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PHARMACOLOGICAL TREATMENTS FOR ANXIETY, OBSESSIVE-COMPULSIVE AND POST-TRAUMATIC STRESS DISORDER: A META-REGRESSION AND MULTILEVEL NETWORK META-ANALYSIS

Tratamentos farmacológicos para transtornos de ansiedade, transtorno obsessivo-compulsivo e transtorno de estresse pós-traumático: uma meta-regressão e metanálise em rede mulinível

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RESUMO

Transtornos de ansiedade, transtorno obsessivo-compulsivo e transtornos relacionados ao estresse frequentemente coocorrem, e os pacientes frequentemente apresentam sintomas de vários domínios; no entanto, metanálises geralmente limitam-se a análises de domínios de sintomas específicos. Consequentemente, a eficácia dos inibidores seletivos da recaptação de serotonina (ISRSs) e dos inibidores da recaptação de serotonina e noradrenalina (IRSNs) em múltiplos domínios de saúde mental ainda não foi avaliada por metanálises relacionadas a esses diagnósticos. Embora os ISRSs e IRSNs sejam os tratamentos farmacológicos de primeira escolha, muitos pacientes não aderem ao tratamento devido ao medo de potenciais eventos adversos, segunda causa mais comum para não adesão; portanto, estimar incidências de eventos adversos e perfis de tolerabilidade de cada medicamento pode ajudar a melhorar a adesão. Apesar disso, nenhuma metanálise avaliou a tolerabilidade comparativa e incidências da maioria dos eventos adversos associados a diversos ISRSs e IRSNs. Os artigos que compõem esta tese têm como objetivo comparar a eficácia nos múltiplos domínios de sintomas e os perfis de tolerabilidade dos ISRSs e IRSNs no tratamento de crianças e adultos diagnosticados com transtornos de ansiedade, obsessivo-compulsivo ou relacionados ao estresse. Para isso, os dados foram coletados por meio de uma revisão sistemática de ensaios clínicos randomizados desenvolvidos para estimar a eficácia de ISRSs ou IRSNs em indivíduos diagnosticados com os transtornos em estudo. As buscas foram realizadas no MEDLINE, PsycINFO, Embase, Cochrane, registros de ensaios clínicos e bancos de dados de empresas farmacêuticas. Não houve restrições com relação a comorbidades ou escalas específicas. O Artigo #1 avalia a aceitabilidade e eficácia de ISRSs e IRSNs nos sintomas internalizantes, explorando a estrutura multinível da eficácia em todos os domínios de sintomas. O Artigo #2 expande os achados do Artigo #1 investigando a tolerabilidade de ISRSs e IRSNs, estimando as taxas de incidência de 17 eventos adversos e ranqueando as medicações para esses eventos. Em ambos artigos, os dados foram analisados por meio de metanálises de rede multinível e modelos múltiplos de meta-regressão, considerando características clínicas e metodológicas. Resultados das análises de eficácia, as quais incluíram 469 desfechos de 135 estudos, demonstram eficácia no desfecho global de sintomas internalizantes, em todos os domínios de sintomas e em pacientes com todas categorias diagnósticas. Comparações pareadas revelaram apenas pequenas diferenças entre medicamentos quanto a eficácia e aceitabilidade. As análises de tolerabilidade, envolvendo 799 desfechos de eventos adversos de 80 estudos, indicam que participantes tratados com medicamentos apresentaram maiores taxas de incidência de eventos adversos quando comparados com grupos em uso de placebo. Foram identificadas diferenças significativas na tolerabilidade dos medicamentos e foram estimados perfis de tolerabilidade distintos para cada fármaco. Esta metanálise de rede multinível contribui para discussões sobre os verdadeiros benefícios dos antidepressivos, fornecendo evidências robustas devido à quantidade significativamente maior de desfechos, maior poder estatístico e avaliação da estrutura multinível de eficácia transdiagnóstica. Além disso, resultados de tolerabilidade podem orientar a tomada de decisão quando médicos consideram um medicamento em relação a outro, potencialmente melhorando a aceitabilidade e a adesão ao tratamento.

Palavras-chave: ansiedade; transtorno obsessivo-compulsivo; transtornos do estresse; antidepressivos; metanálise em rede.

ABSTRACT

Anxiety, obsessive-compulsive, and stress-related disorders frequently co-occur, and patients often exhibit symptoms from multiple domains. However, meta-analyses typically limit the statistical analysis to specific symptom domains. Consequently, the efficacy of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) on multiple mental health domains has not yet been studied through meta-analyses in this field. While SSRIs and SNRIs are the first-line pharmacological treatments, many patients are non-compliant due to their fear of potential adverse events, which is the second leading cause of nonadherence. Therefore, comparing the rates of adverse events and tolerability profiles of each medication may help improve adherence. Despite this, no large-scale quantitative review has evaluated the comparative tolerability and rates of most adverse events associated with all SSRIs and SNRIs. The articles that comprise this thesis aim to compare the efficacy in multiple symptom domains and tolerability profiles of SSRIs and SNRIs in the treatment of children and adults diagnosed with anxiety, obsessive-compulsive, or stress-related disorders. To achieve this, data are gathered from a systematic review of published and unpublished randomized controlled trials that assessed the efficacy of SSRIs or SNRIs in individuals diagnosed with any anxiety, obsessive-compulsive, or stress-related disorder. Searches were conducted in MEDLINE, PsycINFO, Embase, Cochrane, publicly accessible clinical trial registries, and pharmaceutical companies' databases. No restrictions were imposed regarding comorbidities with any other mental disorder, as well as specific assessment instruments, participants' age and sex, date of publication, or study language. Article #1 estimates the acceptability and efficacy of SSRIs and SNRIs in internalizing symptoms of children and adults, also exploring the multilevel structure of efficacy in all symptom domains related to the diagnoses of anxiety, obsessive-compulsive, or stress-related disorders. Article #2 expands on the findings from article #1 by investigating the tolerability of SSRIs and SNRIs, estimating the incidence rates of 17 specific adverse events, and determining treatment rankings for those events. In both articles, data were pooled through three-level network meta-analyses and multiple meta-regression analyses, accounting for clinical and methodological differences. Results of the efficacy analysis, which included 469 outcome measures from 135 studies, support the efficacy of these medications in the overall measure of internalizing symptoms, across all symptom domains, and in patients from all diagnostic categories. Head-to-head comparisons revealed only minor differences between medications in terms of efficacy and acceptability. Tolerability analyses, including 799 outcome measures of adverse events from 80 studies, indicate that participants in medication groups experienced higher rates of adverse events compared to placebo groups. Significant differences in tolerability of medications were identified and distinct tolerability profiles were estimated for each SSRI or SNRI. This three-level network meta-analysis contributes to the ongoing discussion about the true benefits of antidepressants, providing robust evidence due to the significantly larger quantity of data, higher statistical power compared to previous studies, and the assessment of the multilevel structure of transdiagnostic efficacy. Furthermore, the tolerability findings presented here may guide clinical decision-making when clinicians consider one medication over another, potentially enhancing treatment acceptability and compliance.

Keywords: anxiety; obsessive-compulsive disorder; stress disorders; antidepressants; network meta-analysis.

ABBREVIATIONS AND ACRONYMS

CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CMI	Child Mind Institute
CI	Confidence Interval
CINeMA	Confidence in Network Meta¬-Analysis
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5
DSM-III	Diagnostic and Statistical Manual of Mental Disorders-III
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders-III Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders-IV Text Revision
FIPE/HCPA	Fundo de Incentivo à Pesquisa/Hospital de Clínicas de Porto Alegre
ICD-10	International Classification of Diseases-10
GAD	Generalized Anxiety Disorder
NNH	Number Needed to Harm
NNT	Number Needed to Treat
OCD	Obsessive-Compulsive Disorder
OR	Odds Ratio
PTSD	Post-Traumatic Stress Disorder
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RCT	Randomized Controlled Trial
RDoC	Research Domain Criteria

SD	Standard Deviation
SE	Standard Error
SMC	Standardized Mean Change
SMD	Standardized Mean Difference
SNRI	Serotonin and Norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors

SUMMARY

1 INTRODUCTION

1.1 COMORBIDITIES IN ANXIETY, OBSESSIVE-COMPULSIVE, AND STRESS-RELATED DISORDERS

Among psychiatric disorders, anxiety disorders, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD) are the second leading causes of disability worldwide (1,2). Despite affecting approximately 10% of the global population, only 10% of these patients receive appropriate treatment (3,4), and these disorders account for about 33% of mental health-related expenses, particularly due to the loss of productivity (5). Therefore, offering appropriate evidence-based treatments for these conditions is essential not only to alleviate the psychological distress of patients with these diagnoses, but also as an important public health measure.

Given anxiety disorders often begin in childhood or adolescence and early onset of these disorders predicts later higher levels of psychopathology (6,7), it becomes crucial to identify individuals at risk early on and implement interventions during their young ages. For instance, the temporal relationship of comorbidity with depression suggests that the onset of anxiety disorders often occurs earlier (6), and previous evidence on the efficacy of antidepressants for depressive symptoms indicates that children and adolescents do not present a good response to treatments with selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) compared with adults (8). Therefore, aiming to achieve remission of anxiety symptoms before the onset of depression may be an important prevention strategy in clinical practice to be further investigated. Also, children and adolescents respond worse to psychotherapy when compared to adults (9), so the assessment of efficacy and tolerability of pharmacological interventions using a lifespan approach is particularly important to identify effective interventions for specific age groups, such as young people diagnosed with anxiety disorders.

Comorbidity among anxiety disorders is prevalent, with up to half of individuals experiencing one anxiety disorder also being diagnosed with another at some point in their lives, as reported by the National Comorbidity Survey–Replication, a nationally representative community household survey of the prevalence and correlates of mental disorders in the United States of America (10). Anxiety disorders also often co-occur with mood disorders, showing a

particularly strong link between major depression and generalized anxiety disorder, and a moderate association with panic disorder, agoraphobia, and social anxiety disorder. Additionally, anxiety disorders share high rates of comorbidity with OCD and stress-related disorders, such as PTSD (10).

The high level of comorbidity between anxiety disorders, OCD, and stress-related disorders is a well-known phenomenon in the field of mental health, as previously recognized nosologically by being grouped together in the "Anxiety disorders" section of DSM-IV-TR (11) and in the "Neurotic, stress-related and somatoform disorders" section of ICD-10 (12), earlier versions of the two most widely used manuals for standardized diagnostic criteria. These conditions often coexist in individuals, leading to a more complex clinical presentation and treatment challenges. The overlap between these disorders can make it difficult to pinpoint specific diagnostic boundaries, as symptoms may intermingle and intensify.

