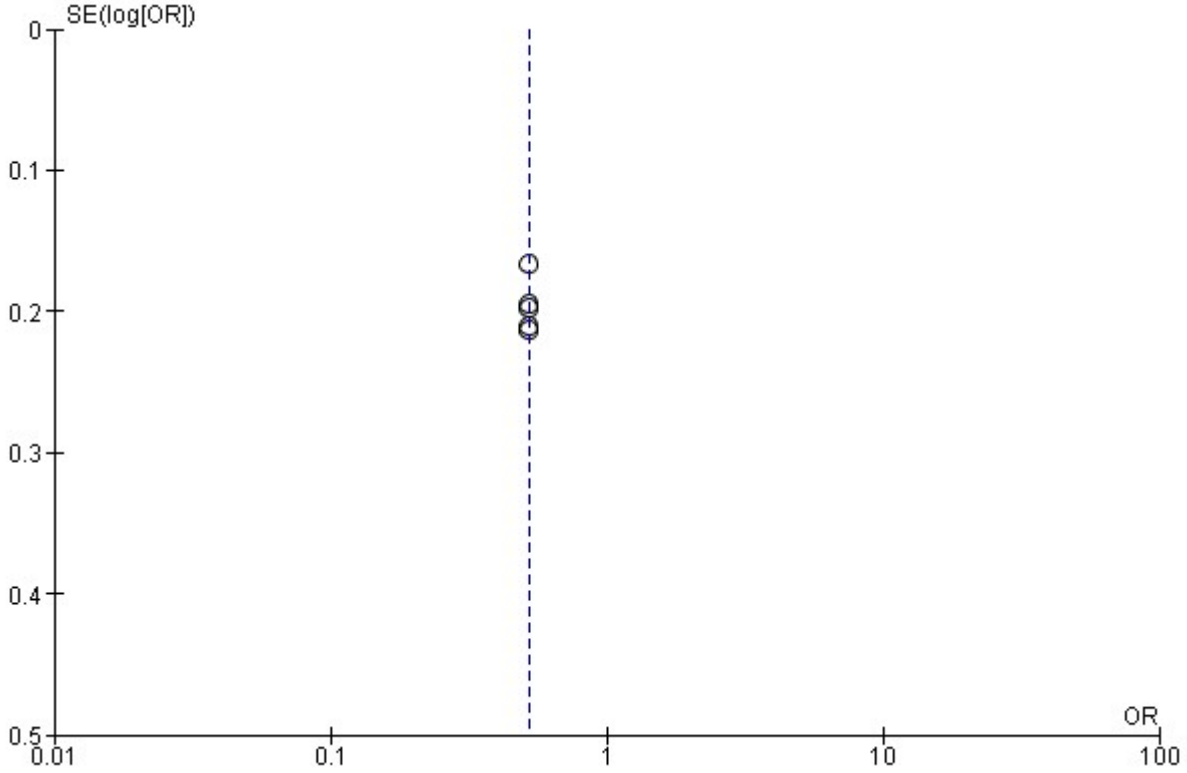
Reporting bias

The NOS quality assessment revealed that the two observational studies are of moderate to high quality. However, there were areas for improvement regarding comparability (**Supplementary Table 2**). Nonetheless, caution must be taken when interpreting evidence reported by the studies or making conclusive remarks on reported outcomes. The risk of bias assessment tool was used to assess the quality of the individual studies, and the overall risk of bias of the 15 randomized trials. In both cases, a low risk of bias was established (**Figure 2, Figure 3**).

