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Comparative Gastrointestinal Effects of Antidepressants for the Acute Treatment of Adults with Major Depressive Disorder: A Network and Dose–Response Meta-Analysis

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Abstract

Objective

Gastrointestinal adverse effects are the most commonly reported adverse effects associated with the use of antidepressants. While existing studies on the gastrointestinal effects of antidepressant medications offer valuable insights, there are still opportunities to enhance the evidence base.

Methods

We included double-blind randomized controlled trials of major depressive disorder (MDD). Eligible studies must focus on comparing the use of 21 commonly used antidepressants in patients with MDD and reporting data on treatment-emergent gastrointestinal SEs. We selected 196 studies that reported specific numbers of individuals with gastrointestinal adverse effects, involving a total of 57,162 patients. A network and dose–response meta-analysis was conducted.

Results

Compared with placebo, 16 antidepressants had higher odds ratios (ORs) for nausea and vomiting, 15 antidepressants had higher ORs for constipation, 8 antidepressants had higher ORs for diarrhoea, 8 antidepressants had higher ORs for anorexia, 12 antidepressants had higher ORs for dry mouth, and 3 antidepressants had higher ORs for dyspepsia.

Conclusions

Commonly used antidepressants have different gastrointestinal effects. Duloxetine, levomilnacipran, and vilazodone carry a higher risk of inducing nausea and vomiting, whereas trazodone, amitriptyline, agomelatine, and mirtazapine tend to be better tolerated.

Amitriptyline, clomipramine, and reboxetine are more prone to induce constipation. Diarrhoea is more commonly associated with vilazodone, fluvoxamine, and sertraline. Amitriptyline, reboxetine, and duloxetine are more likely to cause anorexia. Amitriptyline, reboxetine, and trazodone are related to causing dry mouth. Compared with the placebo, amitriptyline, fluoxetine, and paroxetine were associated with a greater incidence of dyspepsia.

Introduction

MDD is a common illness that affects hundreds of millions globally and imposes substantial health and economic burdens(1-3). Antidepressant medications typically serve as the most crucial treatment for moderate to severe depression and are recommended as a first-line treatment for MDD(4-6). However, the use of these drugs presents a number of challenges, these drugs require a long administration time to obtain a therapeutic effect (7, 8). Their onset of action can take up to 4 weeks, and recovery can require treatment with multiple different agents(6). The prolonged use of medication can result in a number of adverse effects, which may lead to a reduction in patient compliance and an increased probability of spontaneous discontinuation. A study that investigated the reasons for medication interruption in patients with MDD in China has identified concerns about potential long-term side effects was the most frequent cause of spontaneous discontinuation of prescribed medication. (9). In a guideline published by the American College of Physicians (ACP), it is estimated that more than 60% of patients may experience at least one adverse reaction(10). Gastrointestinal adverse effects such as nausea and vomiting were the most commonly reported symptoms

leading to antidepressant discontinuation during clinical trials. (11, 12). The prevalence of gastrointestinal adverse effects differs among various classes of antidepressants. For example, selective serotonin reuptake inhibitors (SSRIs) have been reported to increase the incidence of nausea, decreased appetite, and diarrhoea, whereas tricyclic antidepressants have been shown to be more prone to constipation and weight gain(13). A comparative study of SSRIs and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) indicated that venlafaxine is associated with a higher incidence of nausea and vomiting, whereas sertraline is linked to a greater risk of diarrhoea(14). Furthermore, alterations in appetite and weight are among the symptoms of MDD(15). In clinical practice, medical practitioners should pay particular attention to the potential for gastrointestinal symptoms to be caused by antidepressant drugs when selecting appropriate medication for patients who report this symptom.

Some studies have explored antidepressant-induced gastrointestinal (GI) effects, prior research, such as the meta-analysis by Oliva et al, which included 304 studies, showed that escitalopram and sertraline had the highest gastrointestinal side effects (nausea, diarrhoea), while mirtazapine caused fewer gut issues, only linked to increased appetite(16). The large sample size of this study contributes significantly to understanding the gastrointestinal adverse effects of antidepressants. While existing studies on the gastrointestinal effects of antidepressant medications offer valuable insights, opportunities exist to enhance the evidence base—for example, by expanding the scope of examined drugs, as well as refining the statistical methodologies employed to more comprehensively characterize the gastrointestinal responses induced by antidepressants.

The dose–response relationship between drugs and the incidence of gastrointestinal adverse

effects also remains uncertain. The majority of previous studies on the dose–response relationship between antidepressants and adverse effects have focused on overall drug tolerance, with relatively few studies conducted on the relationship with specific adverse effects(17). It is essential for clinicians to identify the relationship between dosage and gastrointestinal adverse effects to make better use of antidepressants. However, there is still a paucity of studies that address this particular aspect.

We therefore searched double-blind randomized controlled trials (RCTs) of MDD that focused on comparing the use of 21 commonly used antidepressants in patients with MDD. We did a network meta-analysis to systematically evaluate and compare the gastrointestinal effects of 21 antidepressants. Drugs with significant gastrointestinal effects compared with placebo in the network meta-analysis were selected to continue with dose-response meta-analysis to explore the dose–response relationship of each drug.

METHODS

Search strategy

Double-blind randomized controlled trials comparing antidepressants with placebo or another active antidepressant as monotherapy for acute treatment were included. Participants included in the study were adults aged 18 years or older of any sex, who had been diagnosed with major depressive disorder on the basis of standard diagnostic criteria (DSM (any version) and ICD (any version)). The intervention included 21 antidepressants used as monotherapy for acute treatment (agomelatine, amitriptyline, bupropion, citalopram, clomipramine, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran,

milnacipran, mirtazapine, nefazodone, paroxetine, reboxetine, sertraline, trazodone, venlafaxine, vilazodone, vortioxetine). In the network meta- analysis, the comparison was either placebo or another active antidepressant, with primary outcomes focusing on the incidence of treatment-emergent gastrointestinal adverse effects. For the dose–response meta-analysis, we only selected studies that compared antidepressants with placebo.

We systematically searched PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science for articles before Jan 30, 2024. We also searched clinicaltrials.gov for trials. A comprehensive search strategy was employed to identify all potential references to depression, using a combination of broad search terms ("depress," "dysthymi," "adjustment disorder," "mood disorder*," "affective disorder," and "affective symptoms"), gastrointestinal adverse effects (nausea and vomiting, constipation, diarrhoea, anorexia, dry mouth, increased appetite, dyspepsia, and abdominal pain) and the names of antidepressant medications with no language restrictions. We also searched the reference lists of previous systematic reviews and meta-analyses on the topic. The complete search strategy provided in the appendix 1. Two individuals screened each record and extracted the data independently. Discrepancies were resolved through consensus, with input from a third senior author.

Outcomes

The outcome measure was the incidence of treatment-emergent gastrointestinal adverse effects in patients with MDD during short-term antidepressant treatment. The adverse effects include nausea and vomiting, constipation, diarrhoea, anorexia, dry mouth, increased

appetite, dyspepsia, and abdominal pain (18). The number of participants, year of publication, mean age, number of females, dose range, baseline severity, treatment time and number of patients experiencing adverse effects were extracted from each study. In this trial, we set 8 weeks as the main time point for the evaluation. For those trials that were unable to provide data by week 8, we used the data reported closest to that time point.

Risk of bias

The studies' risk of bias was assessed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions(19). This included assessing sequence generation, allocation concealment, blinding of participants, therapists, and assessors, selective reporting bias, and attrition bias. Studies were classified as having low risk of bias if none of these domains were rated as high risk of bias and three or fewer were rated as unclear risk; moderate if one was rated as high risk of bias or none was rated as high risk of bias, but four or more were rated as unclear risk; and all other cases were assumed to have high risk of bias(20).