In cases of comorbidity, the severity and duration of symptoms may be heightened, causing increased distress and impairment in daily functioning. For instance, individuals with comorbid anxiety disorders, OCD, and PTSD may experience a broader range of phobic symptoms, intrusive thoughts, compulsions, and avoidance behaviors, creating a network of correlated and reinforcing symptoms (13,14). Previous evidence suggests that the co-occurrence of these disorders is associated with a more chronic and persistent course, increased utilization of healthcare services, and a reduced quality of life (15,16). The interplay between anxiety disorders, OCD, and PTSD can lead to a greater burden on affected individuals, making the identification and management of these comorbidities crucial.

The coexistence of these disorders can also impact treatment planning and efficacy. The presence of multiple conditions requires a comprehensive and tailored approach to address the various symptom clusters adequately. Treatment modalities that specifically target one disorder inadvertently neglect symptoms of comorbidities, potentially not addressing important bridge symptoms, which are broadly defined as symptoms that connect and reinforce clusters of symptoms of the comorbidity (14,17). This approach may reduce response rates due to persistence of bridge symptoms, given it disregards the fact that patients seek help for overall improvement in symptoms and functioning, rather than improvements in specific symptom domains.

Early recognition of comorbidities is essential for accurate diagnosis and appropriate treatment planning. A comprehensive assessment, taking into account the full spectrum of symptoms, can help mental health professionals develop tailored interventions to address the complexities of comorbid anxiety disorders, OCD, and stress-related disorders. Additionally, psychiatric research should account for the co-occurrence of multiple disorders while estimating the efficacy of interventions for these disorders, considering that the restriction of inclusion of participants to only those without comorbidities does not represent most patients in clinical settings. By targeting interconnected and reinforcing symptoms of comorbid disorders, mental health professionals can support individuals in improving their overall mental health and quality of life.

1.2 EFFICACY OF SSRIs AND SNRIs IN THE TREATMENT OF ANXIETY, OBSESSIVE-COMPULSIVE, AND STRESS-RELATED DISORDERS

The use of medications in the treatment of anxiety, obsessive-compulsive, and stress-related disorders has been associated with significant improvement in health-related quality of life and decreased disability (18). Based on previous evidence of efficacy from randomized controlled trials and meta-analyses, selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are indicated as the first-line pharmacological treatment for these disorders (19–21). While not all SSRIs and SNRIs have received regulatory approval from the US Food and Drug Administration and European Medicines Agency for every anxiety disorder, there are effective medications within each drug class for the treatment of anxiety disorders in adults, adolescents, and, to a lesser extent in terms of available evidence, children (22).

Despite SSRIs and SNRIs being considered first-line medications for the treatment of anxiety, obsessive-compulsive, and stress-related disorders by most international guidelines, there is still debate on their efficacy and acceptability (23). Fewer large-scale quantitative reviews evaluated efficacy data for these conditions, as compared to mood disorders (24) and sufficiently powered comparative efficacy and acceptability assessments across the many agents are lacking (24).

Before this analysis, the most comprehensive network meta-analysis on medications for anxiety disorders (25), despite assessing only generalized anxiety disorder, found results

indicating that SSRIs and SNRIs are effective for generalized anxiety disorder and that there are no significant differences among medications. Nevertheless, this previous work restricted the inclusion of participants to those without comorbidities, which might not represent most patients in clinical settings and possibly restrict statistical power. Bandelow and colleagues also assessed the efficacy of antidepressants for anxiety disorders, including not only generalized anxiety disorder but also social anxiety disorder and panic disorder (26). Bandelow and colleagues' work currently represents the largest meta-analysis in this field, evaluating 206 treatment arms related to the efficacy of medications. Without using a network meta-analysis approach, this work reported effect sizes of 2.09 for SSRIs and 2.25 for SNRIs and indicated substantial differences between medications, ranging from 1.06 for citalopram to 2.75 for escitalopram. These conflicting findings may be due to the use of pre-post effect sizes, which estimate the improvement within one group and not the difference between intervention and placebo groups, suggesting a large variation in placebo response rates in trials assessing different medications for these disorders. Despite being commonly used, pre-post effect estimates have been criticized in the literature (27), given that it is impossible to disentangle which proportion of the effect size is caused by the intervention and which by other processes, such as natural recovery or patients' expectations.

Studies assessing comorbidity in patients with anxiety, obsessive-compulsive, and stress-related disorders report rates above 50% (6); accordingly, two previous meta-analyses explored the benefit of antidepressants for these conditions without restriction of comorbidities (28,29). Roest and colleagues mainly focused on premarketing trials and found an overall effect size of 0.38, including 49 studies (23). Sugarman and colleagues reported similar results, indicating an effect size of 0.34 based on 56 outcome measures (29). Despite the inclusion of comorbidities being a strength of these meta-analyses, an important limitation is the inclusion of only one outcome measure for each primary study. Transdiagnostic systems of psychopathology emphasize that psychosocial impairment is better explained and predicted by transdiagnostic dimensions than traditional diagnoses (30,31). This suggests the need to evaluate the efficacy of treatments in multiple symptom domains, considering that patients seek help for overall improvement in mental health and functioning rather than improvements in specific symptom domains. Also, the inclusion of a limited number of outcome measures for each study substantially restrains statistical power, limiting the possibility of exploring different moderators of efficacy estimates and accounting for clinical and methodological differences when comparing medications.

An additional limitation of these studies is the restriction of inclusion of studies to those using the scales that are most commonly used for the assessment of symptoms in each diagnosis (32,33). There is uncertainty about the most appropriate instruments to measure treatment gains due to the highly inconsistent and heterogeneous assessment landscape (34,35); therefore, the inclusion of studies restricted to specific scales can lead to selective reporting and exclusion of a great number of outcomes related to psychopathology. Hence, a multiple-endpoints design also addresses low item overlap between assessment instruments, ranging from 37% of similarity for anxiety scales to 45% for post-traumatic stress disorder, and diminishes concerns about biases inherent to each scale (34,35).

1.3 TOLERABILITY OF SSRIs AND SNRIs IN THE TREATMENT OF ANXIETY, OBSESSIVE-COMPULSIVE, AND STRESS-RELATED DISORDERS

Even though antidepressants present current evidence of efficacy for anxiety, obsessive-compulsive, and stress-related disorders (19–21), only 10% of individuals affected by these disorders receive appropriate treatment (3). This estimate may be explained not only by the low prescription of recommended treatments for these conditions, but also by the nonadherence of patients. In fact, 77% of these individuals do not properly adhere to these interventions, with fear of potential adverse reactions being the second leading cause of nonadherence, following discontinuity due to remission of symptoms, which is the leading cause (36). Hence, informing patients about incidence rates of specific adverse events and personalizing treatments according to the tolerability profile of each medication may improve treatment acceptability and adherence to these effective medications.

Incidence rates of some specific adverse events of SSRIs and SNRIs during the treatment of anxiety disorders were estimated by four previous meta-analyses (37–40). While Li and colleagues published meta-analyses assessing venlafaxine and duloxetine in the treatment of generalized anxiety disorder (39,40), Liu and colleagues reported estimates restricted to fluvoxamine in the treatment of social anxiety disorder In spite of assessing medications and diagnoses of interest, these studies were limited to the assessment of six specific adverse events (37,39,40). Currently, the most comprehensive meta-analysis was designed to evaluate the tolerability of paroxetine in the treatment of social anxiety disorder. Despite the assessment of 16 distinct side effects, this study included a maximum of 10 studies

for each specific adverse event, indicating that previous meta-analyses were not only limited to estimates of specific medications and diagnoses but also presented low statistical power.

A systematic review designed to assess findings related to efficacy and tolerability of antidepressants in the treatment of children and adolescents diagnosed with anxiety disorders reported incidence rates of 16 specific adverse events (41). As in previously published meta-analyses, this review was limited to the inclusion of a restricted number of studies, reporting findings of a maximum of two and three studies for sertraline and fluoxetine, respectively. Due to the high rates of nonadherence to antidepressant treatments, a recently published international survey ranked the most important adverse events according to the preferences of patients and healthcare professionals to possibly contribute to the understanding of causes for the low rates of adherence to pharmacological treatments (42). Including 1631 patients and 281 healthcare professionals from 44 different countries, 11 side effects were concurrently included in the top 15 most important adverse events by both patients and professionals: insomnia, anxiety, fatigue, weight gain, agitation, sexual dysfunction, dizziness, sleepiness, sweating, headache, and nausea. Despite the importance indicated by individuals diagnosed with anxiety disorders and providers of care, none of the previous studies included all these adverse events.

Even though it is essential to precisely inform patients about incidence rates of adverse events, these estimates may be partially explained by the nocebo effect, which refers to side effects that arise from the expectation or anticipation of experiencing harm or negative outcomes (43). The nocebo effect has been previously studied in the context of medical treatments, showing that individuals who are informed about potential side effects of a medication are more likely to report experiencing those side effects. Mondaini and colleagues conducted a randomized controlled trial that assigned patients diagnosed with benign prostatic hyperplasia to either uninformed treatment or the same medication, finasteride, with information about possible sexual side effects. As hypothesized by the authors, informed patients presented significantly more adverse events than uninformed patients (43.6% vs. 15.3%), indicating a substantial influence of the nocebo effect (44).

The nocebo effect extends beyond clinical interventions and can influence various psychological conditions. In psychiatric disorders, negative expectations can intensify mental health symptoms, leading to a vicious cycle of heightened distress by contributing to worsening of symptoms, reduced treatment adherence, or impaired recovery (45). Previous meta-analyses designed to estimate the nocebo effect in patients diagnosed with bipolar disorder and

schizophrenia reported incidence rates of adverse events of 68.0% and 66.3%, respectively, in individuals randomized to placebo arms of randomized controlled trials (46,47). This suggests that even when patients are given an inert substance, they may experience high rates of emerging adverse events. Mitsikostas and colleagues previously evaluated the impact of the nocebo effect on individuals diagnosed with depression and found that 44.7% of participants randomized to placebo arms presented at least one adverse event (48). This rate is substantially lower than the incidence rates reported for bipolar disorder and schizophrenia, indicating that individuals' diagnosis may be an important moderator of the nocebo effect.

