**Incidence of adverse events and comparative tolerability of selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors for the treatment of anxiety, obsessive-compulsive and stress disorders: a systematic review and network meta-analysis**

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**Abstract**

Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) show similar efficacy as treatments for anxiety, obsessive-compulsive, and stress-related disorders. Hence, comparisons of adverse event rates across medications are an essential component of clinical decision-making. We aimed to compare patterns of adverse events associated with SSRIs, SNRIs, and placebo in the treatment of **these disorders. We did a systematic review and network meta-analysis.** We searched MEDLINE, PsycINFO, Embase, Cochrane Central Register of Controlled Trials, websites of regulatory agencies, and international registers from inception to September 09, 2022, for randomized controlled trials assessing the efficacy of SSRIs or SNRIs in adults and/or children with a diagnosis of any anxiety, obsessive-compulsive, or stress-related disorder. We excluded trials with any kind of previous intervention or selection based on treatment resistance, and treatment arms with any combined intervention. Our primary outcome was the proportion of participants experiencing at least one adverse event. We also analyzed data for the incidence rates of 17 specific adverse events. **We estimated incidence rates and odds ratios (ORs) through network meta-analysis with random effects and three-level network meta-analysis** with random slopes by study for medication and type of symptom**.** This study was registered in PROSPERO (CRD42017069090). **We analyzed 799 outcome measures from 80 studies** (n= 21 338). Participants in medication groups presented higher rates of adverse events (80.22%, 95% CI 76.13-83.76) when compared to placebo groups (71.21%, 67.00-75.09). Nausea was the most common adverse event (25.71%, CI 23.96-27.54), while weight change was the least common (3.56%, 1.68-7.37). We found higher rates of adverse events of medications over placebo for most medications, except sertraline and fluoxetine. Drug-to-drug comparisons indicated that paroxetine and venlafaxine were less well tolerated than sertraline and escitalopram. Duloxetine was less well tolerated than sertraline. We found significant differences between medications for autonomic, gastrointestinal, and sleep related symptoms. 16 (20%) of 80 trials were rated as high risk of bias, 37 (46%) trials as moderate, and 27 (34%) as low; and the certainty of evidence was high to very low. Adverse events are a common reason that patients discontinue SSRIs and SNRIs. Results presented here guide clinical decision-making when clinicians weigh one medication over another. This might improve treatment acceptability and compliance.

**Introduction**

Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are first line pharmacological treatments for anxiety, obsessive-compulsive, and stress-related disorders1, leading causes of disability2. While antidepressants are commonly prescribed3, most patients are non-compliant4, with fear of potential adverse reactions being the second leading cause of nonadherence, after discontinuity due to remission of symptoms, the leading cause4. Hence, data comparing adverse event rates and tolerability profile of each medication may inform attempts to improve adherence. This is particularly important, given the minor differences between medications concerning efficacy5.

Previous meta-analyses assessed the tolerability of SSRIs and SNRIs, but three key questions remain unanswered. First, previous studies restricted their inclusion criteria to specific medications6–10, diagnoses6–10, adverse events11,12, or populations13. Thus, no large-scale quantitative review or network meta-analysis evaluated the comparative tolerability and rates of most adverse events associated with all SSRIs and SNRIS for the treatment of anxiety, obsessive-compulsive, and stress-related disorders. Second, incidence rates for several key adverse events or medications used during the treatment of anxiety disorders were completely unassessed, and estimates for other adverse events or medications had low statistical power8–10,14,15. Third, effects of clinical and methodological moderators were not assessed as they impact comparisons of medications. These limitations create a need to further compare side effect rates and tolerability of these medications while exploring potential moderators of these estimates. Such data may inform medication choices.

We estimated the overall incidence rate of adverse events and the incidence rates of specific adverse events associated with SSRIs, SNRIs, and placebo in the treatment of children and **adults diagnosed with anxiety, obsessive-compulsive, or stress-related disorders. Our secondary objective was to** compare the tolerability of SSRIs, SNRIs, and placebo for the global rate and for the specific adverse events rates in the treatment of individuals diagnosed with these disorders**.** **We used data pooled through network meta-analysis and** multiple meta-regression analyses accounting for clinical and methodological differences.

**Methods**

*Search strategy, selection criteria, and data extraction*

This study is a three-level network meta-analysis designed to evaluate the efficacy and tolerability of SSRIs, SNRIs, and placebo in the treatment of children and **adults diagnosed with anxiety, obsessive-compulsive, or stress-related disorders**5**.** We report this study as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analysis (see supplementary information) 16. This study was registered in PROSPERO (CRD42017069090) in June 12, 2017, during data extraction; we updated the protocol in January 30, 2018, to describe the stage of review and to include collaborators. Ethical approval was not required as this study synthesized data from previous studies.