Data analysis

We conducted Bayesian network meta-analyses based on random-effects models to compare the incidence of each specific adverse effect of antidepressants and placebo comprehensively. Given that all outcome measures in this study are binary variables, the effect size was calculated via ORs and their 95% credible intervals, (CrIs). To rank the drugs, we used the surface under the cumulative ranking curve (SUCRA) and the mean ranks(21). We evaluated

global heterogeneity and inconsistency in our network model via tau^2 and I^2 statistics and checked local inconsistency via the node-splitting method(22). Transitivity was assumed base on pre-specified effect modifiers (ie, mean age, treatment duration, baseline severity) across studies. In case of identification of outliers in these comparisons, sensitivity analyses and meta-regression were done. Publication bias was assessed by comparison-adjusted funnel plots and with Egger's test. We assessed the certainty of evidence contributing to network estimates of the main outcomes with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework(23, 24). For the primary outcome, we did sensitivity analyses focusing on age subgroups by excluding participants ≥65 years, as well as sample size thresholds by removing studies with n ≤20, ≤30, or ≤40 to assess small-study effects, Additionally, we performed network meta-regression on baseline symptom severity, publication year, and treatment duration to explore how these factors influenced gastrointestinal adverse effect estimates(25). All statistical analyses were done in R (version 4.3.3) with the gemtc package. This study was registered with PROSPERO, CRD420251032586.

Drugs with significant gastrointestinal adverse effects compared with placebo in the network meta-analysis were selected to continue with dose–response meta-analysis to observe the relationship between dose and gastrointestinal adverse effects. We included both fixed-dose and flexible-dose studies. For flexible-dose studies, we analyzed using the median of the dose range. We used R to fit a single-stage, random-effects meta-analysis of the dose–response model. Flexible restricted cubic splines were used to conduct the curves to evaluate the nonlinear relationship between antidepressant dose and the OR value of gastrointestinal

adverse effects (26). We established three knots at the 25th, 50th, and 75th percentiles of the dose range to facilitate curve fitting. We also did sensitivity analyses to examine the robustness of the main findings by changing the set of knots and removing flexible doses for reanalysis. Heterogeneity was assessed with a chi-square test of heterogeneity ($p<0.1$) and the I^2 statistic, where we considered I^2 values>50% to suggest considerable heterogeneity(27).

RESULTS

Study selection

We identified 26369 published records and 4352 unpublished records through an electronic search. A total of 544 published and 136 unpublished full-text records were assessed for eligibility, and a total of 234 studies were included. Finally, we selected 196 studies that reported specific numbers of individuals who experienced gastrointestinal adverse effects see Figure 1. The total number of patients included in the trials was 57,162, with a mean age of 44.6 years. The average experimental period was 8 weeks. The specific characteristics of the included studies are depicted in appendix 3. Assessment of transitivity assumption is reported in the appendix 4.

Primary analyses

Nausea and vomiting

A total of 173 RCTs were conducted to compare the incidence of nausea and vomiting for 21 drugs (8 concerning agomelatine, 13 amitriptyline, 8 bupropion, 19 citalopram, 5

clomipramine, 3 desvenlafaxine, 13 duloxetine, 19 escitalopram, 45 fluoxetine, 4 fluvoxamine, 4 levomilnacipran, 5 milnacipran, 8 mirtazapine, 4 nefazodone, 46 paroxetine, 8 reboxetine, 21 sertraline, 6 trazodone, 24 venlafaxine, 4 vilazodone and 11 vortioxetine). Sixteen of the 21 drugs demonstrated a notable incidence of nausea and vomiting in comparison with placebo, as shown in Figure 2. With the exception of milnacipran, trazodone, amitriptyline, agomelatine and mirtazapine, all drugs demonstrated a higher incidence of nausea and vomiting in comparison to the placebo. Duloxetine (OR = 4.38; CrI 3.58-5.38), levomilnacipran (OR = 3.82; CrI 2.54-5.91), vilazodone (OR = 3.65; CrI 2.62-5.12), vortioxetine (OR = 3.26; CrI 2.64-4.04), venlafaxine (OR = 3.16; CrI 2.67-3.77), fluvoxamine (OR = 3.03; CrI 1.84-5.05), sertraline (OR = 2.65; CrI 2.13-3.28), paroxetine (OR = 2.64; CrI 2.29-3.05), clomipramine (OR = 2.51; CrI 1.45-4.39), nefazodone (OR = 2.29; CrI 1.33-4.00), desvenlafaxine (OR = 2.23; CrI 1.37-3.66), citalopram (OR = 2.11; CrI 1.64-2.69), escitalopram (OR = 2.08; CrI 1.66-2.60), fluoxetine (OR = 1.86; CrI 1.58-2.18), bupropion (OR = 1.45; CrI 1.09-1.93), and reboxetine (OR = 1.43; CrI 1.04-1.98)

We selected 12 drugs with significant nausea and vomiting compared with placebo in the network meta-analysis to continue with dose-response meta-analysis excluding fluvoxamine, clomipramine, nefazodone, and desvenlafaxine due to insufficient data, see Figure 2. Within the range of conventional therapeutic doses, citalopram, fluoxetine, levomilnacipran, and venlafaxine demonstrated a dose-dependent increase. For duloxetine and vortioxetine, the curve depicted an inverted U-shaped. Conversely, escitalopram, paroxetine, and sertraline demonstrated a slight decrease in risk. The vilazodone curve exhibited a flattening with increasing dose. The results of the dose–response analysis for bupropion and reboxetine were

not statistically significant.

Constipation

122 RCTs were conducted to compare the incidence of constipation for 20 drugs, excluding vilazodone due to insufficient data (8 concerning agomelatine, 20 amitriptyline, 3 bupropion, 8 citalopram, 4 clomipramine, 4 desvenlafaxine, 11 duloxetine, 8 escitalopram, 26 fluoxetine, 2 fluvoxamine, 3 levomilnacipran, 4 milnacipran, 6 mirtazapine, 5 nefazodone, 37 paroxetine, 13 reboxetine, 11 sertraline, 4 trazodone, 18 venlafaxine and 7 vortioxetine). Compared with the placebo, 15 of the 20 drugs showed a significant incidence of constipation compared to placebo, see Figure 3. With the exception of vortioxetine, fluoxetine, sertraline, citalopram and escitalopram, all drugs demonstrated a greater incidence of constipation in comparison to the placebo. Amitriptyline (OR = 4.47; CrI 3.22-6.34), clomipramine (OR = 4.33; CrI 2.17-8.98), reboxetine (OR = 4.02; CrI 2.90-5.51) , fluvoxamine (OR = 4.00; CrI 1.37-12.5) , levomilnacipran (OR = 3.77; CrI 1.99-7.57) , venlafaxine (OR = 3.19; CrI 2.41-4.30) , agomelatine (OR = 3.14; CrI 1.45-7.21) , nefazodone (OR = 3.05; CrI 1.52-6.34) , milnacipran (OR = 2.57; CrI 1.23-5.63) , mirtazapine (OR = 2.55; CrI 1.49-4.38) , paroxetine (OR = 2.38; CrI 1.92-2.99) , bupropion (OR = 2.38; CrI 1.27-4.52) , trazodone (OR = 2.37; CrI 1.28-4.36), desvenlafaxine (OR = 2.35; CrI 1.36-4.25) and duloxetine (OR = 2.33; CrI 1.71-3.17).

10 drugs with significant constipation compared to placebo in network meta-analysis were selected to continue dose-response analysis, excluding clomipramine, fluvoxamine, nefazodone, milnacipran, and mirtazapine due to insufficient data, see Figure 3. Within the

range of conventional therapeutic doses, paroxetine showed a dose-dependent increase. For desvenlafaxine and duloxetine, the curve depicted an inverted U shape. Conversely, amitriptyline, bupropion, and reboxetine showed a dose-dependent decrease in risk. The curve for levomilnacipran and venlafaxine flattened with increasing dose. The results of the dose–response analysis for agomelatine and trazodone were not statistically significant.