Considering that individuals diagnosed with anxiety disorders often present catastrophic beliefs and pessimistic expectations about treatments, these patients may exhibit possibly higher rates of nocebo response when compared to other psychiatric disorders. As the nocebo effect demonstrates the powerful influence of negative expectations and beliefs on health outcomes, incidence rates of several common events can be substantially explained by the nocebo effect. This highlights the intricate interplay between psychological and physiological processes and emphasizes the importance of addressing patients' expectations and providing accurate information in a realistic but positive way. By understanding and managing the nocebo effect, healthcare professionals can enhance the efficacy of treatments and improve patients' well-being.

Some systematic reviews and meta-analyses have assessed the comparative tolerability of antidepressants for the treatment of anxiety disorders. Despite the availability of nine distinct SSRIs and SNRIs, there are no network meta-analyses comparing the overall tolerability of all SSRIs and SNRIs in the treatment of these disorders, and previous meta-analyses are restricted to specific medications, such as paroxetine, fluvoxamine, venlafaxine, and duloxetine (37–40).

Nevertheless, there are previous meta-analyses aimed at assessing the comparative tolerability of these medications for specific adverse events. Through a network meta-analysis approach, Wang and colleagues assessed the tolerability of SSRIs for gastrointestinal events during the treatment of individuals diagnosed with depression (49). Including 30 studies, this work identified significant differences between medications, indicating fluoxetine as the SSRI with the lowest probability of gastrointestinal events and sertraline with the highest probability. The study also reported a significantly better tolerability of escitalopram over paroxetine and sertraline. Assessing not only SSRIs but also SNRIs, and including participants diagnosed with depression, obsessive-compulsive, and anxiety disorders, Telang and colleagues published a

meta-analysis focused on tolerability estimates of headache (50). While the authors did not find significant differences between SSRIs and SNRIs, they found that only escitalopram was associated with an increased risk of headache when compared to placebo. These mixed findings may be related not only to the assessment of distinct adverse events, but also to the use of pre-post effect sizes, as these estimates evaluate the improvement within one group and not the difference between the intervention and the placebo group (i.e., accounting for the nocebo effect).

Comparative assessments of all available SSRIs and SNRIs and estimates of symptom-specific tolerability profiles, including all adverse events identified by both patients and professionals as the most important symptoms, can substantially contribute to personalized evidence-based practice. Shared decision-making during medication choice should be facilitated by a thoughtful identification of individual patients' preferences and by a discussion of what to expect in terms of tolerability profiles of each medication.

1.4 CURRENT PERSPECTIVES ON META-ANALYSES IN PSYCHIATRY RESEARCH

Systematic reviews and meta-analyses have emerged as powerful tools in evidence-based medicine, providing a comprehensive and systematic approach to synthesizing evidence (51). These methods allow researchers to uncover underlying patterns and evaluate treatment efficacy and tolerability. In psychiatry research, primary studies may produce varying and sometimes contradictory results due to differences in methodological and clinical factors. Meta-analyses address this issue by pooling data from multiple studies, including a larger number of participants than individual studies alone, thereby increasing statistical power (52). This contributes to more accurate estimates of treatment effects and allows appropriate exploration of potential moderators to inform evidence-based practices.

One of the key advantages of meta-analyses in psychiatry research is their possibility to explore the heterogeneity and variability across studies (51). Psychiatric disorders can manifest in diverse ways, and patients' responses to different interventions can vary considerably. By pooling data from multiple studies, meta-analyses allow for the identification of subgroups that may respond differently to treatments. This information is essential in tailoring interventions to specific patient characteristics, improving treatment outcomes, and optimizing clinical decision-making.

Moreover, meta-analyses enable the examination of treatment effects across different study designs and methods. By including studies with varying sample sizes, study durations, and methodological approaches, meta-analyses can assess the consistency and generalizability of findings across different settings and populations. This broader perspective helps to build a more comprehensive understanding of the efficacy and safety of interventions, as well as to identify potential sources of heterogeneity.

Systematic reviews with meta-analyses also contribute to the identification of research gaps and areas for further investigation. By systematically reviewing existing literature, these analyses can highlight areas where evidence is scarce or inconclusive, guiding future research priorities. Furthermore, this approach can also identify potential biases or limitations in the current body of evidence, prompting researchers to address these issues in future studies. This iterative process of evidence accumulation and refinement is crucial for advancing the field of psychiatry research and improving patient care.

In addition to informing clinical decision-making and indicating research priorities, meta-analyses have broader implications for healthcare policies. Policymakers and guideline developers often rely on these comprehensive reviews to formulate evidence-based recommendations, ensuring that interventions are grounded in the best available evidence. The systematic and transparent approach of meta-analyses enhances the credibility and trustworthiness of these recommendations, promoting standardized and effective practices across healthcare systems.

Early statements from the Evidence-Based Working Group, pioneers of the evidence-based medicine movement, together with the Cochrane Collaboration, suggested that systematic reviews with meta-analysis can provide the most robust and reliable scientific evidence, considering both the higher statistical power and the reduced risk of biased conclusions (53). However, there is an ongoing debate suggesting that network meta-analyses should be preferable over traditional meta-analytic approaches (54).

Conventional meta-analyses focus on combining data from studies that directly compare two interventions, estimating an overall treatment effect size by pooling the results of these head-to-head comparisons (51). This approach is valuable when there are sufficient direct comparisons available; however, traditional meta-analyses may face limitations when there are

limited or no head-to-head comparisons, making it challenging to assess the comparative effectiveness of multiple interventions.

Network meta-analyses, on the other hand, expand upon the capabilities of traditional meta-analyses by incorporating both direct and indirect evidence (51). This method considers the entire network of available evidence through the analysis of both head-to-head comparisons and studies that compare interventions indirectly through a common comparator, enabling the estimation of relative treatment effects for all interventions simultaneously. In psychiatry, where the landscape of available interventions is vast and complex, network meta-analyses offer a comprehensive approach to evidence synthesis, given their ability to estimate treatment comparisons that have not been directly studied, allowing a more nuanced understanding of the comparative efficacy and safety of interventions within specific clinical contexts.

Additionally, network meta-analyses facilitate the exploration of treatment hierarchies by estimating the ranking of interventions based on their efficacy or tolerability profiles (55). This ranking of interventions is particularly valuable in psychiatry, where treatment decisions often involve weighing various factors such as efficacy, acceptability, and tolerability. Through the integration of direct and indirect evidence, these analyses can provide a quantitative assessment of treatment superiority or inferiority, allowing clinicians and researchers to identify preferable interventions within particular contexts.

Another advantage of network meta-analyses is the possibility to properly explore heterogeneity and inconsistency across studies. Traditional meta-analyses are limited to examining heterogeneity within direct comparisons. In contrast, network meta-analyses can evaluate heterogeneity across both direct and indirect comparisons, providing insights into the variability of treatment effects. This enables the identification of patient subgroups or contextual factors that may influence treatment outcomes, contributing to the identification of optimal treatment pathways and decision-making algorithms. By considering the relative efficacy of multiple interventions across different patient subgroups, these analyses help tailor treatment strategies to individual characteristics, which may lead to higher response rates.

Publication of network meta-analyses in the psychiatry field is significantly increasing (24), as it has been recognized as the highest level of evidence in several treatment guidelines (54). Nevertheless, an important limitation of standard network meta-analyses is the inclusion of only one outcome measure for each primary study. Since one of the main purposes of meta-

analyses is to provide a comprehensive synthesis of all available evidence, it is contradictory to arbitrarily exclude a great number of outcome measures reported by primary studies. The inclusion of a limited number of outcome measures for each study substantially restrains statistical power, limiting the possibility of exploring different moderators of efficacy estimates and accounting for clinical and methodological differences when comparing medications. Moreover, this restriction of traditional statistical models leads researchers to assess specific symptom domains (8), which does not represent most patients in clinical settings, given that individuals often present symptoms from multiple domains. An additional limitation of standard meta-analyses is that they are often restricted to the inclusion of specific scales for the assessment of symptoms (8,25). There is uncertainty about the most appropriate instruments to measure treatment gains due to highly inconsistent and heterogeneous assessment landscape; therefore, this restriction can lead to selective reporting, biased estimates, and exclusion of a great number of outcomes related to psychopathology.

Statistical independence is one of the core assumptions for pooling effect sizes in a meta-analysis, considering that if there is a dependency between effect sizes, this could artificially reduce heterogeneity and thus lead to false-positive results (56). Thus, the inclusion of only one outcome for each primary study is necessary to correctly analyze data through commonly used statistical approaches, such as random-effects or fixed-effects models (51,56). In spite of that, it is possible to include multiple outcome measures within the same study using an alternative approach. Multilevel meta-analyses account for statistical dependency by integrating additional layers into the structure of the meta-analytic model for variables that indicate that some outcome measures are conceptually more similar (i.e. correlated) to a specific group of outcome measures than to others (56).

Differently from major depression and other narrowly defined psychiatric disorders, which allow a more 'unidimensional' construct assessment, anxiety disorders are a group of highly correlated emotional disorders, requiring a distinct approach. A multilevel design addresses this important issue by aggregating all symptom domains related to these disorders, at the same time allowing to combine direct and indirect information in a network (57–59). Furthermore, different assessment instruments reported in the same study can be included by adding a third layer into the structure of the meta-analysis model, performing three-level analyses that account for the statistical dependency caused by the inclusion of different questionnaires nested within studies.

Network meta-analyses are invaluable tools for evidence-based medicine, particularly in the context of psychiatry research. They provide a powerful approach to synthesizing existing evidence, enabling a more reliable understanding of treatment effects, also allowing a proper exploration of moderators of these estimates. In spite of that, previous meta-analyses are restricted to the inclusion of only one outcome measure for each study, substantially limiting statistical power due to limitations of conventional statistical analyses. Even though there are no previously published three-level network meta-analyses in the field of psychiatry, this approach can circumvent this issue and provide a more comprehensive assessment of all evidence, avoiding the exclusion of a great number of available outcome measures and reducing biases related to specific symptoms or inherent to assessment instruments. By facilitating clinical decision-making, identifying research gaps, and informing healthcare policies, multilevel network meta-analyses can contribute significantly to the advancement of psychiatry research and to the improvement of evidence-based care for individuals with mental health conditions.