*Inclusion criteria*

We included randomized controlled trials (RCTs) assessing the efficacy of SSRIs, SNRIs, and placebo in participants with a primary diagnosis of any anxiety disorder, obsessive-compulsive disorder, or stress-related disorder according to standard diagnostic criteria (Feighner criteria, ICD-10, DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, and DSM-5). No restriction was used regarding comorbidities with any other mental disorder (eg, depression, bipolar disorder), as well as participants’ age and sex, blinding of participants and researchers, date of publication, or study language. Studies had to compare any SSRI or SNRI with each other, with the same medication using distinct doses, or to a placebo group. We excluded trials with any kind of previous intervention (eg, medication after psychotherapy period) or selection based on treatment resistance, and treatment arms with any combined intervention (eg, medication and psychotherapy), given that the primary objective of this review is to evaluate the efficacy and tolerability of these antidepressants as monotherapy.

*Search strategy*

We searched MEDLINE, PsycINFO, Embase, and Cochrane from inception to April 23, 2015, and updated the search in September 09, 2022, using keywords related to study design, interventions, and assessed disorders, defined after discussion with experts in this field (see supplementary information). We supplemented electronic databases searches with manual searches for published and unpublished RCTs registered in ClinicalTrials.gov, ISRCTN registry, European Clinical Trials Database, Pan African Clinical Trial Registry, International Federation of Pharmaceutical Manufacturers & Associations, Australian New Zealand Clinical Trials Registry, Food and Drug Administration database, and pharmaceutical companies’ databases. Reference lists of included RCTs and relevant reviews were inspected to detect any relevant study possibly missed with the electronic search, and experts were asked to indicate additional trials. We also contacted study authors to provide data of unpublished studies and to provide additional data related to incomplete reports of original papers, clarify inconsistencies, and report unpublished results.

*Data extraction and data synthesis*

Four reviewers, all psychiatrists, independently screened abstracts, assessed full-text articles, evaluated risk of bias, and extracted data, and a fifth reviewer doubled checked all data entries. Disagreements and inconsistencies were resolved by consensus of all review group members.

For trials with multiple publications, we included the most informative and complete study report. Any outcome measure of interest reported in only one of the publications was extracted within the same trial data.

Primary outcome was the proportion of participants experiencing at least one adverse event. Secondary outcomes were the incidence rates of agitation, dizziness, dry mouth, headache, sweating, constipation, diarrhea, dyspepsia, nausea, ejaculation dysfunction, erectile dysfunction, loss of libido, asthenia, tremor, insomnia, somnolence, weight change, and the aggregate measure of these symptoms, as an overall estimate of tolerability. Moreover, the specific symptoms were clustered into five groups: autonomic (i.e., agitation, dizziness, dry mouth, headache, and sweating), gastrointestinal (i.e., constipation, diarrhea, dyspepsia, and nausea), sexual (i.e., ejaculation dysfunction, erectile dysfunction, and loss of libido), motor (i.e., asthenia and tremor), and sleep related (i.e., insomnia and somnolence) symptoms. **We also analyzed the incidence rates of suicidal ideation, suicide attempts, and committed suicides. We included all trials with duration between six and 26 weeks of follow-up in the analysis and extracted outcomes that were evaluated in the endpoint.** Primary and secondary outcomes from each set of aims were definedbefore data analysis.

We used group-level data, and extracted information included primary and secondary outcomes, publication data, demographic data, inclusion and exclusion criteria of study population, diagnostic system, intervention regime, control regime, sample comorbidities, items related to industry influence, data analysis method, response and remission rates, discontinuation rates, and internalizing symptoms scores.

*Statistical analysis*

We performed a frequentist network meta-analysis and calculated summary odds ratios (ORs), number needed to harm (NNH), and corresponding 95% confidence intervals (CI) for primary and secondary outcomes. To emphasize continuity, we report together the confidence intervals of NNH and of number needed to treat (NNT) for nonsignificant estimates of NNH (i.e., when the confidence interval for the absolute risk reduction includes zero)17. We estimated between-study variance through *τ2* estimates and evaluated heterogeneity through *I*2 and *Q* statistic. Heterogeneity was interpreted as significantly high when *I*2 was higher than 50% and when *p*<0.1 for the *Q* statistic. We synthesized data as different networks for the primary outcome (i.e., the proportion of participants experiencing at least one adverse event) and for each specific symptom using random effects models. We analyzed the aggregate measures of all specific symptoms and of the five clusters of symptoms as distinct networks using three-level models with random slopes by study for medication and type of symptom18. League tables and P-scores were used to compare the treatment effects and to estimate treatment rankings, respectively. The P-scores are based on the point estimates and standard errors of the network meta-analyses estimates and ranged from 0.00 (worst) to 1.00 (best). We assessed small study effects through comparison-adjusted funnel plots. We present the relative frequencies of adverse events with a circular bar plot, which indicate all specific adverse events rates for each medication. The transitivity assumption underlying network meta-analysis was evaluated by comparing the distribution of clinical and methodological variables across treatment comparisons. We assessed network consistency using the design-by-treatment test and by comparing indirect and direct evidence19.