Certainty of evidence

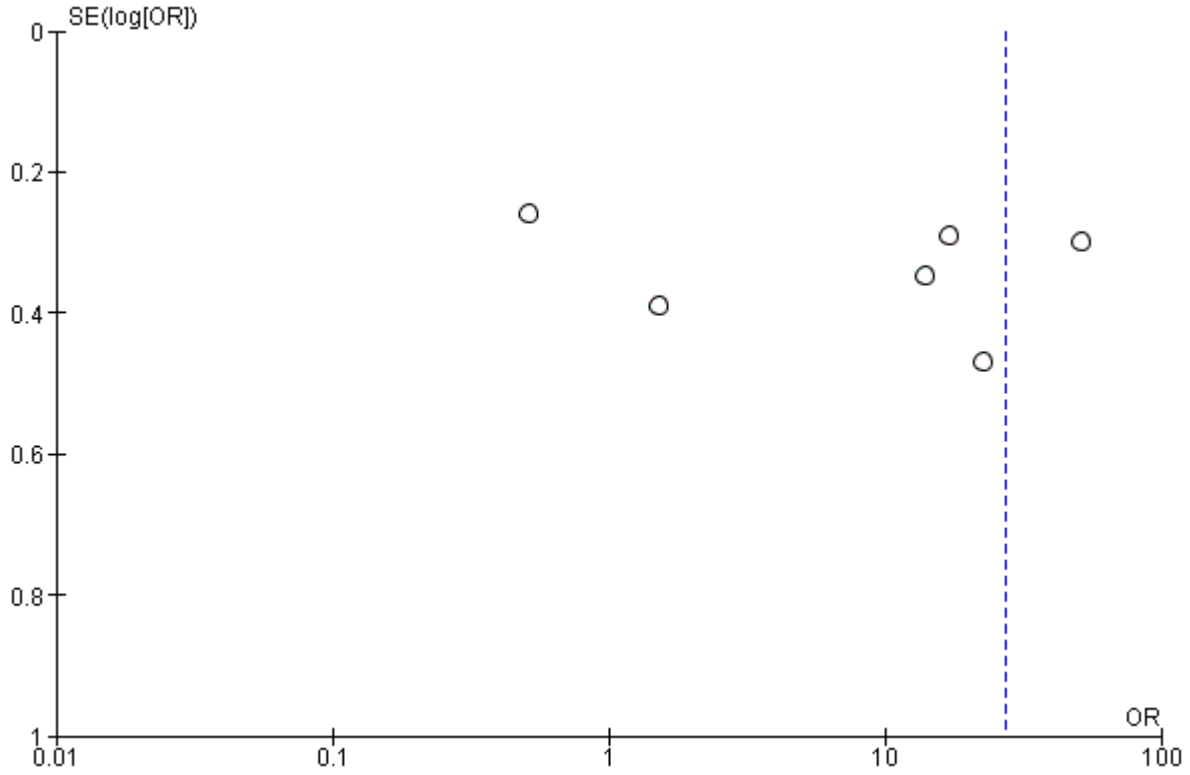
The Egger's test was used to assess the potential publication bias of studies reporting the efficacy of Desvenlafaxine 50 mg/d in MDD. The plot is symmetrical by visual inspection, suggesting an unlikelihood of publication bias [26], [27]. However, caution must be taken when interpreting the study outcomes due to the small number of studies [45]. The symmetry of the graph suggests high certainty of evidence reported by the five studies (**Figure 9**).

Figure 9: Funnel plot for reduced severity of depression in MDD.