Diarrhoea

A total of 85 RCTs were conducted to compare the incidence of diarrhoea for 20 drugs, excluding clomipramine due to insufficient data (3 concerning agomelatine, 3 amitriptyline, 6 bupropion, 6 citalopram, 1 desvenlafaxine, 6 duloxetine, 8 escitalopram, 26 fluoxetine, 3 fluvoxamine, 2 levomilnacipran, 3 milnacipran, 5 mirtazapine, 1 nefazodone, 27 paroxetine, 2 reboxetine, 13 sertraline, 2 trazodone, 9 venlafaxine, 3 vilazodone and 5 vortioxetine). Eight of the 20 drugs showed a significant incidence of adverse effects compared to placebo, see Figure 4. Vilazodone (OR = 3.88; CrI 2.69-5.64), fluvoxamine (OR = 3.15; CrI 1.30-7.59), sertraline (OR = 2.90; CrI 2.23-3.74), citalopram (OR = 2.60; CrI 1.53-4.47), agomelatine (OR = 2.17; CrI 1.09-4.47), fluoxetine (OR = 1.95; CrI 1.56-2.44), escitalopram (OR = 1.87; CrI 1.36-2.66), paroxetine (OR = 1.62; CrI 1.34-1.97).

5 drugs with significant diarrhoea compared to placebo in network meta-analysis were selected to continue dose-response analysis excluding agomelatine fluvoxamine and vilazodone due to insufficient data, see Figure 4. Escitalopram fluoxetine paroxetine and sertraline all showed a dose-dependent increase. The results of dose-response analysis for citalopram were not statistically significant.

Anorexia

A total of 42 RCTs were conducted to compare the incidence of anorexia for 14 drugs, excluding clomipramine due to insufficient data (1 concerning amitriptyline, 2 bupropion, 2 citalopram, 3 desvenlafaxine, 9 duloxetine, 5 escitalopram, 9 fluoxetine, 1 milnacipran, 10 paroxetine, 4 reboxetine, 2 sertraline, 1 trazodone, 11 venlafaxine, and 5 vortioxetine). Eight of the 14 drugs showed a significant incidence of adverse effects compared to placebo, see Figure 5. Amitriptyline (OR = 8.23; CrI 2.07-33.20), reboxetine (OR = 5.43; CrI 3.26-9.30), duloxetine (OR = 4.57; CrI 3.16-6.69), fluoxetine (OR = 4.37; CrI 2.79-7.03), venlafaxine (OR = 3.86; CrI 2.65-5.64), paroxetine (OR = 3.42; CrI 2.37-5.09), desvenlafaxine (OR = 2.67; CrI 1.52-5.00), escitalopram (OR = 2.02; CrI 1.18-3.70). 7 drugs with significant diarrhoea compared to placebo in network meta-analysis were selected to continue dose-response analysis excluding amitriptyline due to insufficient data, see Figure 5. Almost all drugs showed a dose-dependent increase except for fluoxetine, which exhibits an inverted U-shape. The results of dose-response analysis for reboxetine and escitalopram were not statistically significant.

Dry mouth

153 RCTs were conducted to compare the incidence of constipation for 21 drugs, excluding (5 concerning agomelatine, 23 amitriptyline, 8 bupropion, 10 citalopram, 6 clomipramine, 4 desvenlafaxine, 13 duloxetine, 11 escitalopram, 32 fluoxetine, 3 fluvoxamine, 4 levomilnacipran, 5 milnacipran, 10 mirtazapine, 5 nefazodone, 42 paroxetine, 12 reboxetine, 19 sertraline, 5 trazodone, 20 venlafaxine, 3 vilazodone and 10 vortioxetine).

Compared with the placebo, 12 of the 21 drugs showed a significant incidence of dry mouth compared to placebo, see Figure 6. Amitriptyline (OR = 7.89; CrI 5.68-11.00), reboxetine (OR = 4.12; CrI 2.93-5.80), trazodone (OR = 4.01; CrI 2.30-7.03), clomipramine (OR = 3.93; CrI 2.20-7.04), mirtazapine (OR = 3.15; CrI 2.03-4.88), venlafaxine (OR = 2.60; CrI 1.96-3.46), duloxetine (OR = 2.59; CrI 1.89-3.55), bupropion (OR = 2.43; CrI 1.68-3.54), milnacipran (OR = 2.23; CrI 1.16-4.27), paroxetine (OR = 2.02; CrI 1.63-2.51), sertraline (OR = 1.76; CrI 1.28-2.43), fluoxetine (OR = 1.55; CrI 1.19-2.02).

8 drugs with significant dry mouth compared to placebo in network meta-analysis were selected to continue dose-response analysis, excluding amitriptyline, clomipramine, milnacipran and mirtazapine due to insufficient data, see Figure 6. Within the range of conventional therapeutic doses, all drugs showed a dose-dependent increase. The results of the dose–response analysis for sertraline and trazodone were not statistically significant.

Increased appetite

There are 8 RCTs conducted to compare the incidence of increased appetite for 8 drugs (2 concerning amitriptyline, 1 citalopram, 1 escitalopram, 1 fluoxetine, 4 mirtazapine, 1 paroxetine, 1 reboxetine, 3 sertraline). The results demonstrated that none of the drugs exhibited a statistically significant difference when compared to a placebo, see appendix 5.

Dyspepsia

A total of 37 RCTs were conducted to compare the incidence of diarrhoea for 13 drugs, other drugs were not included in the comparison due to insufficient data (2 concerning

agomelatine, 4 amitriptyline, 1 bupropion, 1 citalopram, 2 escitalopram, 12 fluoxetine, 1 milnacipran, 2 mirtazapine, 3 nefazodone, 16 paroxetine, 4 reboxetine, 8 sertraline, 4 venlafaxine).

The forest plots for each drug are shown in appendix 5. Three of the 13 drugs showed a significant incidence of adverse effects compared to placebo, they are amitriptyline (OR = 4.27; CrI 1.86-10.4), fluoxetine (OR = 1.63; CrI 1.23-2.13) and paroxetine (OR = 1.44; CrI 1.12-1.90). Appendix 5 also shows the dose-response curves for fluoxetine and paroxetine excluding amitriptyline due to insufficient data. Fluoxetine exhibited a dose-dependent decrease, whereas paroxetine's results were nonsignificant.

Abdominal pain

There are also 26 RCTs conducted to compare the incidence of abdominal pain for 14 drugs (1 concerning agomelatine, 1 amitriptyline, 1 bupropion, 2 citalopram, 1 desvenlafaxine, 2 escitalopram, 9 fluoxetine, 1 milnacipran, 2 mirtazapine, 2 nefazodone, 10 paroxetine, 4 reboxetine, 6 sertraline, 1 trazodone). The results demonstrated that none of the drugs exhibited a statistically significant difference when compared to a placebo, see appendix 5. In the network meta-analysis, heterogeneity among individual studies was low for nearly all outcomes ($\tau^2 = 0.058$, $I^2 = 3\%$ for nausea and vomiting, $\tau^2 = 0.098$, $I^2 = 4\%$ for constipation, $\tau^2 = 0.008$, $I^2 = 0.6\%$ for diarrhoea, $\tau^2 = 0$, $I^2 = 4\%$ for anorexia, $\tau^2 = 0.07$, $I^2 = 2\%$ for dry mouth, $\tau^2 = 0.003$, $I^2 = 6\%$ for increased appetite, $\tau^2 = 0.016$, $I^2 = 0.0\%$ for dyspepsia, $\tau^2 = 0.026$, $I^2 = 0.0\%$ for abdominal pain). The local inconsistency was explored using the node-splitting approach see appendix 6. The results of the risk of bias assessment are provided in

the appendix 7. Many domains were rated as unclear and the overall risk of bias was rated as low in 92 (47%) studies, moderate in 104 (53%). Comparison-adjusted funnel plots (pre-assuming the direction of bias) and Egger's test see appendix 8. The p-value of Egger's test is 0.0408 for dry mouth and 0.0089 for increased appetite, indicating a certain degree of publication bias.