We performed all pairwise comparisons of medications for the aggregated measures of adverse events rates using a multiple meta-regression model with clinical and methodological moderators. In these models, we considered the following variables: medication, comparator, equivalent dose (estimated using fluoxetine equivalents based on previous studies)20, trial duration, primary diagnosis, sample age, publication year, benzodiazepine use, placebo lead-in, and study funding. We classified study funding as academic, governmental or non-profit, industry, or unclear according to the funding sources statement of the primary studies. We categorized all studies that did not explicitly report academic, governmental or non-profit, or industry funding sources or did not present any funding source statement as having an unclear funding. We estimated treatment rankings for the overall tolerability accounting for the clinical and methodological moderators using the multiple meta-regression model. We also estimated P-scores for efficacy using the multiple meta-regression model of our previous work on this network meta-analysis, which evaluated the improvement of internalizing symptoms accounting for the same moderators5. The correlation between the effect sizes and between the treatment rankings for tolerability and efficacy were estimated with Pearson correlation coefficients. Two-sided p-values less than 0.05 were considered statistically significant. All analyses were performed in R (version 4.1.2), using packages ‘netmeta’ and ‘metafor’21.

The risk of bias appraisal was performed using the Cochrane Collaboration’s Risk of Bias Tool for RCTs22. We classified studies as having low risk of bias if none of the domains in the instrument was rated as high risk of bias and three or less 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 rated as having high risk of bias23. We assessed certainty of evidence using the Confidence in Network Meta­-Analysis framework (CINeMA)24. We decided to evaluate certainty of evidence after registration of the study protocol in PROSPERO in order to improve results reporting.

**Results**

We screened 5,655 titles and abstracts and evaluated 420 full text articles for inclusion (see supplementary information). We included 80 studies in the meta-analysis, which reported 799 outcome measures, comprising 21 338 patients. All included studies were classified as double-blind. We did not find any study assessing desvenlafaxine that met the inclusion criteria for this meta-analysis. Generalized anxiety disorder was the main disorder assessed in 21 (26.25%) of 80 trials, whereas social anxiety disorder was studied in 18 (22.50%), panic disorder in 12 (15.00%), obsessive-compulsive disorder in 15 (18.75%), and post-traumatic stress disorder in 14 (17.50%). The mean age of participants in placebo groups was 35.70 years (SD, 9.05) compared with 36.79 years (SD, 7.95) in medication groups. Moreover, 69 (86.25%) trials were designed to assess adults and 11 (13.75%) studies evaluated children and adolescents. Mean proportion of women was 55.60 (SD, 16.46) in the placebo group compared with 56.00 (SD, 15.05) in medication groups. Of included studies, seven (17.04%) were single center trials. The median number of sites from multicenter trials was 21 (interquartile range, 10 to 43). Concerning diagnostic criteria, DSM-IV was used in 51 (63.75%) studies, whereas 16 (20.00%) trials utilized DSM III-R, DSM IV-TR was used in five (6.25%) and DSM III in two (2.50%). Diagnostic criteria were not clear in six (7.50%) of included studies (see supplementary information).

Overall, 16 (20.00%) trials were rated as high risk of bias, 37 (46.25%) trials as moderate, and 27 (33.75%) as low (see supplementary information). Visual inspection of comparison-adjusted funnel plots did not suggest that small studies gave different results from larger studies in most medication-placebo comparisons, with the exception of the agitation, loss of libido, and ejaculation dysfunction models (see supplementary information).

The certainty of the evidence for the primary outcomes as measured with CINeMA varied from moderate to high. The majority of the comparisons involving aggregate measures (115 comparisons) and specific adverse events (396 comparisons) were rated as moderate or high. Full information on CINeMA is described in supplementary information.

We identified that the proportion of participants experiencing adverse events in medication groups (80.22%, 95% CI 76.13 to 83.76) was higher than those found in placebo groups (71.21%, 95% CI 67.00 to 75.09), as expected. Incidence rates of at least one adverse ranged from 62.85% (95% CI, 40.48 - 80.80) for fluoxetine to 89.04% (95% CI, 80.38 - 94.16) for fluvoxamine (Table 1). For the pooled medication group, nausea was the most common adverse event (25.71%, 95% CI 23.96 to 27.54), while weight change presented the lowest incidence rate (3.56%, 95% CI 1.68 to 7.37) (Table 2). Figure 1 reports the relative frequencies of specific adverse events by medication.

We found significant ORs indicating higher rates of adverse events for medications over placebo for the pooled medication group (OR 1.65, 95% CI 1.52 to 1.79) and for most individual medications, with the exception of sertraline and fluoxetine (Figure 2) (moderate to high certainty of evidence). The network diagram of direct comparisons is presented in supplementary information.