2 JUSTIFICATION

Anxiety, obsessive-compulsive, and stress-related disorders are associated with a range of negative health outcomes (4)and are highly prevalent and often co-occurring diagnoses (60). Although SSRIs and SNRIs are indicated as first-line pharmacological agents for these disorders (19,21), some limitations of current evidence persist, and there are aspects of the literature that remain unclear. There is still debate about the true efficacy of pharmacological antidepressants in treating anxiety, obsessive-compulsive, and stress-related disorders (23). Part of this uncertainty is justified by the lack of statistical power for the comparative evaluation of all these medications due to restricted search strategies or inclusion criteria and the possibility of confounding factors that were not properly explored (61). Furthermore, despite the high comorbidity rates, meta-analyses often include only specific assessment instruments or only patients without any co-occurring disorder (25), leading to a biased understanding of current evidence for the efficacy of SSRIs and SNRIs, as it may not fully represent clinical reality. Therefore, it is essential to evaluate the efficacy of pharmacological therapies for these disorders in multiple symptom domains, not restricting to any specific scale, while also exploring potential clinical and methodological moderators of these estimates. This study will be the first network meta-analysis in the field of psychiatry to evaluate the efficacy of pharmacological interventions in multiple symptom domains using a multilevel design. The data obtained can inform patients, healthcare professionals, and public health organizations about the comparative levels of overall efficacy and of efficacy in all symptom domains. When combined with data on major depression (62), this should address concerns about the benefit of SSRIs and SNRIs on global mental health, as one of the main criticisms of previous studies is their failure to account for multiple domains of emotional distress (63).

Additionally, previous meta-analyses that assessed the tolerability of SSRIs and SNRIs in the treatment of non-depressive disorders restricted their inclusion criteria to specific medications (37–40,64), diagnoses (37–40,64), adverse events (49,50), or populations (41)and did not account for the effect of clinical and methodological moderators. As a result, no large-scale quantitative review or network meta-analysis has 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. Moreover, incidence rates for several key adverse events or medications used during the treatment of anxiety disorders were completely unassessed, and no previous meta-analyses have evaluated all adverse events that

are currently identified as the most important during the treatment of these disorders by both patients and professionals. These limitations create a need to further compare side effect rates and tolerability of these medications in the treatment of non-depressive disorders while exploring potential moderators of these estimates. To the best of our knowledge, this is the most comprehensive meta-analysis to date to evaluate the tolerability of SSRIs and SNRIs 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 to the extensive search for both published and unpublished trials with no restrictions regarding specific medications, diagnoses, or populations. This evidence can help clinicians share decision-making with patients during medication choice by careful discussing what to expect concerning adverse events when starting an SSRI or SNRI. When adverse events are present, this information can also help select the medication with the lowest chances of causing the same side effect and reduce the clinical journey to find an acceptable pharmacological agent according to each individual's preferences.

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3 OBJECTIVES

3.1 OVERALL OBJECTIVE

To investigate the efficacy, acceptability, and tolerability of SSRIs, SNRIs, and placebo for the treatment of children and adults diagnosed with anxiety, obsessive-compulsive, or stress-related disorders, and also to explore moderators of these estimates**.**

3.2 SPECIFIC OBJECTIVES

A. To estimate the efficacy of SSRIs, SNRIs, and placebo in internalizing symptoms of children and adults diagnosed with anxiety, obsessive-compulsive, or stress-related disorders (article #1).

    a. To estimate the efficacy of SSRIs and SNRIs, when compared to placebo, in the aggregate measure of internalizing symptoms.

    b. To compare the efficacy of SSRIs and SNRIs in the aggregate measure of internalizing symptoms.

    c. To estimate the efficacy of SSRIs and SNRIs in the treatment of individuals diagnosed with distinct primary diagnosis.

    d. To estimate the efficacy of SSRIs and SNRIs, when compared to placebo, in specific symptom domains.

    e. To evaluate the multilevel structure of efficacy in all specific symptom domains related to each primary diagnosis.

    f. To explore potential clinical and methodological moderators of efficacy estimates.

B. To estimate the acceptability of SSRIs and SNRIs for the treatment of children and adults diagnosed with anxiety, obsessive-compulsive, or stress-related disorders (article #1).

a. To compare the acceptability of SSRIs and SNRIs through treatment discontinuation rates due to any cause.

b. To compare the acceptability of SSRIs and SNRIs through treatment discontinuation rates due to adverse events.

C. To estimate the tolerability of SSRIs, SNRIs, and placebo for the treatment of children and adults diagnosed with anxiety, obsessive-compulsive, or stress-related disorders (article #2).

a. To estimate incidence rates of adverse events for specific SSRIs and SNRIs.

b. To estimate the tolerability of each SSRI and SNRI for specific adverse events when compared to placebo.

c. To estimate treatment rankings of SSRIs and SNRIs for specific adverse events.

d. To compare the tolerability of SSRIs and SNRIs for clusters of specific adverse events.

e. To explore potential clinical and methodological moderators of tolerability estimates.

4 **ARTICLE #1**

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Selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors for anxiety, obsessive-compulsive and stress disorders: A three-level network meta-analysis

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Abstract

Background: Anxiety, obsessive-compulsive and stress-related disorders frequently co-occur, and patients often present symptoms of several domains. Treatment involves the use of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), but data on comparative efficacy and acceptability are lacking. We aimed to compare the efficacy of SSRIs, SNRIs, and placebo in multiple symptomatic domains on patients with these diagnoses over the lifespan through a three-level network meta-analysis.

Methods and Findings: We searched for published and unpublished randomized controlled trials that aimed to assess the efficacy of SSRIs or SNRIs on participants (adults and children) with diagnosis of any anxiety, obsessive-compulsive or stress-related disorder in MEDLINE, PsycINFO, Embase, and Cochrane from inception to April 23, 2015, with an update in November 11, 2020. We supplemented electronic database searches with manual searches for published and unpublished randomized controlled trials registered in publicly accessible clinical trials registries and pharmaceutical companies' databases. No restriction was made regarding comorbidities with any other mental disorder, as well as participants' age and sex, blinding of participants and researchers, date of publication, or study language. Primary outcome was the aggregate measure of internalizing symptoms of these disorders**.** Secondary outcomes include specific symptomatic domains and treatment discontinuation rates. We estimated standardized mean differences (SMDs) with three-level network meta-analysis with random slopes by study for medication and assessment instrument**.** Risk of bias appraisal was performed using the Cochrane Collaboration's Risk of Bias

Tool. This study was registered in PROSPERO (CRD42017069090). We analyzed 469 outcome measures from 135 studies (n= 30 245). All medications were more effective than placebo for the aggregate measure of internalizing symptoms (SMD -0·56, 95% CI -0·62 to -0·51, p-value <.001), for all symptomatic domains, and in patients from all diagnostic categories. We also found significant results when restricting to most used assessment instruments in each diagnosis; nevertheless, this restriction has led to exclusion of 72.71% of outcome measures. Pairwise comparisons revealed only small differences between medications in efficacy and acceptability. Limitations include the moderate heterogeneity found in most outcomes and the moderate risk of bias identified in most of the trials.

Conclusions: In this study, we observed that all SSRIs and SNRIs were effective for multiple symptom domains, and in patients from all included diagnostic categories. We found minimal differences between medications concerning efficacy and acceptability. This three-level network meta-analysis contributes to an ongoing discussion about the true benefit of antidepressants with robust evidence, considering the significantly larger quantity of data and higher statistical power when compared to previous studies. The three-level approach allowed to properly assess the efficacy of these medications on internalizing psychopathology, avoiding potential biases related to the exclusion of information due to distinct assessment instruments, and to explore the multilevel structure of transdiagnostic efficacy.

Author summary

Why was this study done?

Studies assessing comorbidity in patients with anxiety, obsessive-compulsive and stress-related disorders report rates above 50% and patients often present symptoms of multiple symptoms domains.

The efficacy of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) on multiple mental health domains has not yet been studied by network meta-analysis in this field, to the best of our knowledge.

Meta-analyses often restrain the statistical analysis to most commonly used assessment instruments.

What did the researchers do and find?

We conducted a systematic review and three-level network meta-analysis of 469 outcome measures, including all available measures of outcomes related to anxiety, obsessive-compulsive and stress-related disorders.

Antidepressants presented small to moderate effect sizes for global improvement of mental health of participants from all diagnostic categories.

We also found small to moderate effect sizes in our sensitivity analysis restricting to most used assessment instruments; however, this restriction has led to exclusion of 72.71% of all outcome measures.

What do these findings mean?

Our results support previous findings related to the efficacy of SSRIs and SNRIs, indicating that these medications are effective on multiple health domains

This study improved the evidence of the benefit of SSRIs and SNRIs for anxiety disorders. These results should guide psychiatrists, patients, clinicians, and policy makers on better evidence-based decisions for the initial treatment of these disorders.

Introduction

Anxiety, obsessive-compulsive, and stress-related disorders are among the main causes of years lived with disability due to psychiatric disorders worldwide, being the leading cause in some countries [1,2]. While these conditions affect around 10% of world's population, only 10% of those affected receive appropriate treatment [3]. Costs associated with these disorders account for approximately 33% of mental health related expenditures, particularly related to loss of productivity [4]. Therefore, offering appropriate evidenced-based treatment is crucial.

Controversy concerning antidepressants on treatment of mood disorders [5,6] obscures vital questions for other entities, such as anxiety, obsessive-compulsive, and stress-related disorders. While selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are considered first line pharmacological treatments [7], fewer large-scale quantitative reviews evaluate efficacy data for these conditions, as compared to mood disorders [8]. Accordingly, key questions remain unanswered. First, there is still debate on their efficacy and acceptability [9]. Second, across the many agents, sufficiently powered comparative efficacy and acceptability assessments are lacking [8]. Third, anxiety, obsessive-compulsive (OCD), and stress-related disorders often co-occur [10]; however, efficacy of these medications for global improvement of its transdiagnostic dimensions was never studied [8]. Fourth, there is uncertainty about the most appropriate instruments to measure treatment gains due to highly inconsistent and heterogeneous assessment landscape [11,12]. Therefore, inclusion of studies restricted to specific scales, as commonly performed by previous network meta-analysis [13,14], can lead to selective reporting, biased estimates, and exclusion of great amount of the outcomes related to psychopathology. Lastly, effects of clinical and methodological moderators on the efficacy estimate of antidepressants need to be taken into account when investigating comparability across medications [6]. Hence, it is essential to assess the efficacy of these medications on multiple symptomatic domains, not restricting to any scale, and also to explore potential moderators of these estimates. Such

data may inform patients, clinicians, and policy makers on relative levels of efficacy on these many domains.

We aimed to evaluate the efficacy and acceptability of SSRIs, SNRIs, and placebo in internalizing symptoms of children and adults diagnosed with anxiety, obsessive-compulsive, or stress-related disorders, also exploring the multilevel structure of efficacy on all symptomatic domains related to these diagnoses. We used data pooled through three-level network meta-analysis and multiple three-level meta-regression analyses accounting for clinical and methodological differences.