Sensitivity analysis

To address concerns about robustness, we conducted sensitivity analyses focusing on age subgroups by excluding participants ≥65 years, as well as sample size thresholds by removing studies with n ≤20, ≤30, or ≤40 to assess small-study effects, with details reported in appendix 9. Additionally, we performed network meta-regression on baseline symptom severity, publication year, and treatment duration to explore how these factors influenced gastrointestinal adverse effect estimates. The findings of the sensitivity analyses were largely similar to those of the main analysis. We additionally performed reanalysis of the dose-response meta-analysis by adjusting the set of knots and excluding flexible-dose studies see Appendix 9. While the number of fixed-dose studies available for certain antidepressants and gastrointestinal adverse effects was limited, resulting in fewer statistical outputs than in the primary analysis, dose-response relationships for outcomes with adequate fixed-dose data were largely consistent with those observed in the primary analysis. These consistent findings provide partial validation for the reliability of our initial dose-response conclusions. Future research should prioritize conducting more fixed-dose studies to further strengthen the robustness of these findings. The GRADE assessments are presented in Appendix 10.

Overall, the certainty of evidence spanned a range from moderate to very low across all analyses conducted.

Discussion

In the current study, network and dose–response meta-analyses were conducted to evaluate and quantify the gastrointestinal effects of antidepressants, focusing on five types of effects: nausea and vomiting, constipation, diarrhoea, dyspepsia, and abdominal pain. In the network meta-analysis for nausea and vomiting, all but agomelatine, amitriptyline, mirtazapine, milnacipran, and trazodone among 21 antidepressants demonstrated significant effects, with duloxetine, levomilnacipran, and vilazodone exhibiting the highest incidence rates. With regard to constipation, the majority of 20 drugs exhibited a high incidence, with the exception of vortioxetine, fluoxetine, sertraline, citalopram, and escitalopram. Amitriptyline, clomipramine, and reboxetine had the highest rates. In the case of diarrhoea, eight out of the 20 drugs under consideration, notably vilazodone, fluvoxamine, and sertraline, demonstrated a significant incidence. With regard to dyspepsia, amitriptyline, fluoxetine, and paroxetine were the three out of the 13 drugs with a significant incidence compared with placebo. However, the dose-response meta-analysis demonstrated that the effects on the gastrointestinal system are not always increased linearly along with the dose increase for the 21 antidepressants.

This study systematically evaluated the gastrointestinal side effects of 21 antidepressants by integrating network and dose-response meta-analysis and found significant differences in the frequency and dose-response of side effects between different drugs. The findings indicated

that SSRIs, including fluoxetine, paroxetine and escitalopram, and SNRIs, such as duloxetine and venlafaxine, were associated with an elevated risk of developing anorexia and dry mouth. These results are consistent with the meta-analysis by Oliva et al(16), but there are also important differences. The study by Oliva et al. focused on 15 second-generation antidepressants and found that escitalopram and sertraline had the worst gastrointestinal tolerability, while mirtazapine was only associated with increased appetite. This study further expanded the range of drugs to include tricyclics (such as amitriptyline and clomipramine) and other newer drugs (such as vortioxetine) and provided more details: for example, amitriptyline and clomipramine have a significantly higher risk of constipation than other drugs, which is consistent with the characteristics of tricyclics that were not included in Oliva's study. In addition, Oliva et al did not find a significant association between mirtazapine and nausea and vomiting, whereas this study also found that drugs such as mirtazapine and trazodone have a lower risk of these side effects, further supporting their potential as a choice for gastrointestinal-sensitive patients.

In this study, drugs that affect serotonin levels or serotonin receptors demonstrated a higher incidence of nausea and vomiting, including SSRIs, SNRIs, bupropion, reboxetine, vilazodone, levomilnacipran, and vortioxetine. The reason may be attributed to the fact that 5-HT and its receptors play an essential role in gastrointestinal motility (11). The dose-response curve of different drugs varies according to the dose-response analysis, which may be linear, inverted U-shaped, or relatively flat. Although the trends of these curves are different, the incidence of nausea and vomiting is consistently higher at high doses than at low doses. This finding is consistent with the results of previous studies on antidepressant

tolerance (7). Mirtazapine trazodone and amitriptyline demonstrated no statistically significant incidence of nausea and vomiting compared with the placebo. These drugs have been demonstrated to exert antihistaminergic effects and antagonistic activity at 5-HT2A serotonergic receptors (14). In light of these findings, it can be concluded that these drugs have a relatively favorable safety profile with regard to the occurrence of nausea and vomiting. Indeed, in a study conducted by Cangemi DJ, mirtazapine was regarded as a promising agent for the management of nausea and vomiting in a range of medical conditions(28).

The results indicate that the majority of antidepressant medications have the potential to induce constipation, with the highest prevalence of this adverse effect observed in patients who have been prescribed tricyclic drugs. Our research results also revealed that some SSRIs do not induce constipation, yet all have been associated with the potential for diarrhoea. This may be attributed to the peripheral anticholinergic effect of TCAs(29), whereas SSRIs exhibit a diminished peripheral anticholinergic effect. In our research findings, in addition to SSRIs, vilazodone and agomelatine have also been demonstrated to cause diarrhoea, this finding is consistent with the findings of the most recent Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical Guidelines(8).

In the analysis of dyspepsia, there was no discernible difference in the incidence of digestive disorders between most drugs and placebo. However, amitriptyline, paroxetine, and fluoxetine were observed to potentially induce dyspepsia. This is consistent with some studies reporting that dyspepsia is one of the most frequently reported side effects associated with the use of SSRIs and SNRIs(11). Some antidepressants may help with functional

dyspepsia according to recent studies(30, 31). Therefore, more research is needed to clarify the specific relationship.

It is noteworthy that relevant studies have demonstrated that mirtazapine exerts a significant appetite-stimulating effect; however, this effect did not reach statistical significance in the present study(16, 32). One potential explanation is that the small sample size and limited number of events have resulted in insufficient statistical power. Relatively few randomized controlled trials specifically report "increased appetite" as an adverse event of mirtazapine. Additionally, heterogeneity in the reporting and coding of adverse events across included trials may further obscure this effect. For instance, some studies may categorize "increased appetite" under broader terms (e.g., "weight-related adverse events") rather than documenting it as a distinct gastrointestinal effect—this inconsistency leads to gaps in data extraction. Future research should address this gap by investigating appetite changes using validated patient-reported outcome (PRO) scales, which would enable more reliable quantification of this effect(33, 34).

This study has limitations. First, the exclusion of adolescents under 18 and patients with physical comorbidities may limit the generalizability of our findings. Second, the short follow-up period of eight weeks restricts our ability to predict long-term outcomes. Third, this study included flexible-dose studies in the dose-response analysis. Although we used the median of the dose range to standardize flexible-dose data and minimize variability, flexible dosing regimens are adjusted based on individual patient factors, potentially leading to discrepancies between actual exposure doses and the median values. This uncertainty in dose data may have biased the estimated dose-response association by over- or underestimating the

true effect. Future studies should prioritize including more fixed-dose RCTs and increasing sample sizes to improve the accuracy of dose-response analyses. Fourth, our manuscript was completed in November 2024, and the PROSPERO registration date is April 2025. Fifth, in this study, many domains in the risk of bias assessment were rated as unclear, this uncertainty in critical domains of experimental rigor may introduce systematic errors, potentially compromising the validity of pooled effect estimates. With 47% of studies having a low overall risk of bias and 53% having a moderate risk of bias. This indicates that there is potential for bias to affect the results. Regarding the heterogeneity observed in the analyses, the results show that for nearly all outcomes, the heterogeneity among individual studies was low. Low heterogeneity implies that the studies included in the meta - analysis are relatively consistent in their findings. This is beneficial as it increases the reliability of the overall results. However, in some dose - response analyses, high heterogeneity was observed, which might be due to differences in sample size, treatment durations, or the range of antidepressant doses used. These differences can affect the precision of the estimates, leading to wider 95% credible intervals. Therefore, results of spline curve analyses for specific drugs should be interpreted cautiously. Sixth, the lack of uniform funding source reporting in original studies prevents a comprehensive assessment of potential financial biases. Lastly, a lack of a unified standard for specific adverse effects is also a limitation of this research.