We performed pairwise comparisons through the multiple meta-regression model, accounting for clinical and methodological moderators. For the aggregate measure of all specific symptoms, when compared to sertraline, paroxetine (OR 1.51, 95% CI 1.19 to 1.92; very low), venlafaxine (OR 1.52, 95% CI 1.22 to 1.91; very low), and duloxetine (OR 1.57, 95% CI 1.06 to 2.31; low) and, when compared to escitalopram, paroxetine (OR 1.36, 95% CI 1.07 to 1.73; low) and venlafaxine (OR 1.37, 95% CI 1.05 to 1.78; low) had significantly higher adverse events rates, with no further significant differences between all other medications (Figure 3). We also found significant differences in pairwise comparisons of medications concerning the five clusters of symptoms: a) autonomic: paroxetine was less tolerated than fluvoxamine (OR 1.97, 95% CI 1.14 to 2.41; low) and escitalopram (OR 1.48, 95% CI 1.04 to 2.11; low), venlafaxine was less tolerated than fluvoxamine (OR 2.13, 95% CI 1.21 to 3.74; moderate), escitalopram (OR 1.60, 95% CI 1.09 to 2.34; moderate), and sertraline (OR 1.47, 95% CI 1.04 to 2.09; low), and duloxetine was less tolerated than fluvoxamine (OR 2.25, 95% CI 1.14 to 4.45; moderate) (see supplementary information); b) gastrointestinal: venlafaxine was less tolerated than fluoxetine (OR 1.97, 95% CI 1.10 to 3.51; high) and sertraline (OR 1.63, 95% CI 1.21 to 2.19; moderate), duloxetine was less tolerated than fluoxetine (OR 2.27, 95% CI 1.05 to 4.91; high) and sertraline (OR 1.88, 95% CI 1.11 to 3.18; moderate) (see supplementary information); c) sleep: paroxetine was less tolerated than sertraline (OR 1.49, 95% CI 1.07 to 2.06; low), and venlafaxine was less tolerated than sertraline (OR 1.62, 95% CI 1.14 to 2.30; low) (see supplementary information). There were no significant differences between medications concerning motor (low to high) and sexual adverse events (low to high) (see supplementary information). In general, medications were less tolerated than placebo for most specific adverse events (very low to high), with the exception of headache, dyspepsia, and weight change (very low to high; forest plots are presented in supplementary information). Figure 4 presents treatment rankings concerning specific adverse events. Although treatment rankings for acceptability and efficacy were not significantly correlated (r -0.53, 95% CI -0.90 to 0.27) (see supplementary information), we found a strong positive correlation between the effect sizes of efficacy and incidence rates of adverse events (r 0.71, 95% CI 0.08 to 0.93) (see supplementary information). The design-by-treatment interaction models did not identify global inconsistency in the networks and we did not find significant heterogeneity estimates for medication-placebo models, with *I*2 ranging from 0% to 34.1%.

We did not find significant ORs suggesting differences of medications over placebo for suicidal ideation (OR 1.61, 95% CI 0.89 to 2.92; moderate) (see supplementary information). There were a limited number of suicide attempts and completed suicides. While there were two suicide attempts in the placebo group, there were two suicide attempts venlafaxine and paroxetine groups25–27. The only completed suicide was related to a participant receiving paroxetine in a RCT designed to evaluate individuals with social anxiety disorder; nevertheless, authors of the primary study considered the suicide probably to be unrelated to study medication26.

We performed a multiple three-level meta-regression analysis to investigate potential sources of heterogeneity in medication-placebo comparisons for the aggregate measure of all specific adverse events, as an overall estimate of tolerability. The multiple meta-regression model indicated higher rates of adverse events for four factors. (a) paroxetine relative to sertraline, (b) higher doses of medications relative to low doses, (c) participants diagnosed with generalized anxiety disorder in comparison to patients diagnosed with panic disorder, and (d) studies that used placebo lead-in periods compared to those that did not include these periods in trials (see supplementary information).

**Discussion**

This network meta-analysis provides a comprehensive comparison of antidepressants tolerability for anxiety, obsessive-compulsive, and stress-related disorders, based on 80 studies, which reported 799 outcome measures of 17 types of adverse events, comprising 21,338 individuals. Our results revealed high rates of adverse events for both placebo and medication groups; however, most individual medications presented higher rates of adverse events over placebo, except sertraline and fluoxetine. For individuals receiving medications, the most common adverse event (25.71%) was nausea, while weight change was the least common (3.56%). Moreover, estimates of tolerability were moderated by dose, medication, patient diagnosis, and use of placebo lead-in periods. Finally, concerning pairwise comparisons, we found that paroxetine and venlafaxine were less well tolerated than sertraline and escitalopram, and duloxetine was also less well tolerated than sertraline for the aggregated measure of all adverse events. We also found significant differences between medications for autonomic, gastrointestinal, and sleep-related symptoms. When evaluating outcomes related to suicidality, we did not find significant differences between medications over placebo.

All included SSRIs and SNRIs have shown incidence rates of adverse events comparable to benzodiazepines and antipsychotics, drug classes that present some evidence supporting their efficacy of these medications for anxiety symptoms28,29. Notwithstanding, these pharmacological agents present distinct tolerability profiles. While benzodiazepines and antipsychotics are frequently associated with serious and potentially dangerous adverse events such as physical dependence, extrapyramidal symptoms, and metabolic side effects30,31, we have found less severe adverse events as most commonly associated with SSRIs and SNRIs. Given we have found that nausea, headache, insomnia, asthenia, and somnolence are the most frequent symptoms associated with these medications, clinicians should inform patients not only about the high incidence rate of adverse events, but also about the frequency of these common events.