Methods

We report this study as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analysis (Table A in S1 Appendix) [15]. This study was prospectively registered in PROSPERO (CRD42017069090; S2 Appendix) in June 12, 2017, during data extraction, and updated the register 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 already published studies.

Inclusion criteria

We included randomized controlled trials (RCTs) assessing efficacy of SSRIs, SNRIs, and placebo for participants with a primary diagnosis of any anxiety disorder, OCD, or stress-related disorder according to standard diagnostic criteria (Feighner criteria, ICD-10, DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5, and RDoC). 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 we aimed to evaluate the efficacy of these antidepressants as monotherapy.

Search strategy

We searched MEDLINE, PsycINFO, Embase, and Cochrane from inception to April 23, 2015, and updated in November 11, 2020, using keywords related to study design, interventions, and assessed disorders, defined after discussion with experts in this field (search terms are depicted in the Text A in S1 Appendix). 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, 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 (MAC, MBJ, LSM, and JF), all psychiatrists, independently screened abstracts, assessed full-text articles, evaluated risk of bias, and extracted data, and a fifth reviewer (NPG) 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 studies was also extracted within the same trial data.

Primary outcome was the aggregate measure of internalizing symptoms (i.e. emotions and behaviors related to fear and response to stress). This measure is composed of any assessment of obsessive-compulsive, stress-related, or anxiety disorders, which encompasses domains of generalized anxiety disorder, social anxiety disorder, panic disorder, agoraphobia, specific phobias, separation anxiety disorder, as well as somatic symptoms and overall symptom severity. Subscale scores were included in the internalizing aggregate only if the total score of the higher factor was not reported within the same study. Secondary outcomes were treatment discontinuation rates due to any cause,

discontinuation rates due to adverse events, and clusters of symptomatic scales classified by the authors into seven groups based on DSM-5 diagnostic criteria (generalized anxiety, social anxiety, somatic symptoms, panic, specific phobias, OCD, and post-traumatic stress disorder).

We included all baseline data and outcomes reported between six and 26 weeks of follow-up in the analysis. We considered outcome measures as close to 12 weeks as possible. If information at 12 weeks was not available, we preferred the timepoint closer to 12 weeks; if equidistant, the longer. Primary and secondary outcomes were defined before 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, discontinuation rates, response and remission rates.

Statistical analysis

We performed a three-level network meta-analysis. We estimated efficacy as standardized mean difference (SMD), which was calculated by first estimating the standardized mean change (SMC) subtracting the initial score from the final scores of any mental health related symptom to calculate change for each intervention group. After that, we subtracted the SMC from medication and placebo intervention [16], assuming a correlation between initial and final means of 0.25, based on previous reports of this measure concerning mental health assessments [17]. When not available, standard deviations (SD) of baseline means were imputed using the mean of reported SDs of outcome measures evaluated with the same assessment instrument, as suggested by previous studies [18]. We interpreted SMDs of 0.2, 0.5 and 0.8 as small, moderate and large size differences, respectively [19]. We present the multilevel structure of transdiagnostic efficacy with a circular bar plot, which indicate the effect of medications for each diagnosis and also the effect medications in specific symptom domains within each diagnosis. We report the estimated effect sizes for all included outcome measures with a caterpillar plot. This method presents the same structure of a forest plot, except that the estimates are ordered by their magnitude. This is preferable when there is a large number of estimates, focusing on the general pattern, given individual estimates are not fully discernible [20]. We assessed comparative efficacy using

pairwise comparisons. Acceptability was measured by odds ratios (OR) of treatment discontinuation rates due to any cause and discontinuation rates due to adverse events. We estimated corresponding 95% confidence intervals (CI) for all measures. Two-sided P values less than 0.05 were considered statistically significant.

We conducted all meta-analysis and meta-regression models using three-level models with random slopes by study for medication and assessment instrument (Text B in S1 Appendix) [21]. We estimated the between-study variance through τ^2 estimates and heterogeneity through I^2. Given that placebo could be used in multiple comparisons, sample size of the placebo group was divided by the number of treatment comparisons [22]. We assessed network consistency using a local approach evaluating agreement between direct and indirect estimates of medications comparisons through the Bucher method [23]. Comparative acceptability was assessed using pairwise comparisons among dropout rates of medications, using multilevel models with study as random variable, given that the same trial may report rates of distinct medication groups. All analyses depict sample size (n), number of studies (k), and number of outcome measures (o). Analyses were performed using R (version 3.5.1), with package 'metafor' [24].

Assessment of bias

Risk of bias appraisal was performed using the Cochrane Collaboration's Risk of Bias Tool for RCTs [25]. 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 bias [26]. We assessed small study effects through funnel plots.

Meta-regression analysis

Univariate and multiple meta-regression models considered the following variables: medication, comparator, equivalent dose (estimated using fluoxetine equivalents based on previous studies) [27], time to outcome measure, main diagnosis, sampling, sample age, publication year, benzodiazepine use, placebo lead-in, analysis method, 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. Medication class was assessed only through univariate meta-regression. Since we evaluated each individual medication in the multiple meta-regression model, the inclusion of medication class would implicate multicollinearity. Also, we performed univariate meta-regressions with medication as moderator for each symptomatic domain. We performed all pairwise comparisons of medications for both efficacy and acceptability using the multiple meta-regression model with clinical and methodological moderators.

Subgroup and sensitivity analyses

We performed a subgroup analysis for each included diagnosis using the multilevel aggregate measure. We also conducted a subgroup analysis restricting to most used assessment instruments in each diagnosis, as commonly performed by previous network meta-analysis [13,14]. We conducted sensitivity analyses of efficacy estimates for the primary outcome considering imputation of baseline SD with the largest SD of assessment instrument, no baseline SD imputation, endpoint SMD as efficacy estimate, correlation between initial and final means of 0.5 and 0.7, only published trials, and only studies at low risk of bias. Moreover, concerning RCTs designed to evaluate patients diagnosed with OCD, we performed a sensitivity analysis excluding studies that included participants diagnosed with tic-related OCD, hoarding, repetitive behaviors of autism, or Tourette's syndrome, given that these conditions are associated with lack of pharmacological responsiveness [28].

Results

Study characteristics

We screened 5447 titles and abstracts and evaluated 420 full text articles for inclusion (Fig A in S1 Appendix). Of those, 23 (5.48%) full text articles or complete reports were only available through direct contact with authors. We included 135 studies in the meta-analysis (124 published trials and 11 unpublished reports), which reported 469 outcome measures, comprising 30 245 patients. Of those, we included 94 studies in the meta-regression analyses, due to incomplete report of moderators. All included studies were classified as double-blind. Generalized anxiety disorder was the main disorder assessed in 35 (25.93%) of 135 trials, whereas social anxiety disorder was studied in 28 (20.74%), panic disorder in 25 (18.52%), OCD in 22 (16.30%), post-traumatic stress disorder in 20 (14.81%), and five

(3.70%) trials were designed to evaluate more than one disorder. The mean age of participants in placebo groups was 35.69 years (SD, 10.59) compared with 36.10 years (SD, 9.50) in medication groups. Moreover, 117 (86.67%) trials were designed to assess adults and 18 (13.33%) studies evaluated children and adolescents. Mean proportion of women was 53.80 (SD, 19.17) in the placebo group compared with 55.06 (SD, 17.93) in medication groups. Of included studies, 23 (17.04%) were single center trials. The median number of sites from multicenter trials was 22 (interquartile range, 11 to 46). Concerning diagnostic criteria, DSM-IV was used in 76 (56.30%) studies, whereas 33 (24.44%) trials utilized DSM III-R, DSM IV-TR was used in 14 (10.37%) and DSM III in three (2.22%). Diagnostic criteria were not clear in nine (6.67%) of included studies (primary studies information is depicted in S3 Appendix).

Outcomes

We found significant SMDs favoring medications over placebo for the pooled medication group (SMD -0.56, 95% CI -0.62 to -0.51, p-value <.001) and for all individual medications (Table 1), indicating moderate effect size on internalizing symptoms [26]. Those differences reflect that standardized mean changes (SMCs) from initial to final means in medications (SMC -1.70, 95% CI -1.83 to -1.57, p-value <.001) were higher than those found in placebo groups (SMC -1.11, 95% CI -1.22 to -1.00, p-value <.001) (Table B in S1 Appendix). We found moderate heterogeneity [22] for most outcomes. Fig 1 and Fig 2 report the multilevel structure of the study and the network diagram of direct comparisons. The caterpillar plot of all included outcome measures is presented in Fig 3.

Medication type did not significantly moderate treatment response. However, pairwise efficacy comparisons indicated that, when compared to sertraline, both paroxetine (SMD -0.32, 95% CI -0.53 to -0.11, p-value = 0.003) and escitalopram (SMD -0.32, 95% CI -0.61 to -0.03, p-value=0.03) were significantly more effective for the aggregate measure of internalizing symptoms, with no further significant differences between all other medications. Direct estimates were consistent with these findings (Table C in S1 Appendix). We also performed pairwise comparisons assessing acceptability differences among medications. No differences among medications were found for discontinuation rates due to any cause (Fig 4). Nevertheless, in comparison with all other medications, except fluoxetine,

fluvoxamine was associated with higher rates of discontinuation rates due to adverse events (Fig 5).

All symptom domains related to anxiety, OCD, or stress disorders, exhibited a favorable SMD on medication-placebo comparisons, which could be classified as small to moderate (Table 2) [19]. Analyses also considered univariate meta-regressions for each included symptomatic domain with medication as moderator. Only fluvoxamine was more effective for generalized anxiety disorder symptoms when compared to fluoxetine (SMD -0.44, 95% CI -0.86 to -0.02, p-value=0.04). For social anxiety disorder, panic disorder, post-traumatic stress disorder, and OCD symptoms, no significant differences between medications were found (Table D in S1 Appendix).

Univariate and multiple meta-regression analyses

We performed univariate (Table E in S1 Appendix) and multiple (Table F in S1 Appendix) three-level meta-regression analyses to investigate potential sources of heterogeneity in medication-placebo comparisons for the primary outcome. The multiple meta-regression model indicated higher efficacy for the aggregate measure of internalizing symptoms for four factors. These comprised: (a) older relative to newer studies, (b) studies with outcomes assessments in weeks 12 to 14 when compared to those evaluating outcomes between weeks 6 to 8 and 9 to 11, (c) participants diagnosed with generalized anxiety disorder in comparison to other diagnoses, and (d) studies funded by academic institutions in comparison to all other sources of funding.