Conclusion

The findings indicate that duloxetine, levomilnacipran, and vilazodone are more likely to cause nausea and vomiting, whereas amitriptyline, clomipramine, and reboxetine are more

prone to induce constipation. Diarrhoea is more commonly associated with vilazodone, fluvoxamine, and sertraline. Amitriptyline, reboxetine, and duloxetine are more likely to cause anorexia. Amitriptyline, reboxetine, and trazodone are related to causing dry mouth. Compared with the placebo, amitriptyline, fluoxetine, and paroxetine were associated with a greater incidence of dyspepsia. The dose–response relationships for these drugs are inconsistent. This study provides novel recommendations for patients with depression who experience intolerance gastrointestinal to adverse effects. When a specific drug must be used, a dose range with fewer adverse effects can be selected based on the recommendations of the dose-response curve.

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Conflict of Interest

All the authors declare that they have no financial or conflicts of interest.

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Figure Legends

Figure 1 PRISMA flow diagram

Figure 2 Forest plot of network and dose–response curves of individual antidepressant drugs for nausea and vomiting. A: Forest plot of network. B: Dose–response curves. OR=odds ratio; CrI=credible interval; N=number of studies; n=number of subjects; Het=heterogeneity; NA=not accessible because there was only one study. Antidepressants were compared with placebo. The solid line represents the dose–response curve, and the dashed line represents the upper and lower limits of the 95% credible interval.

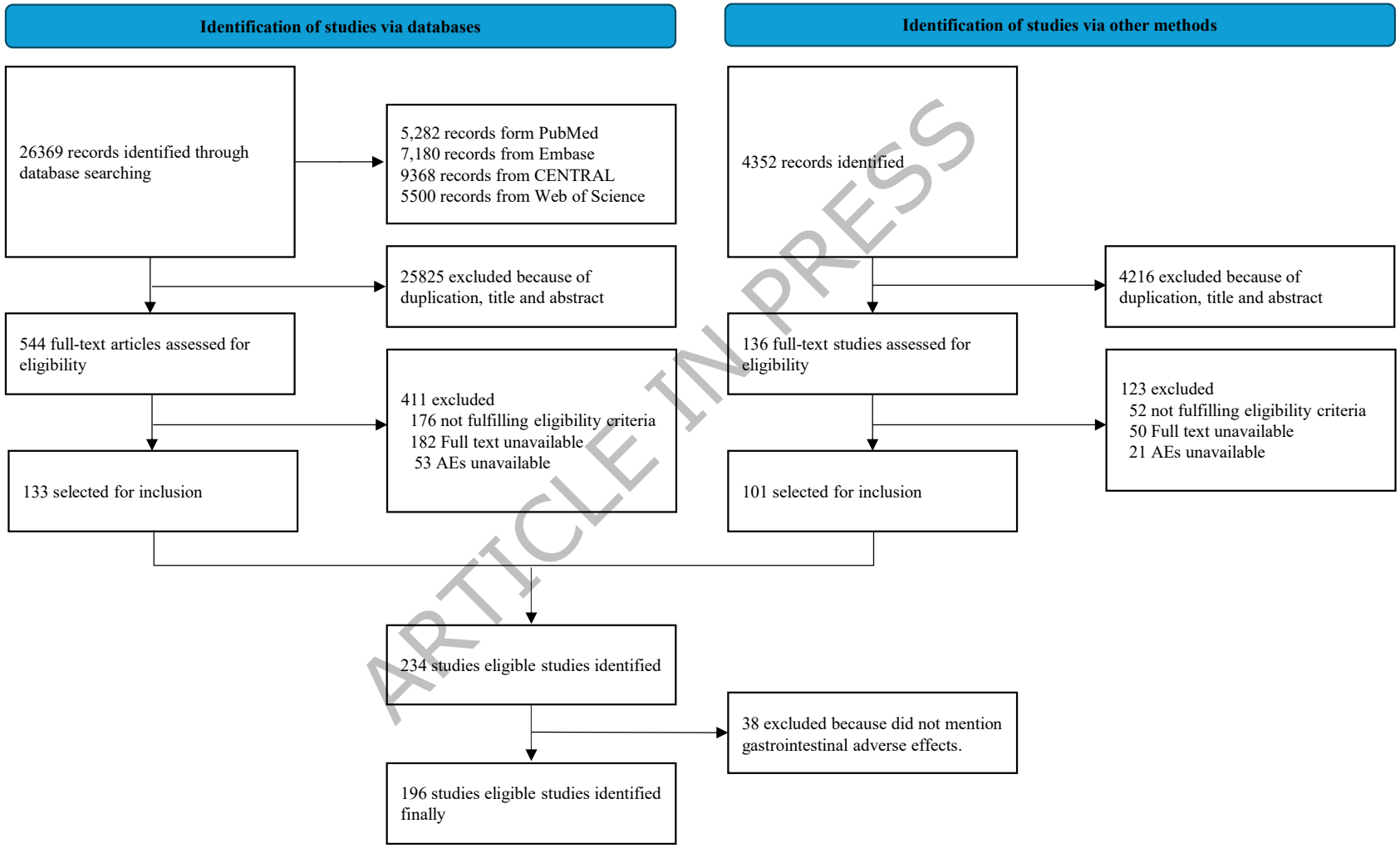
Figure 3 Forest plots of network and dose–response curves of individual antidepressant drugs for constipation. A: Forest plot of network. B: Dose–response curves. OR=odds ratio; CrI=credible interval; N=number of studies; n=number of subjects; Het=heterogeneity; NA=not accessible because there was only one study. Antidepressants were compared with placebo. The solid line represents the dose–response curve, and the dashed line represents the upper and lower limits of the 95% credible interval.

Figure 4 Forest plots of the network meta-analysis and dose–response curves of individual antidepressant drugs for diarrhoea. A: Forest plot of network. B: Dose–response curves. OR=odds ratio; CrI=credible interval; N=number of studies; n=number of subjects; Het=heterogeneity; NA=not accessible because there was only one study. Antidepressants were compared with placebo. The solid line represents the dose-response curve, and the dashed

line represents the upper and lower limits of the 95% credible interval.

Figure 5 Forest plots of the network meta-analysis and dose–response curves of individual antidepressant drugs for anorexia. A: Forest plot of network. B: Dose–response curves. OR=odds ratio; CrI=credible interval; N=number of studies; n=number of subjects; Het=heterogeneity; NA=not accessible because there was only one study. Antidepressants were compared with placebo. The solid line represents the dose–response curve, and the dashed line represents the upper and lower limits of the 95% credible interval.

Figure 6 Forest plots of the network meta-analysis and dose–response curves of individual antidepressant drugs for dry mouth. A: Forest plot of network. B: Dose–response curves. OR=odds ratio; CrI=credible interval; N=number of studies; n=number of subjects; Het=heterogeneity; NA=not accessible because there was only one study. Antidepressants were compared with placebo. The solid line represents the dose–response curve, and the dashed line represents the upper and lower limits of the 95% credible interval.