In line with large estimates of the placebo effect in studies designed to assess the efficacy of antidepressants for anxiety, obsessive-compulsive, and stress-related disorders5, we found that 71.21% of participants present adverse events due to the nocebo effect, considering that these individuals were randomized to placebo arms in RCTs. These estimates are substantially higher than those associated with antidepressants for depression treatment32, psychotropic medications for other mental disorders33,34, and common interventions for clinical conditions35–37, suggesting individuals’ diagnosis as an important moderator of the nocebo effect possibly due to catastrophic beliefs and pessimistic expectations of individuals diagnosed with anxiety disorders. Moreover, headache, the second most frequent event in medication arms, dyspepsia, and weight change were not significantly more common in individuals using SSRIs and SNRIs when compared to placebo and NNH values were considerably high for some specific adverse events, indicating that incidence rates of several common events can be substantially explained by the nocebo effect. Given 77% of individuals diagnosed with anxiety disorders do not properly adhere to pharmacological treatment 4, with fear of potential adverse reactions being the second leading cause of nonadherence4, and that the interaction between patient and clinician influences the likelihood of the nocebo effect38, the exploration of patients’ expectations and realistic and precise description of potential benefits and harmful events in a positive way may substantially contribute to successful treatments.

Comparative assessments of medications revealed that escitalopram and sertraline are better tolerated than paroxetine, venlafaxine, and duloxetine for the aggregate measure of adverse events. Moreover, based on treatment rankings and pairwise comparisons accounting for clinical and methodological moderators, we found distinct symptom-specific tolerability profiles for each medication, especially for autonomic, gastrointestinal, and sleep-related adverse events. These findings can substantially contribute for personalized evidence-based practice. Clinicians should be able to integrate the results from this systematic research with individual clinical expertise by considering other factors such as patient’s prior experience with medications, physician’s own experience, and potential budgetary constraints. Furthermore, shared decision making for medication choice should be facilitated by thoughtful identification of individual patients' preferences and discussion of what to expect in terms of tolerability profiles of specific adverse events for each medication39.

In spite of its well stablished benefit of SSRIs for improvement of depressive symptoms40, concerns have been raised about the risk of suicidal behavior associated with these medications41. Our findings did not indicate significant differences of SSRIs or SNRIs over placebo for suicidal ideation, suicide attempts, or committed suicides, indicating that these agents are not associated with increased risk of suicide in patients with a primary diagnosis of anxiety, obsessive-compulsive, or stress-related disorders. Given so, clinicians and policy makers should be reassured about safety of these effective antidepressants.

This study has some major strengths. To the best of our knowledge, this is the most comprehensive and the largest meta-analysis to date to evaluate the tolerability of antidepressants for the treatment of patients diagnosed with anxiety, obsessive-compulsive, or stress-related disorders, due to the inclusion of multiple autonomic, gastrointestinal, sexual, motor, and sleep-related adverse events, and extensive search for both published and unpublished trials with no restriction regarding participants’ age, date of publication, or study language. This approach allows a **well-powered comparison of tolerability among these medications,** estimating the incidence rates of 17 adverse events through 799 outcome measures. Moreover, we extracted detailed clinical and methodological information of each included study, exploring potential moderators of tolerability estimates. Also, we evaluated suicidality based on **incidence rates of suicidal ideation, suicide attempts, and committed suicides.**

Nevertheless, our study has some limitations. First, the systematic review was planned to include RCTs with efficacy estimates of antidepressants on internalizing symptoms; however, it is unlikely that there are studies primarily designed to evaluate tolerability of these medications without any estimate of efficacy that would lead to study inclusion. Second, we were not able to analyze possible changes in rates of adverse events within the same trial, since these outcomes are usually reported for the endpoint and rarely reported in other timepoints. Third, there were a limited number of outcome measures for some specific adverse events and for outcomes related to suicidality; therefore, we were not able to perform pairwise comparisons for specific adverse events through the multiple meta-regression model due to lack of statistical power. Nonetheless, these comparisons were made through clusters of these specific symptoms. Fourth, we identified moderate heterogeneity in our data analysis, as expected in meta-analyses with a large numbers of outcome measures42. Accordingly, we explored and identified potential sources of heterogeneity through meta-regression analysis. Last, although most comparisons were rated as moderate or high according to CINeMA, we rated some significant findings as low or very low certainty of evidence, especially for the aggregate measure of autonomic and sleep related symptoms and for the aggregate measure of all adverse events, indicating that these results should be interpreted cautiously.