Risk of bias assessment

Overall, 32 (23.70%) trials were rated as high risk of bias, 65 (48.15%) trials as moderate, and 38 (28.15%) as low (Fig A and Table E in S3 Appendix). Visual inspection of funnel plots did not suggest that small studies gave different results from larger studies in medication-placebo comparisons (S1 Appendix).

Subgroup and sensitivity analyses

We found significant results for efficacy on the aggregate measure of internalizing symptoms for all groups of standardized diagnosis of participants (Table 3), ranging from a SMD of -0.41 (95% CI -0.65 to -0.18, p-value <.001) for post-traumatic stress disorder to a SMD of -0.65 (95% CI -0.74 to -0.56, p-value <.001) for social anxiety disorder. Only one study assessed participants with primary diagnosis of specific phobia, so it was not included in the analysis stratified by mental disorder, given that it would not represent a pooled three-level estimate. We also found significant results when restricting to most used assessment instruments in each diagnosis for all groups of standardized diagnosis of participants (Table 4), ranging from a SMD of -0.13 (95% CI -0.24 to -0.02, p-value=0.02) for panic disorder to a SMD of -0.64 (95% CI -0.75 to -0.53, p-value <.001) for SAD; however, this restriction has led to exclusion of 341 (72.71%) of all available outcome measures. Concerning sensitivity analyses, all efficacy estimates remained within the 95% CI interval of the main analysis (Table 5). In RCTs designed to assess OCD, we found a SMD of -0.53 (95% CI -0.71 to -0.35, p-value<.001) and of -0.53 (95% CI -0.66 to -0.41, p-value <.001) for RCTs that included and excluded patients diagnosed with tic-related OCD, hoarding, repetitive behaviors of autism, or Tourette's syndrome, respectively.

Discussion

In this study, we aimed to assess the efficacy and acceptability of SSRIs, SNRIs, and placebo in internalizing symptoms of children and **adults diagnosed with anxiety, obsessive-compulsive, or stress-related disorders,** accounting for clinical and methodological differences. Our results revealed higher efficacy of medications in comparison with placebo on the aggregate measure of internalizing symptoms. Effect sizes were small to moderate in overall psychopathology for all considered diagnoses and in all symptomatic domains. We also found significant results when restricting to most used assessment instruments in each diagnosis; however, this restriction has led to exclusion of 72.71% of all available outcome measures. Moreover, estimates of efficacy were moderated by patient diagnosis, treatment duration, funding, and year of publication. Finally, concerning pairwise comparisons, we found small differences between medications for paroxetine and escitalopram when compared to sertraline, considering

efficacy. When evaluating acceptability through discontinuation rates due to any cause, no differences among medications were found; nevertheless, fluvoxamine was associated with higher rates of discontinuation rates due to adverse events than all other medications, except fluoxetine.

To our knowledge, this is the first meta-analysis to evaluate the efficacy of antidepressants on multiple mental health domains of patients diagnosed with anxiety, obsessive-compulsive, or stress-related disorders using a three-level approach [8]. All included SSRIs and SNRIs have shown greater reduction in overall psychopathology than placebo, with effect sizes comparable to other interventions in medicine [29]. Combined with data on major depression [30], this should address concerns on the benefit of SSRIs and SNRIs on global mental health, given that one of main criticisms about previous studies is not to account for multiple domains of emotional distress [5]. Moreover, our findings provide support for transdiagnostic systems of psychopathology, which emphasize that psychosocial impairment is better explained and predicted by transdiagnostic dimensions than traditional diagnoses [31,32]. Studies assessing comorbidity in patients with anxiety, obsessive-compulsive and stress-related disorders report rates above 50% [10]. Standard network meta-analyses are designed to evaluate symptomatic domains separately [14], which might not represent most patients in clinical settings; thus, current evidence may be potentially misleading. This suggests the need to evaluate efficacy of treatments in multiple symptomatic domains, given that patients seek help for overall improvement in symptoms and functioning rather than improvements in specific symptomatic domains. In addition, there is no gold standard for assessing symptom severity on anxiety disorders, and standard network meta-analyses often restrict outcome measures to specific scales [13,14]. We also found small to moderate effect sizes when restricting to most used assessment instruments in each diagnosis in our sensitivity analysis; nevertheless, this restriction has led to exclusion of 72.71% of all available outcome measures. This may indicate that great amount of the literature is not included in previous studies, which significantly constraint current evidence and limit power. Hence, multiple-endpoints design also addresses low item overlap between assessment instruments, ranging from 37% of similarity for anxiety scales to 45% for post-traumatic stress disorder, and concerns about biases inherent to each scale, given the inconsistent and highly heterogeneous current assessment landscape [11,12].

Publication of network meta-analyses in psychiatry field is significantly increasing [8] as it has been recognized as the highest level of evidence in treatment guidelines [33]. Nonetheless, differently from major depression and other narrowly defined psychiatric disorders, which allow a more 'unidimensional' construct assessment, anxiety disorders are a group of highly correlated emotional disorders, which require a distinct approach. The three-level design addresses this important issue, at the same time allowing to combine direct and indirect information in a network [34–36]. Although susceptible to the quality of primary studies, as standard meta-analyses, three-level network meta-analyses may represent a significant methodological advancement to be used in this research field.

Cross-medication comparisons revealed lower efficacy of sertraline over paroxetine and escitalopram, and lower acceptability related to adverse events of fluvoxamine when compared to all other medications, except fluoxetine. These findings could inform evidence-based medication choices. Nonetheless, these results should be interpreted cautiously, since differences concerning efficacy indicated small effect sizes and statistically significant findings related to acceptability presented noteworthy wide confidence intervals. Therefore, clinicians should also consider factors beyond efficacy and acceptability, such as patient's prior experience with medication, the physician's own experience, and potential budgetary constraints [37].

The most comprehensive network meta-analysis on medications for anxiety disorders before this analysis [14], which assessed only generalized anxiety disorder, found results consistent with our findings, indicating that SSRIs and SNRIs are effective for generalized anxiety disorder and that are no significant differences among medications. Nevertheless, this previous work assessed 89 outcome measures, which represent 18.98% of the 469 evaluated in our study. This significant difference is partially related to the exclusion of comorbidities. Given that anxiety disorders often co-occur, we understand that the inclusion of distinct disorders is a crucial aspect of this field. Bandelow and colleagues also assessed the efficacy of antidepressants for anxiety disorders, including not only generalized anxiety disorder, but also social anxiety disorder and panic disorder [38]. Bandelow and colleagues work represent the largest meta-analysis in this field, evaluating 206 treatment arms related to the efficacy of medications. Without using a network meta-analysis approach, this work reported effect sizes of 2.09 for SSRIs and 2.25 for SNRIs and indicated substantial differences between medications, ranging from 1.06 for citalopram to 2.75 for escitalopram. These conflicting findings may be due to the use of

pre-post effect sizes, which estimate the improvement within one group and not the difference between the intervention and the placebo group. This suggests a large variation in placebo response rates in trials assessing different medications for these disorders. Despite being commonly used, pre-post effect estimates have been criticized in the literature [17], given that it is impossible to disentangle which proportion of the effect size is caused by the intervention and which by other processes, such as natural recovery or expectations of the patients.

Anxiety, obsessive-compulsive and stress-related disorders often co-occur; given so, two previous meta-analyses explored the benefit of antidepressants for these conditions. Roest and colleagues mainly focused on premarketing trials and found an overall effect size of 0.38, including 49 studies [9]. Sugarman and colleagues reported similar results, indicating an effect size of 0.34 based on 56 outcome measures [39]. These discrepancies when compared to our findings and to our number of outcome measures reflect a major difference related to our three-level approach. All previous meta-analyses included only one outcome measure for study. We took these dependencies into account with the three-level meta-analytical model [21], using assessment instrument as a random variable, also using a network meta-analysis approach, including medication as a random variable. Moreover, these studies restricted assessment instruments to the scales most commonly used in each diagnosis, which can lead to biased estimates and not account for co-occurring symptoms of distinct domains. Furthermore, our larger quantity of data allowed to explore different potential moderators, given the higher statistical power.

We found no age-group moderation effect, indicating that SSRIs and SNRIs are also effective in anxiety symptoms of younger individuals. These findings contrast with previous evidence on efficacy of antidepressants for depressive symptoms, which indicate that children and adolescents do not present good response to treatments with SSRIs or SNRIs as compared with adults [13]. Given that the temporal relationship of comorbidity suggests that the onset of anxiety disorders often occur earlier, aiming to reduce psychopathology and morbidity before onset of depression may be an important prevention strategy in clinical practice to be further investigated. Also, children and adolescent respond worse to psychotherapy when compared to adults [40], so pharmacological interventions may be of great importance.

Strengths and limitations of the study

This study has some major strengths. To the best of our knowledge, this is the first three-level network meta-analysis in the field of psychiatry and the largest meta-analysis to date to evaluate the efficacy of antidepressants on mental health symptoms of patients diagnosed with anxiety, obsessive-compulsive or stress-related disorders, due to full inclusion of all available outcome measures in this field, 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 efficacy and acceptability among these medications,** exploring the multilevel structure of efficacy and avoiding exclusion of great amount of available outcome measures and biases related to specific symptoms or inherent to assessment instruments. Moreover, we extracted detailed clinical and methodological information of each included study, exploring potential moderators of efficacy estimates.

Nevertheless, our study has some limitations. First, the risk of bias assessment indicated some sources of potential bias, possibly restricting interpretation of results; however, our sensitivity analysis of trials with low risk of bias indicated estimates concurrent with our main findings. Second, visual inspection of funnel plots indicated that small studies present different results from larger studies in some symptom domains, which may suggest a publication bias in this research field. Through extensive search for both published and unpublished trials, we aimed to reduce the impact of this finding. Despite our larger quantity of data and resulting statistical power when compared to other meta-analyses, our results should also be interpreted cautiously. Third, standard deviations of baseline measures are not informed in all included studies and correlation between baseline and endpoint means were sparsely reported and, for this reason, were imputed or assumed. Nonetheless, imputation method followed previous recommendations for meta-analyses [18] and the assumed correlation was based on previous reports concerning mental health [17]. Lastly, we identified moderate heterogeneity in our data analysis, as expected in meta-analyses with a three-level design and with a great amount of studies [41]. Accordingly, we explored and identified potential sources of heterogeneity through meta-regression and sensitivity analysis.