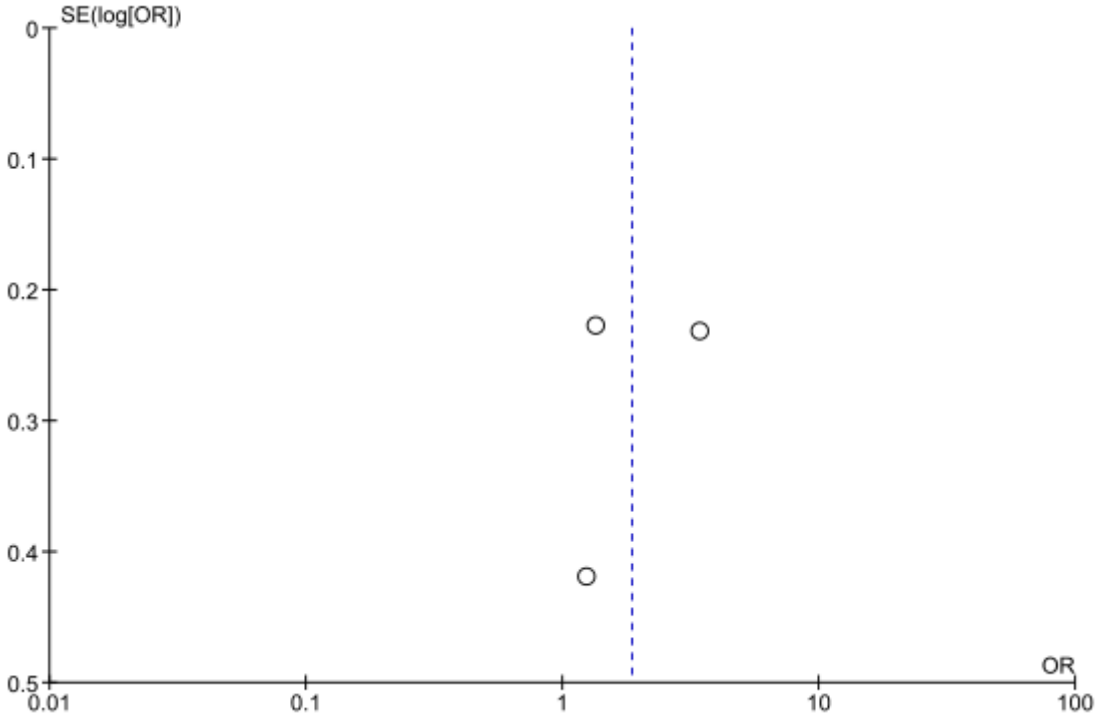
The publication bias of the three studies reporting the adverse effects of Vortioxetine 10-20 mg/d in MDD was assessed through Egger's test. By visual inspection, the plots are scattered all over the graph (figure 10). the asymmetrical graph suggests potential publication bias [46].

Figure 10: A funnel plot of adverse effects of Vortioxetine 10-20 mg/d



The publication bias of the three studies reporting the efficacy of AXS-50 in MDD was assessed through Egger's test. A visual inspection of the graph reveals a symmetrical plot [26], [27], suggesting the unlikelihood of publication bias (Figure 11). The unlikelihood of publication bias suggests high certainty of evidence. Nonetheless, caution must be taken when interpreting the study outcomes due to the small number of studies [45].

Figure 11: Funnel plot of MADRS scores of AXS-50 in MDD



Discussion

Drug safety and efficacy are crucial in drug design and clinical applications. The drug efficacy and safety profile study is critical to enhancing patient safety, optimizing treatment, and informing decision-making on patient management and education training [47]–[50]. Even though existing meta-analyses investigated the drug's safety and efficacy, there has not been much focus on MDD medications. The present meta-analysis investigates the safety and efficacy of antidepressants used to treat MDD to elucidate facts and report outcomes across different studies. These outcomes will influence clinical decision-making and indication of MDD.

In February 2008, the Food and Drug Administration approved Desvenlafaxine following clinical outcomes cited by multiple randomized trials [51]. Desvenlafaxine's approval was based on a substantial reduction of symptoms of depression, as reported in HAMD-17, reduced incidences of chronic pain, no severe symptoms resulting from discontinued use of the 50 mg dose, improved psychological well-being, and reduced disability.

A preliminary analysis revealed that Desvenlafaxine reduces symptoms of depression among males, females, children, and perimenopausal and postmenopausal women, with fewer adverse effects between 8 and 24 months. A pooled effects estimate OR was significant < 1, indicating statistical significance favoring reduced severity of depression in the treatment group. In addition, the present meta-analysis found high confidence and precision in the estimate, and a more significant uncertainty implied by the wider interval (OR: 0.52, 95% CI[0.44, 0.62], P < 0.00001). Clinically, the high confidence and precision of the estimates strongly suggest the practicality of the outcome. A preliminary analysis of the results strongly suggests the efficacy of 50 mg desvenlafaxine against MDD [52], [53]. The results suggest that Desvenlafaxine can be indicated for MDD patients with severe depressive symptoms. Desvenlafaxine's efficacy against depressive symptoms is of great interest since depression is one of the critical signs of MDD.