There are currently nine SSRIs and SNRIs available for treating anxiety, obsessive-compulsive and stress-related disorders. Given the lack of major efficacy differences among medications, other factors should play a role in this selection, such as availability (e.g., what is available in the public health system), cost, and, possibly one of the most important factors, the tolerability profile. Here we provided evidence that pharmacological agents vary substantially in their profile of adverse events. Also, we provided evidence on the average number necessary to harm for multiple adverse events. We hope this evidence can help clinicians share the decision-making with patients on what to expect regarding adverse events when starting an SSRI/SNRI. When adverse events are present, this can also help select the medication with the lower chances of having the same side effect and diminish the clinical journey to find an acceptable pharmacological agent according to preferences of each individual.

**Contributors**

NPG and GAS conceived, designed, had full access to all data in the study and takes responsibility for the integrity of data and accuracy of data analysis. NPG, MAC, MBJ, and JF selected the articles and extracted the data. NPG and GAS analyzed the data. NPG, MAC, MBJ, JF, LS, GGM, SC, PC, DSP, and GAS. interpreted the data and contributed to the writing of the manuscript. All authors have reviewed and approved the final submitted version of this Article. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

**Declaration of interests**

We declare no competing interests.

**Data sharing**

All data relevant to the study are included in the article or uploaded as supplementary information.

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| **Table 1 Incidence rates of adverse events of each medication class and each medication within the same class** |  |
| **Intervention** | **k (n)** | **Incidence (%) (95%CI)** | **NNH (95%CI)** | **τ (95%CI)** | **τ2 (95%CI)**  | **Heterogeneity I2 (%) (95%CI)** |  |
| **Placebo** | 55 (7,090) | 71.21 (67.00 - 75.09) | Reference | 0.709 (0.675 – 1.025) | 0.502 (0.456 – 1.050) | 92.0 (90.4 - 93.4) |  |
| **SSRIs and SNRIs** | 55 (7,541) | 80.22 (76.13 - 83.76) | 13 (11 - 16) | 0.023 (0.000 – 0.037) | 0.001 (0.000 – 0.002) | 13.3 (00.0 - 38.5) |  |
| **SSRIs** | 37 (4,827) | 78.47 (72.24 - 83.62) | 14 (11 - 19) | 0.032 (0.000 – 0.054) | 0.001 (0.000 – 0.003) | 28.7 (0.00 – 52.6) |  |
| Fluoxetine | 4 (484) | 62.85 (40.48 - 80.80) | 24 (NNT, 25 ∞ 8, NNH)\* | 0.051 (0.000 – 0.346) | 0.003 (0.000 – 0.120) | 40.1 (00.0 - 79.7) |  |
| Sertraline | 5 (509) | 76.07 (29.60 - 96.00) | 41 (NNT, 32 ∞ 12, NNH)\* | 0.044 (0.000 – 0.188) | 0.002 (0.000 – 0.035) | 47.8 (00.0 - 80.9) |  |
| Paroxetine | 13 (1,964) | 80.60 (69.27 - 88.45) | 15 (11 - 23) | 0.017 (0.000 – 0.057) | 0.001 (0.000 – 0.003) | 5.55 (00.0 - 59.0) |  |
| Fluvoxamine | 7 (653) | 89.04 (80.38 - 94.16) | 9 (7 - 14) | 0.012 (0.000 – 0.014) | 0.000 (0.000 – 0.021) | 20.6 (00.0 - 64.1) |  |
| Citalopram | 3 (390) | 71.50 (66.82 - 75.77) | 8 (5 – 18) | 0.000 (0.000 – 0.136) | 0.000 (0.000 – 0.019) | 00.0 (00.0 - 89.6) |  |
| Escitalopram | 5 (827) | 72.52 (63.91 - 79.73) | 14 (9 - 34) | 0.000 (0.000 – 0.050) | 0.000 (0.000 – 0.002) | 00.0 (00.0 - 79.2) |  |
| **SNRIs** | 18 (2,714) | 83.22 (79.43 - 86.43) | 12 (10 - 16) | 0.000 (0.000 – 0.025) | 0.000 (0.000 – 0.001) | 0.00 (0.00 – 50.0) |  |
| Venlafaxine | 14 (2,093) | 83.73 (78.80 - 87.70) | 13 (10 - 19) | 0.000 (0.000 – 0.028) | 0.000 (0.000 – 0.001) | 00.0 (00.0 – 55.0) |  |
| Duloxetine | 4 (621) | 82.04 (78.81 - 84.87) | 8 (6 - 14) | 0.000 (0.000 – 0.016) | 0.000 (0.000 – 0.001) | 00.0 (00.0 – 84.7) |  |
| k, number of studies; n, sample size; CI, confidence interval; NNH, number needed to harm; NNT, number needed to treat; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors. NNHs were estimated using the placebo group as reference. \*Non-significant differences are presented with the NNT to the left and NNH on the right |  |