Conclusions

To our knowledge, our three-level network meta-analysis represents the most comprehensive review of available evidence to date regarding efficacy of SSRIs and SNRIs

on anxiety, obsessive-compulsive, and stress-related disorders treatment, considering not only specific domains but all assessments of internalizing symptoms related to these disorders. Our findings, estimated using a three-level approach, improved the evidence of the benefit SSRIs and SNRIs for anxiety disorders, given that previous meta-analyses were restricted to specific scales or specific symptomatic domains, which reduces statistical power and does not reflect clinical practice. This method allowed to properly estimate assess the efficacy of these medications on overall psychopathology, avoiding potential biases related to assessment instruments, and also to explore the multilevel structure of transdiagnostic efficacy. Our study might contribute to help and guide psychiatrists, patients, clinicians, and policy makers on better evidence-based decisions for the initial treatment of these disorders.

Supporting information

S1 Appendix. Supplementary methods and results.

S2 Appendix. PROSPERO registration and review protocol.

S3 Appendix. Primary studies information.

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Author Contributions

N.P.G. and G.A.S. conceived, designed, had full access to all data in the study and takes responsibility for the integrity of data and accuracy of data analysis. N.P.G., M.A.C., M.B.J., L.S.M., and J.F. selected the articles and extracted the data. N.P.G. and GAS analyzed the data. N.P.G., M.A.C., M.B.J., L.S.M., J.F., L.S., G.G.M., P.C., D.S.P., and G.A.S. interpreted the data and contributed to the writing of the manuscript. All authors have approved the final draft of the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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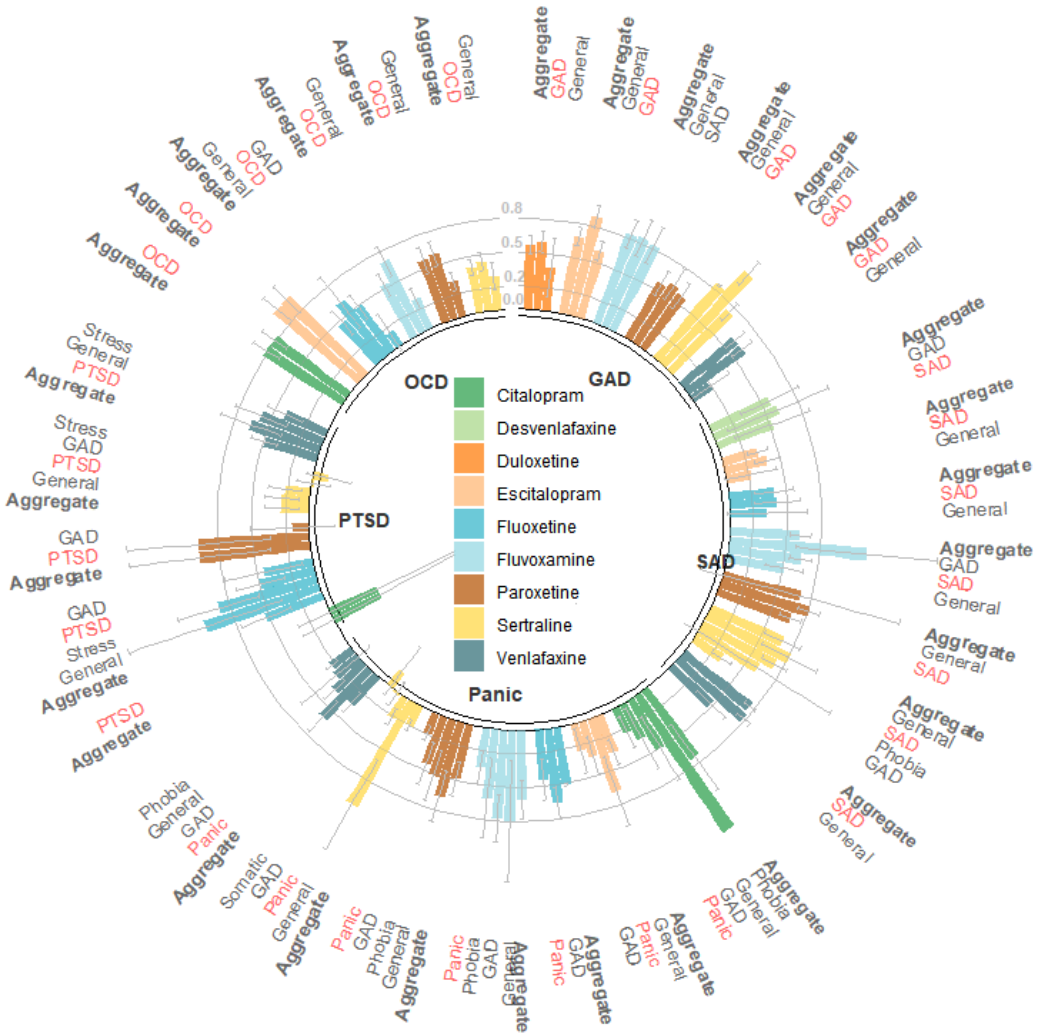
Table 1. Standardized mean difference between medication and placebo for the primary outcome (aggregate measure of mental health related symptoms) according to each medication class and each medication within the same class

Medication	o/k (n)	Estimated SMD (95%CI)	SE	p value	τ^2	Heterogeneity I^2 (%)
SSRIs and SNRIs	469/135 (30 245)	-0.56 (-0.62 to -0.51)	0.03	<.001	0.045	42.09
SSRIs	396/111 (22 146)	-0.57 (-0.64 to -0.50)	0.03	<.001	0.039	37.68
Fluoxetine	64/16 (1797)	-0.52 (-0.68 to -0.36)	0.08	<.001	0.074	39.19
Sertraline	98/25 (4071)	-0.43 (-0.57 to -0.29)	0.07	<.001	0.091	58.83
Paroxetine	132/36 (8790)	-0.60 (-0.72 to -0.49)	0.06	<.001	0.091	64.05
Fluvoxamine	50/19 (2276)	-0.68 (-0.88 to -0.49)	0.10	<.001	0.162	68.55
Citalopram	19/6 (1487)	-0.65 (-1.08 to -0.22)	0.22	0.003	0.196	66.24
Escitalopram	33/13 (3725)	-0.61 (-0.76 to -0.46)	0.08	<.001	0.048	46.47
SNRIs	73/28 (8099)	-0.54 (-0.65 to -0.44)	0.05	<.001	0.063	56.08
Venlafaxine	52/21 (5621)	-0.55 (-0.68 to -0.41)	0.07	<.001	0.094	65.58
Duloxetine	19/8 (2418)	-0.56 (-0.71 to -0.41)	0.08	<.001	0.021	31.44
Desvenlafaxine	2/1 (60)	-0.58 (-1.14 to -0.03)	0.28	0.04	0.00	0.00

o, number of outcomes; k, number of studies; n, sample size; SMD, **standardized mean difference;** SE standard error; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors

Fig 1. Standardized mean differences in the studied domains within the five diagnoses


0.8
0.5
0.2
0.0
OCD
GAD
PTSD
SAD
Panic
Citalopram
Desvenlafaxine
Duloxetine
Escitalopram
Fluoxetine
Fluvoxamine
Paroxetine
Sertraline
Venlafaxine

Legend: GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder. Patients' diagnoses are presented in the center of the circular bar plot and symptom domains are described outside. Effect sizes are presented as standardized mean differences (SMD) and error bars represent estimated standard errors. SMDs related to the primary outcome (i.e. aggregate measure of the available symptom domains evaluated in patients within the same diagnosis) are highlighted in bold and related to symptom domains that are concurrent with patients' diagnosis are highlighted in red. Outcome measures classified as general represent scales designed to assess overall psychopathology

Table 2. Standardized mean difference between all medication and placebo for each symptomatic domain in the included studies

Symptomatic domain	o/k (n)	Estimated SMD (95%CI)	SE	p value	τ^2	Heterogeneity I^2 (%)
GAD	128/68 (16 495)	-0.55 (-0.64 to -0.46)	0.05	<.001	0.078	56.83
Social Anxiety	57/28 (6668)	-0.67 (-0.76 to -0.58)	0.05	<.001	0.005	9.78
Panic	55/17 (4040)	-0.30 (-0.37 to -0.23)	0.04	<.001	0.034	36.16
Specific Phobias	23/11 (2651)	-0.51 (-0.78 to -0.25)	0.13	<.001	0.008	16.49
PTSD	49/20 (2907)	-0.42 (-0.67 to -0.17)	0.13	0.001	0.206	71.04
OCD	63/22 (3835)	-0.59 (-0.70 to -0.48)	0.06	<.001	0.001	1.34

o, number of outcomes; k, number of studies; n, sample size; SMD, **standardized mean difference;** SE, standard error; GAD, generalized anxiety disorder; PTSD, post-traumatic stress disorder; OCD, obsessive-compulsive disorder

Table 3. Standardized mean differences between medication and placebo for the primary outcome (aggregate measure of mental health related symptoms) according to standardized diagnosis of the participants of included studies

DSM-5 diagnosis	o/k (n)	Estimated SMD (95%CI)	SE	p value	τ^2	Heterogeneity I^2 (%)
GAD	92/35 (10 564)	-0.64 (-0.73 to -0.55)	0.05	<.001	0.044	45.25
Social Anxiety	75/28 (6454)	-0.65 (-0.74 to -0.56)	0.05	<.001	0.025	32.97
Panic	134/25 (5995)	-0.43 (-0.55 to -0.31)	0.06	<.001	0.101	64.30
PTSD	69/20 (2907)	-0.41 (-0.65 to -0.18)	0.12	<.001	0.195	71.62
OCD	91/22 (3849)	-0.53 (-0.64 to -0.42)	0.05	<.001	0.003	2.99

GAD, generalized anxiety disorder; PTSD, post-traumatic stress disorder; OCD, obsessive-compulsive disorder; o, number of outcomes; k, number of studies; n, sample size; SMD, **standardized mean difference;** SE, standard error

Table 4: Standardized mean differences between medication and placebo in most used assessment instruments according to standardized diagnosis of participants