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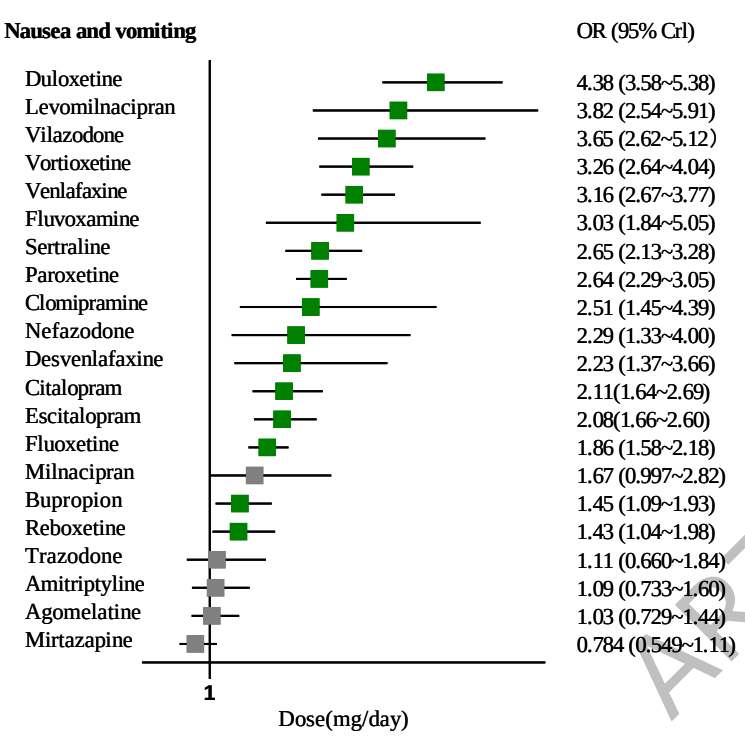

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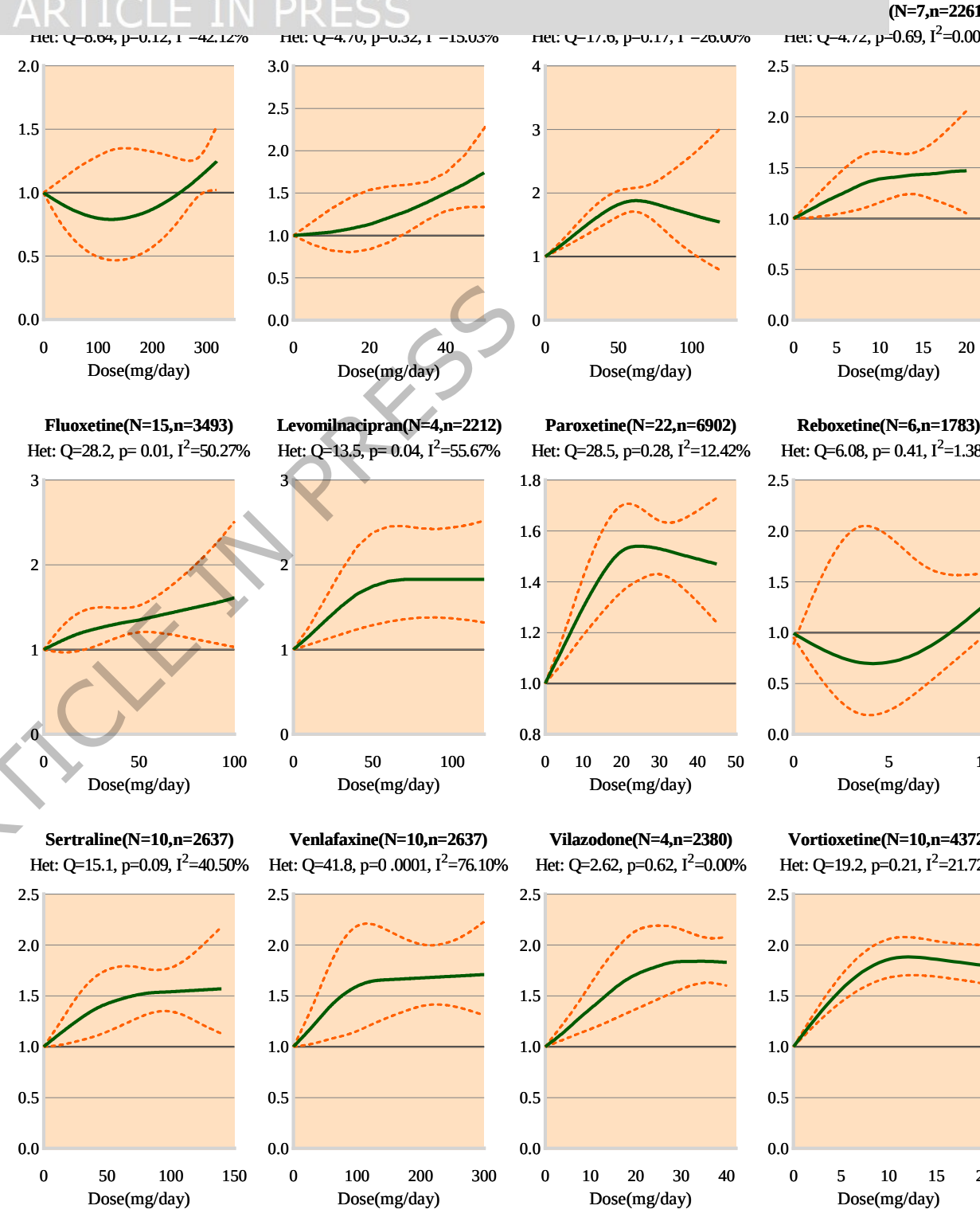

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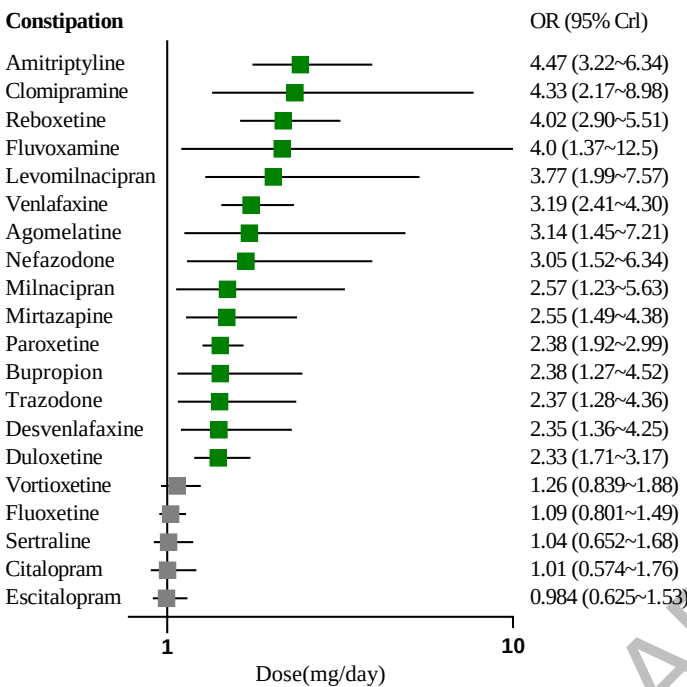

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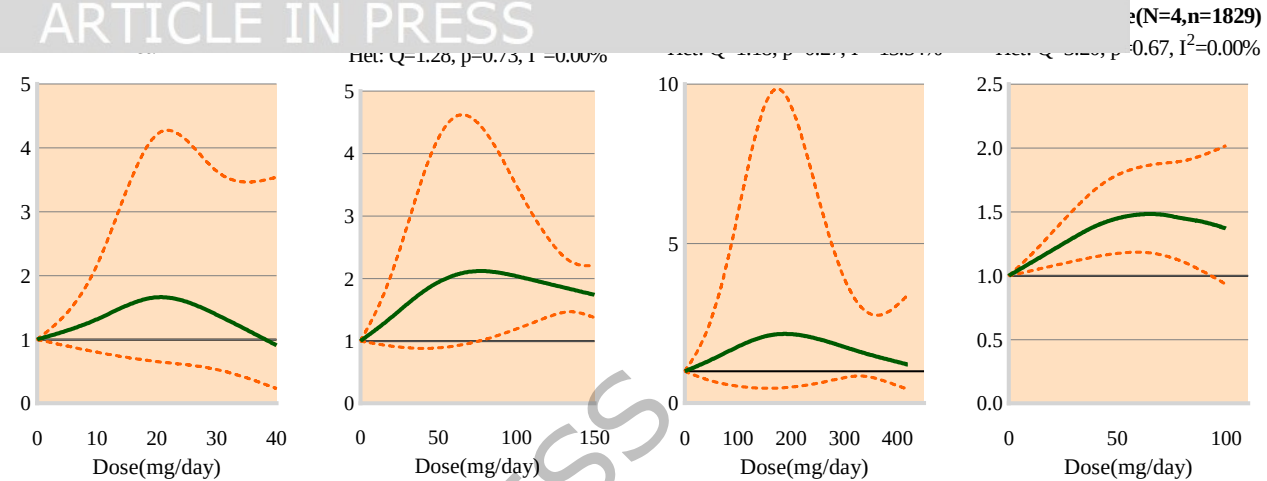
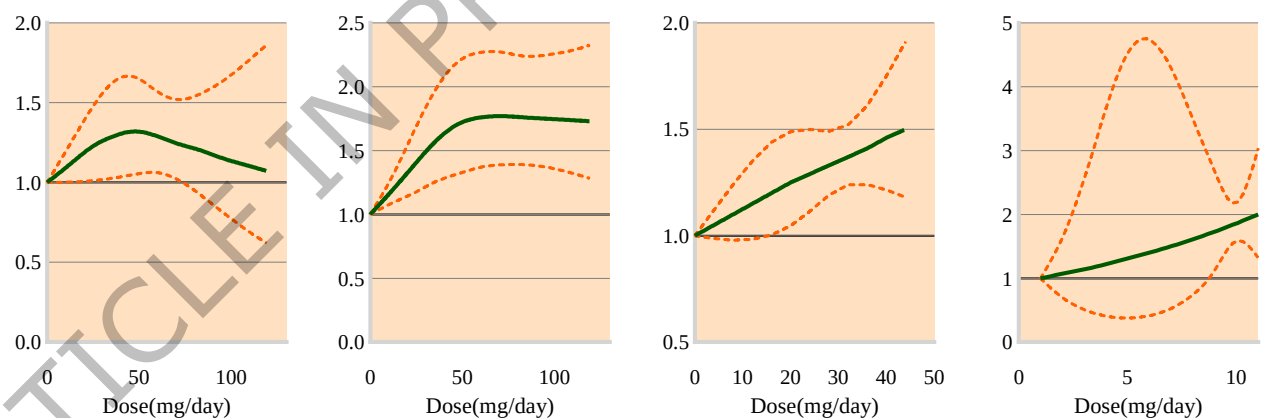