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| **Table 2 Incidence rates of specific adverse events of placebo and medications’ classes** |  |
|  | **Placebo** | **SSRIs and SNRIs** | **SSRIs** | **SNRIs** |  |
| **Adverse event** | **k (n)** | **Incidence (%) (95%CI)** | **k (n)** | **Incidence (%) (95%CI)** | **NNH (95%CI)** | **k (n)** | **Incidence (%) (95%CI)** | **NNH (95%CI)** | **k (n)** | **Incidence (%) (95%CI)** | **NNH (95%CI)** |  |
| Headache | 55 (5,653) | 18.91 (16.59 - 21.47) | 55 (6,092) | 20.48 (18.01 - 23.19) | 189 (NNT, 149 ∞ 58, NNH)\* | 46 (4,962) | 21.48 (18.84 - 24.38) | 213 (NNT, 93 ∞ 50, NNH)\* | 9 (1,130) | 14.95 (9.36 - 23.01) | 115 (NNT, 83 ∞ 34, NNH)\* |  |
| Nausea | 97 (11,249) | 11.88 (10.92 - 12.90) | 97 (11,583) | 25.71 (23.96 - 27.54) | 7 (6 - 8) | 69 (7,904) | 23.25 (21.45 - 25.15) | 9 (8 - 11) | 28 (3,679) | 31.59 (28.46 - 34.89) | 5 (4 - 6) |  |
| Insomnia | 74 (8,650) | 10.13 (8.85 - 11.57) | 74 (8,881) | 17.94 (15.92 - 20.16) | 14 (12 - 18) | 54 (6,206) | 19.29 (16.81 - 22.05) | 15 (12 - 20) | 20 (2,675) | 14.77 (11.75 - 18.39) | 13 (10 - 19) |  |
| Dizziness | 53 (5,950) | 8.61 (7.56 – 9.79) | 53 (6,179) | 13.79 (12.15 – 15.60) | 19 (15 – 26) | 33 (3,724) | 11.87 (9.94 – 14.12) | 25 (17 – 53) | 20 (2,455) | 16.99 (14.70 – 19.57) | 13 (11 – 17) |  |
| Asthenia | 62 (7,409) | 7.61 (6.57 – 8.79) | 62 (7,627) | 16.69 (15.06 – 18.47) | 12 (11 – 14) | 42 (5,109) | 18.20 (16.06 – 20.55) | 11 (10 – 14) | 20 (2,518) | 13.95 (11.86 – 16.35) | 13 (11 – 17) |  |
| Diarrhea | 48 (5,458) | 6.98 (5.65 – 8.59) | 48 (5,607) | 11.98 (9.86 – 14.49) | 24 (18 - 33) | 40 (4,382) | 13.34 (10.93 – 16.17) | 21 (16 - 28) | 8 (1,225) | 6.87 (3.53 – 12.95) | 60 (NNT, 98 ∞ 23, NNH)\* |  |
| Somnolence | 75 (9,783) | 6.75 (5.89 - 7.73) | 75 (10,120) | 14.33 (12.57 - 16.29) | 13 (11 - 16) | 51 (6,798) | 15.76 (13.58 - 18.22) | 12 (10 - 15) | 24 (3,322) | 11.57 (8.94 - 14.84) | 17 (13 - 24) |  |
| Dyspepsia | 9 (891) | 6.32 (3.80 - 10.33) | 9 (1,047) | 8.77 (4.82 - 15.41) | 32 (NNT, 28 ∞ 10, NNH)\* | 8 (891) | 10.43 (5.88 - 17.82) | 28 (NNT, 24 ∞ 9, NNH)\* | 1 (156) | 1.92 (0.62 - 5.79) | 154 (NNT, 47 ∞ 29, NNH)\* |  |
| Dry mouth | 70 (8,598) | 5.92 (5.09 – 6.88) | 70 (8,686) | 13.78 (12.48 – 15.19) | 14 (12 – 16) | 43 (5,026) | 12.82 (11.17 – 14.67) | 17 (14 – 22) | 27 (3,660) | 15.15 (13.18 – 17.35) | 11 (9 – 13) |  |
| Agitation | 19 (1,947) | 5.43 (3.67 - 7.96) | 19 (1,962) | 9.17 (6.71 - 12.41) | 38 (22 – 161) | 15 (1,549) | 9.83 (6.98 - 13.68) | 35 (20 – 161) | 4 (a413) | 5.53 (1.95 - 14.70) | 53 (NNT, 31 ∞ 14, NNH)\* |  |
| Constipation | 48 (5,976) | 4.24 (3.48 - 5.15) | 48 (6,160) | 9.86 (8.74 - 11.11) | 20 (16 - 25) | 26 (2,931) | 9.94 (8.08 - 12.16) | 23 (16 - 39) | 22 (3,229) | 9.88 (8.65 - 11.26) | 18 (15 - 22) |  |
| Weight change | 7 (973) | 3.51 (1.54 - 7.80) | 7 (947) | 3.56 (1.68 - 7.37) | 345 (NNT, 119 ∞ 71, NNH)\* | 6 (818) | 4.16 (1.96 - 8.61) | 1111 (NNT, 75 ∞ 67, NNH)\* | 1 (129) | 0.78 (0.11 - 5.29) | 128 (NNT, 75 ∞ 35, NNH)\* |  |
| Sweating | 45 (5,700) | 3.39 (2.68 – 4.28) | 45 (5,964) | 11.56 (9.99 – 13.34) | 13 (11 – 15) | 28 (3,551) | 11.29 (9.17 – 13.83) | 14 (11 - 17) | 17 (2,413) | 12.08 (9.91 – 14.65) | 12 (10 - 15) |  |
| Loss of libido | 35 (4,945) | 2.65 (2.20 - 3.18) | 35 (4,828) | 8.96 (7.84 - 10.22) | 16 (14 – 20) | 24 (3,129) | 9.84 (8.46 - 11.43) | 15 (12 – 19) | 11 (1,699) | 7.36 (5.83 - 9.25) | 20 (15 – 30) |  |
| Tremor | 29 (2,925) | 2.24 (1.73 – 2.91) | 29 (3,090) | 7.38 (6.15 – 8.82) | 22 (18 – 30) | 20 (1,845) | 8.29 (6.63 – 10.31) | 19 (14 – 27) | 9 (1,245) | 6.02 (4.75 – 7.61) | 29 (20 – 29) |  |
| Erectile dysfunction | 21 (2,899) | 1.87 (1.38 - 2.52) | 21 (2,789) | 6.74 (5.07 - 8.91) | 24 (17 – 47) | 14 (1,902) | 4.96 (3.32 – 7.36) | 37 (20 – 244) | 7 (887) | 9.72 (6.37 – 14.57) | 15 (11 – 20) |  |
| Ejaculation dysfunction | 46 (6,292) | 1.81 (1.41 - 2.31) | 46 (6,299) | 13.80 (11.38 - 16.64) | 7 (6 – 9) | 36 (5,039) | 14.23 (11.31 - 17.74) | 7 (6 – 9) | 10 (1,260) | 12.44 (10.24 - 15.03) | 9 (7 – 12) |  |
| SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; k, number of studies; n, sample size; CI, confidence interval; NNH, number needed to harm; NNT, number needed to treat. NNHs were estimated using placebo group as reference. \*Non-significant differences are presented with the NNT to the left and NNH on the right |  |