Results of the present meta-analysis slightly agree with the literature and reported information on MDD management using 50 mg/d Desvenlafaxine. One of the previous studies reports that 50 mg/d of Desvenlafaxine is an effective MDD treatment among postmenopausal and perimenopausal women, with clinical outcomes like functional outcomes and pain relief reported by participants as early as 14 days after treatment [54]. None of the participants discontinued Desvenlafaxine 50 mg/d due to adverse effects. Desvenlafaxine's main adverse effects include constipation, dizziness, dry mouth, and yawning. The incidence of low adverse effects indicates the tolerability, safety, and efficacy of 50 mg of Desvenlafaxine [55], [56]. Given Desvenlafaxine's short-term use, the high safety and efficacy profile strongly suggests its importance in MDD management [57]. The consistent clinical trials in previous studies suggest potential Desvenlafaxine's efficacy against MDD. Additionally, the low heterogeneity implied relative consistency of the evidence reported by the included studies [58].

The combined p-values of HAMD-17 scores reported by the individual studies gave an insight into Desvenlafaxine's 50 mg/d on the severity of depression. Individually, four out of the five studies reported statistically significant outcomes on the reduction of the severity of depression among MDD patients in the intervention than control. The combined p-values of reported HAMD-17 scores suggest the overall statistical significance of reduced severity of depression in the treatment than control ($p = 1.2729 * 10^{-7}$). Our finding indicates that Desvenlafaxine 50 mg/d significantly decreases the severity of depression among MDD patients. These findings concur with evidence from previous studies indicating that Venlafaxine extended release, of 75 mg/d to 375 mg/d, significantly reduces symptoms of depression in MDD irrespective of the baseline of patients' anxiety [59]–[61]. The findings of the present meta-analysis suggest underscore SNRIs' importance in MDD management. More so, Desvenlafaxine 50 mg/d implies that SNRIs are essential for reducing the severity of depression in MDD.

While the efficacy of antidepressants in MDD remains stark, adverse effects among treated patients arose. The present study focused on the adverse effects of Vortioxetine 10-20 mg/d, a serotonin modulator among 6, 669 MDD patients. By the mechanism of action, vortioxetine elevates serotonin, restoring mood balance [62]. The 9 studies reported headache, vomiting, nausea, diarrhea, dizziness, somnolence, suicidal ideation, and nasopharyngitis as adverse effects of Vortioxetine treatment in MDD. However, headache and nausea were consistent adverse effects across the 9 studies. Considering the large study group, the incidence of headache and nausea in the treatment group can be generalized. The incidence of headache and nausea among MDD patients treated with Vortioxetine 10-20 mg/d was statistically significant ($p = 0.0757$). A meta-analysis of the 9 studies produced statistically significant results on the incidence of nausea and headache (OR: 15.25, 95% CI [12.55, 18.52], $P < 0.00001$). This finding is aligned with the perspectives of literature where Vortioxetine treatment has been associated with an increased risk of nausea and headache [63], [64]. Clinically, physicians should monitor MDD patients for exacerbated headaches and nausea. Alternatively, Vortioxetine dosage should be gradually decreased until the patients recover from headache and the risk of nausea. However, the high variability ($I^2 = 98\%$) implies poor predictive value and suggests that these outcomes are likely to impugn conclusions regarding Vortioxetine's adverse effects in MDD [45], [65].

However, a preliminary analysis revealed variability that can be attributed to different study methods, population variance, or varying assessment measures. However, the variance is insignificant enough to impugn deducing or associating Vortioxetine with nausea and headache [66], [67]. The variance can affect the generalization of the adverse effects other than headache and nausea. The data analysis revealed one incidence of headache and 182 cases of nausea following Vortioxetine treatment. Despite the variance and the outliers, clinicians should

expect MDD patients to present the above-stated adverse effects. Therefore, clinicians should consider patient management guidelines to monitor MDD patients for adverse effects.

The present study's findings align with existing literature on the incidence of headache, vomiting, nausea, diarrhea, dizziness, somnolence, suicidal ideation, and nasopharyngitis among MDD patients treated with Vortioxetine. Generally, most antidepressants, including Vortioxetine, bear unique adverse effects, including an increased risk of nausea and headache [68]. These findings implicate crucial clinical practice protocols where clinicians should work together and adhere to treatment guidelines to deliver patient-centered care. To prevent the adverse effects from overriding the established efficacy outcomes, clinicians should monitor MDD patients closely while administering Vortioxetine. Lastly, these findings underscore the clinical profile of serotonin modulators in managing MDD. The incidence of adverse effects prompts caution while administering Vortioxetine, especially when the drug can exacerbate any adverse effects in the patients.