Duloxetine(N=8,n=2461)
Het: Q=12.8, p=0.16, I^2=30.05%

Levomilnacipran(N=3,n=1855)
Het: Q=1.02, p=0.96, I^2=0.00%

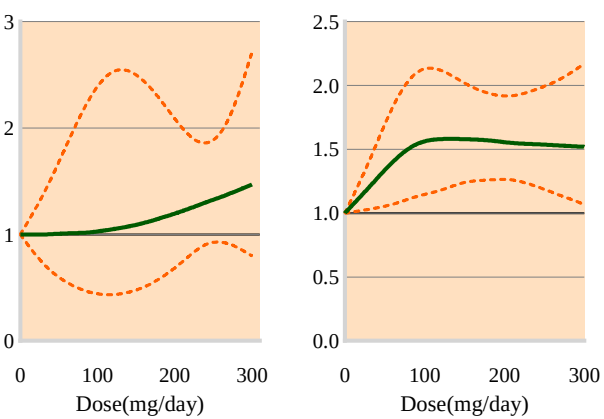
Paroxetine(N=17,n=5851)
Het: Q=24.5, p=0.22,I^2=18.32%

Reboxetine(N=9,n=2262)
Het: Q=14.3, p=0.11,I^2=37.26%



Trazodone(N=2,n=253)
Het: Q=0.19, p=0.66,I^2=0.00%

Venlafaxine(N=9,n=2397)
Het: Q=13.7, p=0.13,I^2=34.26%



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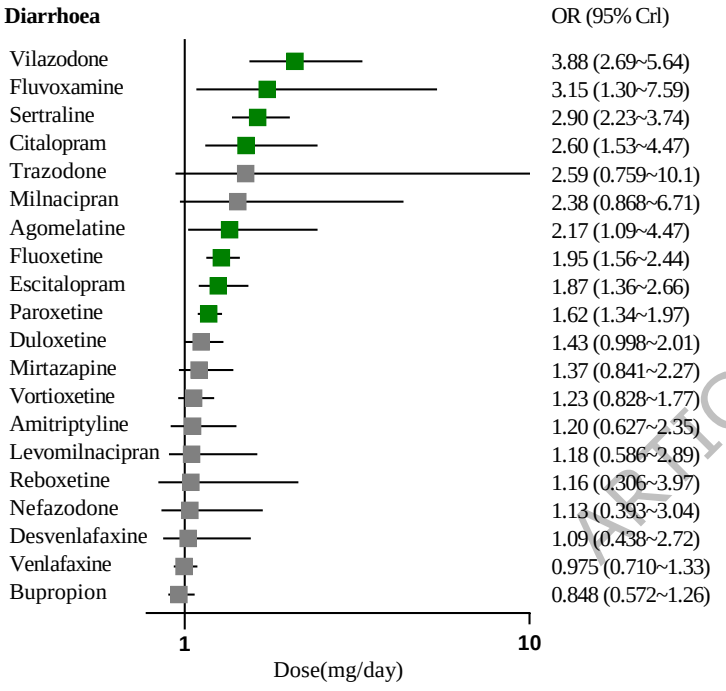

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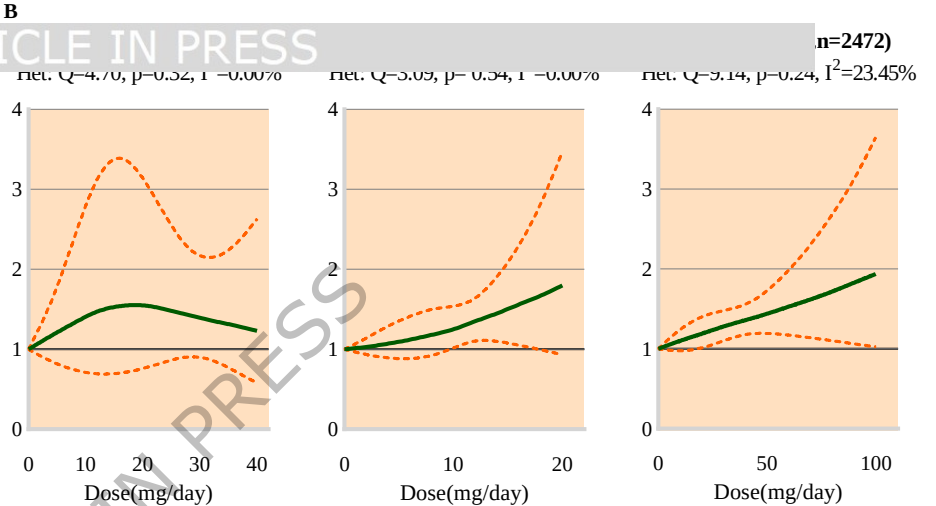