**Figure 1 Relative frequencies of specific adverse events by medication /** Legend: Effect sizes are presented as odds ratios, and error bars represent estimated standard errors. Specific adverse events are described outside of the circular bar plot and are colored according to the corresponding adverse event domain.

**Figure 2 Forest plot of network meta-analysis for overall tolerability**



Legend: OR, odds ratio; CI, Confidence Interval. Medications are ordered from best to worst according to treatment rankings based on P-scores. Antidepressants were compared to placebo, which was the reference intervention.

**Figure 3 Comparisons of all SSRIs and SNRIs for the aggregate measure of all adverse events in the multiple meta-regression model**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Sertraline |  |  |  |  |  |  |  |
| 1.07 (0.70; 1.63) 0.75 | Fluoxetine |  |  |  |  |  |  |
| 1.09 (0.77; 1.53) 0.63 | 1.01 (0.63; 1.62) 0.95 | Fluvoxamine |  |  |  |  |  |
| 1.11 (0.82; 1.52) 0.50 | 1.04 (0.67; 1.62) 0.87 | 1.02 (0.68; 1.54) 0.91 | Escitalopram |  |  |  |  |
| 1.38 (0.90; 2.11) 0.15 | 1.28 (0.77; 2.15) 0.34 | 1.27 (0.77; 2.09) 0.36 | 1.24 (0.84; 1.82) 0.28 | Citalopram |  |  |  |
| **1.51 (1.19; 1.92) <0.001** | 1.41 (0.95; 2.10) 0.09 | 1.39 (0.98; 1.98) 0.07 | **1.36 (1.07; 1.73) 0.01** | 1.10 (0.75; 1.62) 0.63 | Paroxetine |  |  |
| **1.52 (1.22; 1.91) <0.001** | 1.42 (0.94; 2.15) 0.10 | 1.40 (0.97; 2.01) 0.07 | **1.37 (1.05; 1.78) 0.02** | 1.11 (0.73; 1.67) 0.63 | 1.01 (0.83; 1.22) 0.95 | Venlafaxine |  |
| **1.57 (1.06; 2.31) 0.02** | 1.46 (0.84; 2.55) 0.18 | 1.44 (0.94; 2.22) 0.10 | 1.41 (0.92; 2.15) 0.11 | 1.14 (0.68; 1.91) 0.62 | 1.04 (0.70; 1.53) 0.86 | 1.03 (0.71; 1.50) 0.88 | Duloxetine |
|  Treatment Aggregate measure of all adverse events (OR with 95% CI / p-value)  |  |

Legend: SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; OR, odds ratio; CI, Confidence Interval. Medications are ordered from best to worst according to treatment rankings based on P-scores estimated using the multiple meta-regression model. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. ORs above 1 indicate better tolerability for the column-defining treatment. Significant results are in bold.

**Figure 4 Treatment rankings for each specific adverse event**

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