A meta-analysis of evidence reported by 3 studies yielded results on the efficacy of AXS-50 in the treatment group. There was a consistent decrease in MDD symptomatology over 6 weeks of treatment, with statistically insignificant outcomes favoring the placebo group (OR: 1.85, 95% CI [0.93, 3.70], P = 0.08). The number of patients reporting decreased symptomatology increased as early as week 2 of treatment, suggesting the early onset of action of the drug. This outcome suggests a quick onset of action and the effectiveness of aminoketone antidepressants. Generally, the present study's findings align with previous studies and the existing literature on the efficacy of aminoketone antidepressants. Literature indicates that aminoketone antidepressants, including bupropion, improve symptomatology in MDD [69], [70]. The alignment of these findings with the literature set the efficacy profile of aminoketone antidepressants on a high profile for indication in MDD. This finding aligns with the perspective of literature on AXS-50 on the reduction of MDD symptomatology [71]. The high heterogeneity means low predictive values as the results cannot be used to ascertain conclusions on decreasing MADRS scores in MDD [65], [71]. Despite the high heterogeneity, improved symptomatology was evident within 2 weeks of AXS-50 treatment. The quick onset of action promises resistance to depression and high efficacy [72], [73]. Additionally, the statistical analyses indicated medium variance in the decrease of weekly MADRS and a significant difference across the three groups. The differences result from the study populations differences in the studies.

Conclusion

Adverse effects and positive outcomes characterize MMD treatment using antidepressants. To decipher the efficacy of antidepressants used to treat MDD, an investigation on SNRIs, serotonin modulators, and aminoketone antidepressants was examined across randomized trials and observational studies. The clinical outcomes and adverse effects of the drugs investigated suggest or inform the indication and importance in the clinical management of MDD.

The present meta-analysis demonstrated statistically significant efficacy of Desvenlafaxine 50 mg/d in the reduction of the severity of symptoms of depression in MDD. The combined p-values of reported HAMD-17 scores in the individual studies support the efficacy of Desvenlafaxine 50 mg/d. Desvenlafaxine’s efficacy represents the SNRI class of antidepressants and supports the clinical indication for MDD. Likewise, the AXS-50 efficacy profile emerged in a meta-analysis of 3 studies through evidence collected based on MADRS scores. The progressive decrease in MDD’s symptomatology over the 6 weeks projected AXS-50’s efficacy, substantiating its rationale of indication in MDD. AXS-50’s efficacy results indicate the absence of tachyphylaxis since the efficacy of the medications did not diminish in successive weeks.

On the other hand, antidepressants used to treat MDD featured adverse effects, including reported headache, vomiting, nausea, diarrhea, dizziness, somnolence, suicidal ideation, and nasopharyngitis. The incidence of these adverse effects, with the consistency of headache and nausea, following Vortioxetine 10-20 mg/d treatment suggested the potential reactions in MDD management. The consistency of the adverse effects in 9 studies suggests the prominence of the adverse reactions following antidepressant administration in MDD. Thus, physicians should monitor patients to prevent exacerbation.

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APPENDICES

Supplementary Table 1: Adverse effects of antidepressants

Study	Headache	Nausea	Total events in the treatment group
Findling et al., 2022	23	21	147
Mahabelshwarkar et al., 2015	20	51	154
Mahabelshwarkar et al., 2015	24	47	154
Nishimura et al., 2018	19	27	148
Inoue et al., 2018	13	25	123
Ngen et al., 2019	1	3	76
Di Nicola et al., 2022	2	10	56
Mattingly et al., 2022	15	81	416
Wang et al., 2022	13	182	419

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Supplementary Table 2: Quality assessment of the observational studies

Study	Selection of case and controls				Comparability of cases and controls	Exposure		
	Is the case definition adequate	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of treatment and placebo based on design	Ascertainment of exposure	The same method ofascertainment for treatment and placebo	Non-Response Rate
Wang et al., 2022	☆	☆	☆	☆	☆☆	☆	☆	☆
Mattingly et al., 2022	☆	☆	☆	☆	☆☆	☆	☆	☆

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