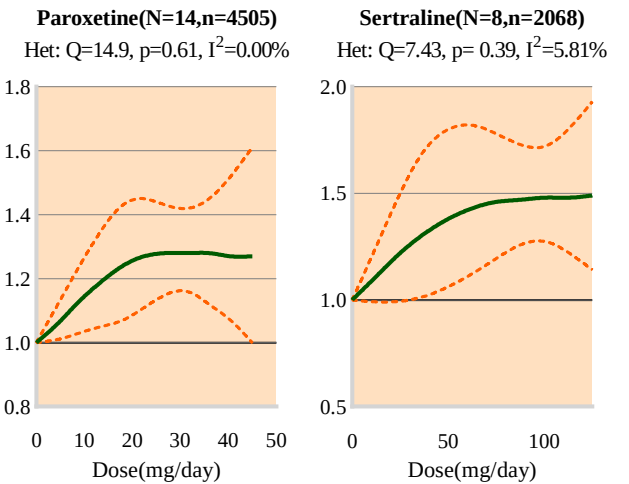

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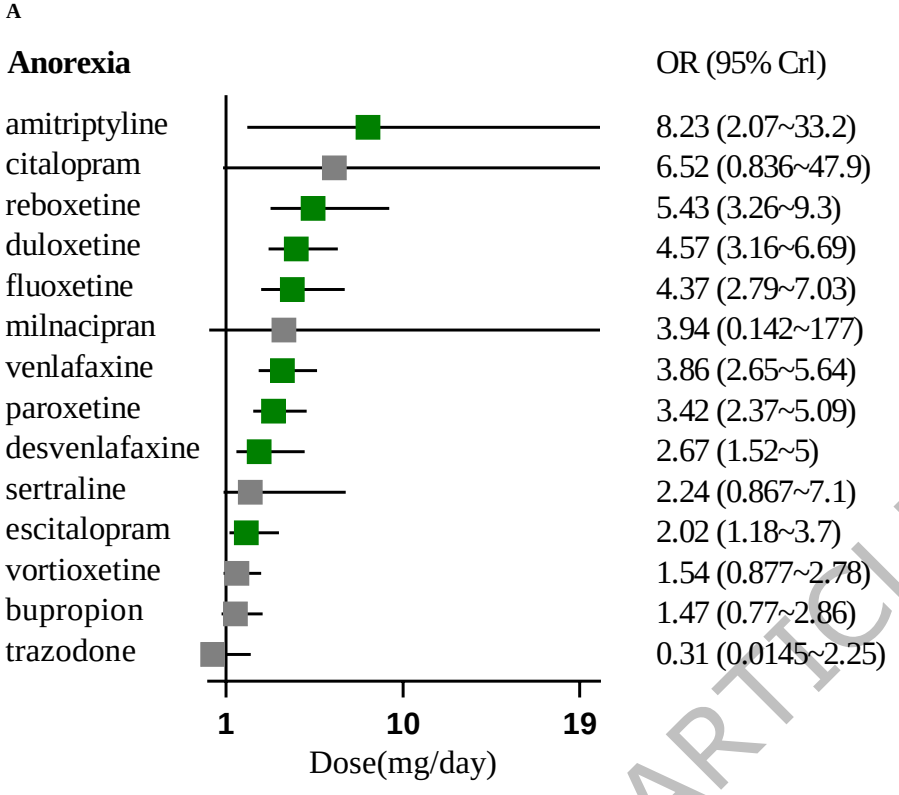

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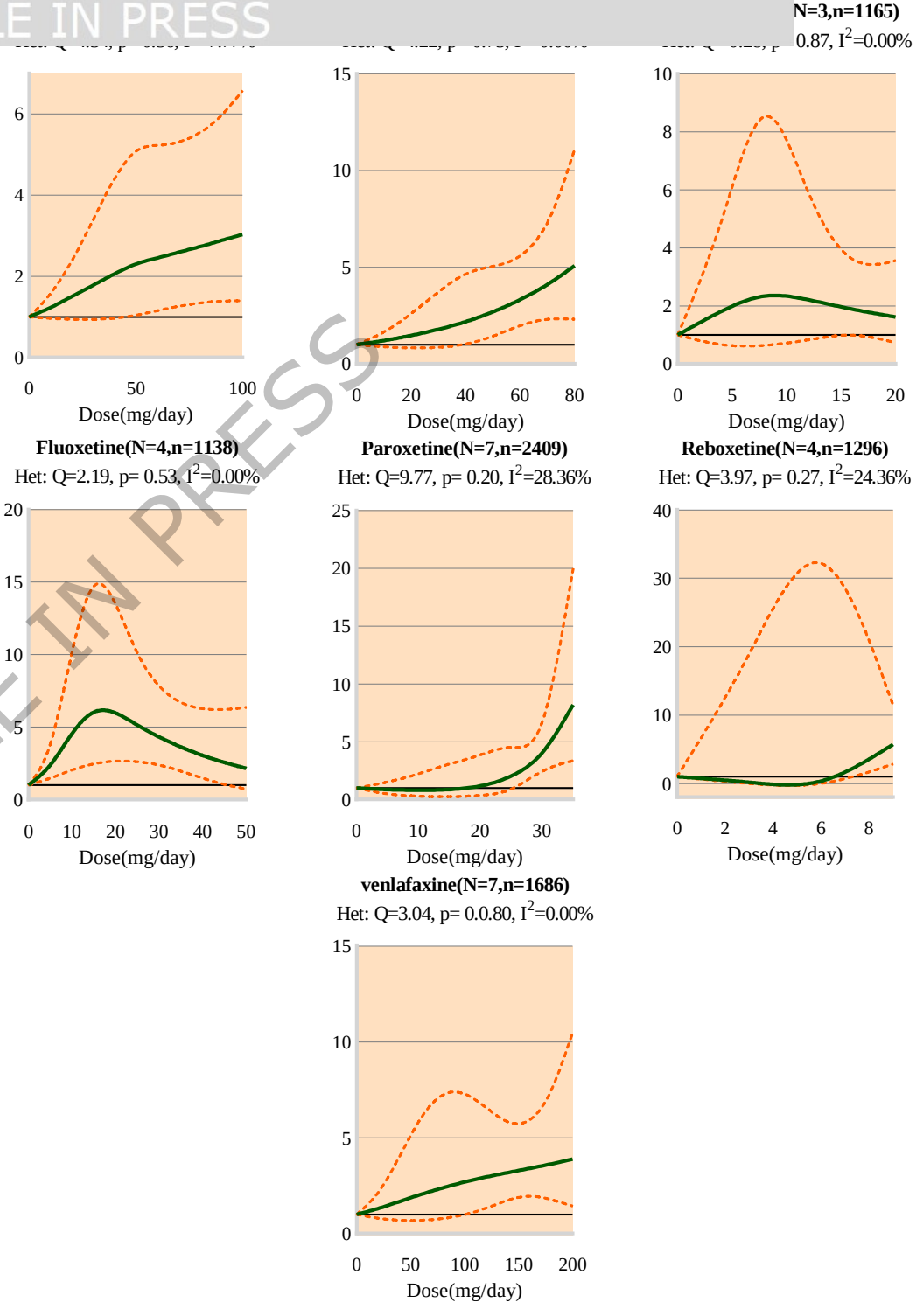

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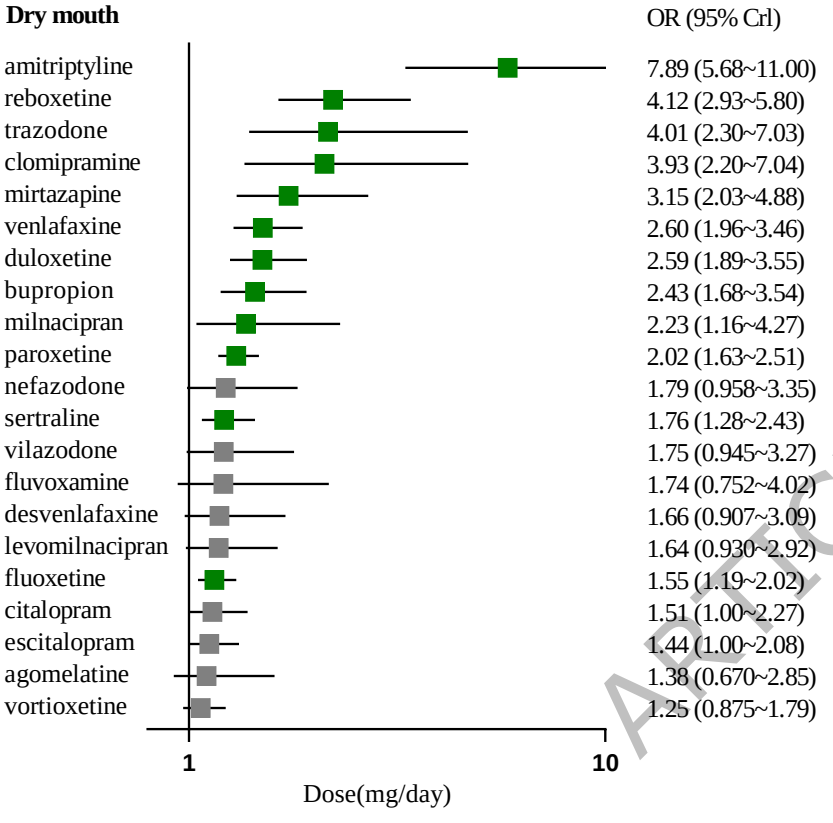

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