DSM-5 diagnosis	o/k (n)	Estimated SMD (95%CI)	SE	p value	τ^2	Excluded outcomes (%)	Excluded studies (%)	Excluded participants (%)	Heterogeneity I^2 (%)
Aggregate	128/93 (23 330)	-0.56 (-0.63 to -0.49)	0.04	<.001	0.045	341 (72.71)	42 (31.11)	6915 (22.86)	40.00
HAM-A	42/32 (9962)	-0.61 (-0.72 to -0.50)	0.05	<.001	0.035	50 (54.35)	3 (8.57)	602 (5.70)	61.51
LSAS	28/22 (5433)	-0.64 (-0.75 to -0.53)	0.06	<.001	0.023	47 (62.67)	6 (21.43)	1021 (15.82)	30.09
Panic attacks (PAAS/week)	15/9 (2265)	-0.13 (-0.24 to -0.02)	0.06	0.02	0.00	119 (88.81)	16 (64.0)	3730 (62.22)	0.00
CAPS	18/15 (2570)	-0.51 (-0.71 to -0.31)	0.10	<.001	0.044	51 (73.91)	5 (25.0)	337 (11.59)	29.46
YBOCS	25/15 (3100)	-0.63 (-0.82 to -0.45)	0.09	<.001	0.062	66 (72.53)	7 (31.82)	749 (19.46)	39.30

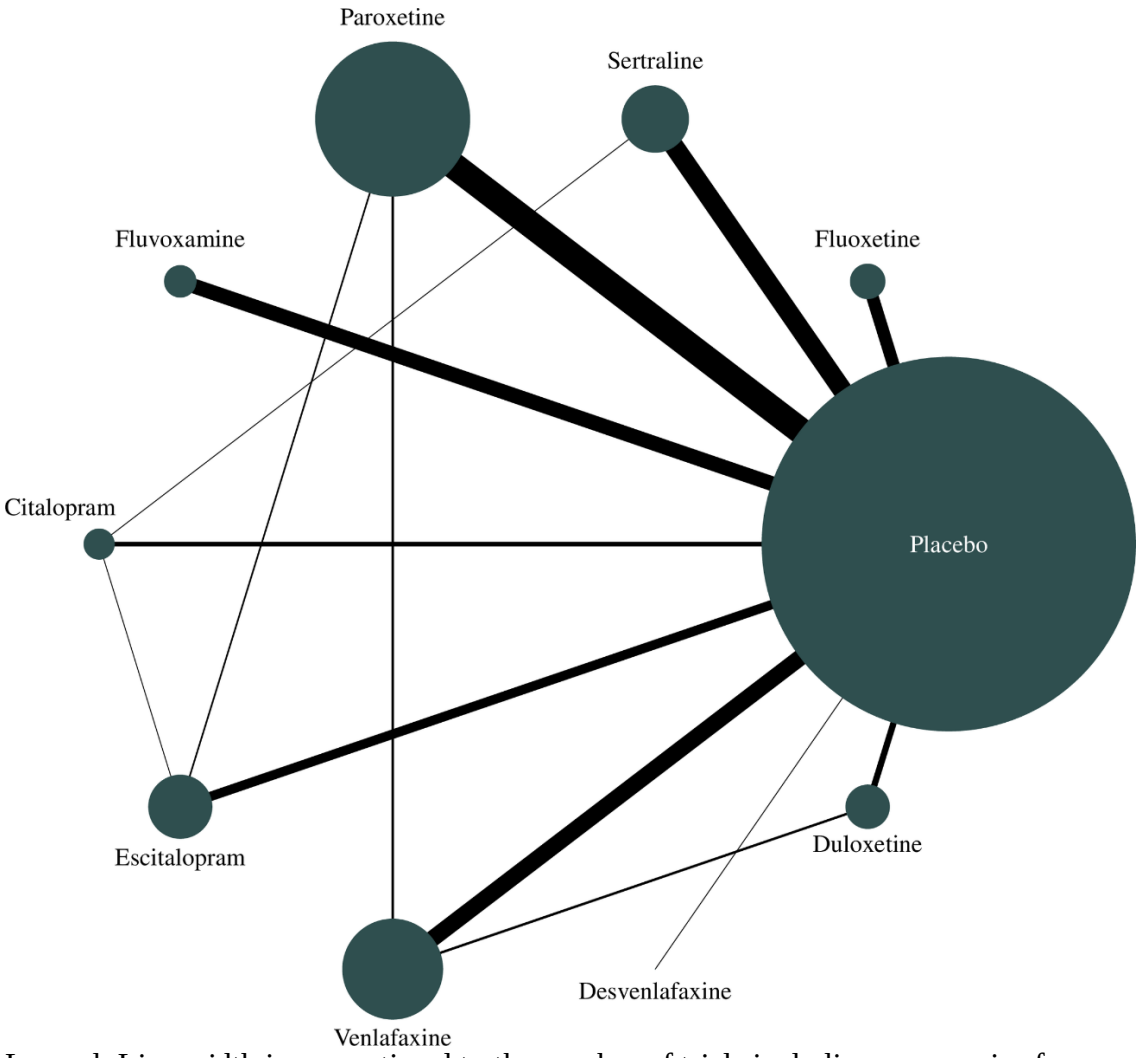
HAM-A, Hamilton Anxiety Rating Scale; LSAS, Liebowitz Social Anxiety Scale; PAAS, Panic and Anticipatory Anxiety Scale; CAPS, Clinician-Administered PTSD Scale; YBOCS, Yale-Brown Obsessive-Compulsive Scale; o, number of outcomes; k, number of studies; n, sample size; SMD, **standardized mean difference;** SE, standard error

Table 5. Sensitivity analysis of each method of measure of association estimate between medication and placebo for the primary outcome (aggregate measure of mental health related symptoms)

Method	o/k (n)	Estimated measure (95%CI)	SE	p value	τ^2	Heterogeneity I^2 (%)
Only published	432/124 (28 196)	-0.58 (-0.64 to -0.52)	0.03	<.001	0.061	49.64
SD imputation (max. SD)	469/135 (30 245)	-0.52 (-0.57 to -0.46)	0.03	<.001	0.074	55.50
No SD imputation	425/121 (27 228)	-0.55 (-0.61 to -0.49)	0.03	<.001	0.078	55.51
Correlation of 0.5	469/135 (30 245)	-0.56 (-0.62 to -0.50)	0.03	<.001	0.079	63.02
Correlation of 0.7	469/135 (30 245)	-0.56 (-0.61 to -0.50)	0.03	<.001	0.068	66.75
Excluding outliers	462/132 (29 955)	-0.55 (-0.60 to -0.49)	0.03	<.001	0.063	51.19
Endpoint standardized mean difference	185/53 (8256)	-0.43 (-0.50 to -0.36)	0.04	<.001	0.047	58.20
Only studies at low risk of bias	179/38 (9291)	-0.56 (-0.67 to -0.45)	0.06	<.001	0.100	60.19

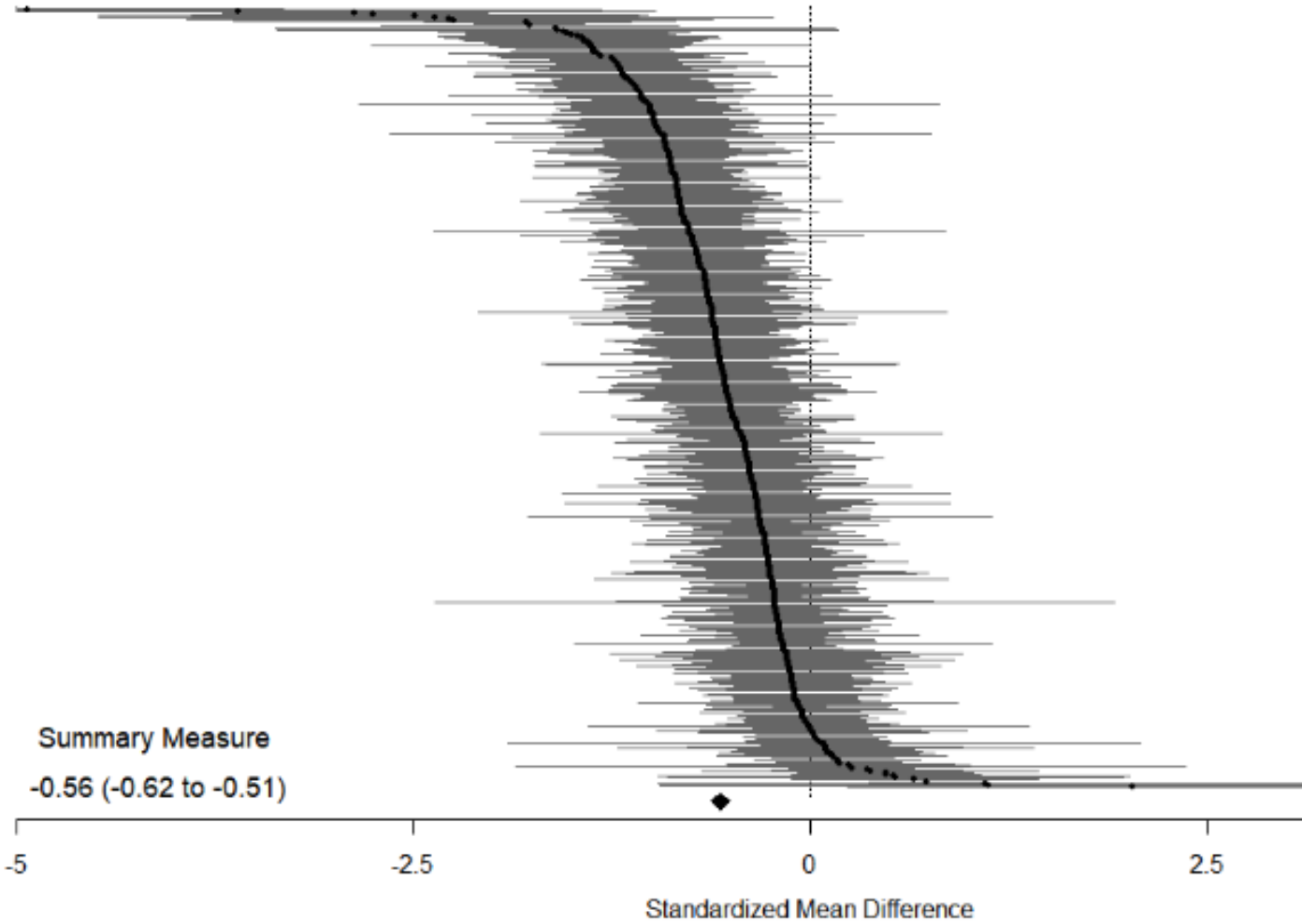
k, number of studies; n, sample size; o, number of outcomes; SE, standard error

Fig. 2. Network meta-analysis of available comparisons



Legend: Line width is proportional to the number of trials including every pair of treatments (direct comparisons). Circle size is proportional to the total number of participants randomly assigned for each treatment in the network

Fig 3. Caterpillar plot of all outcome measures included in the meta-analysis



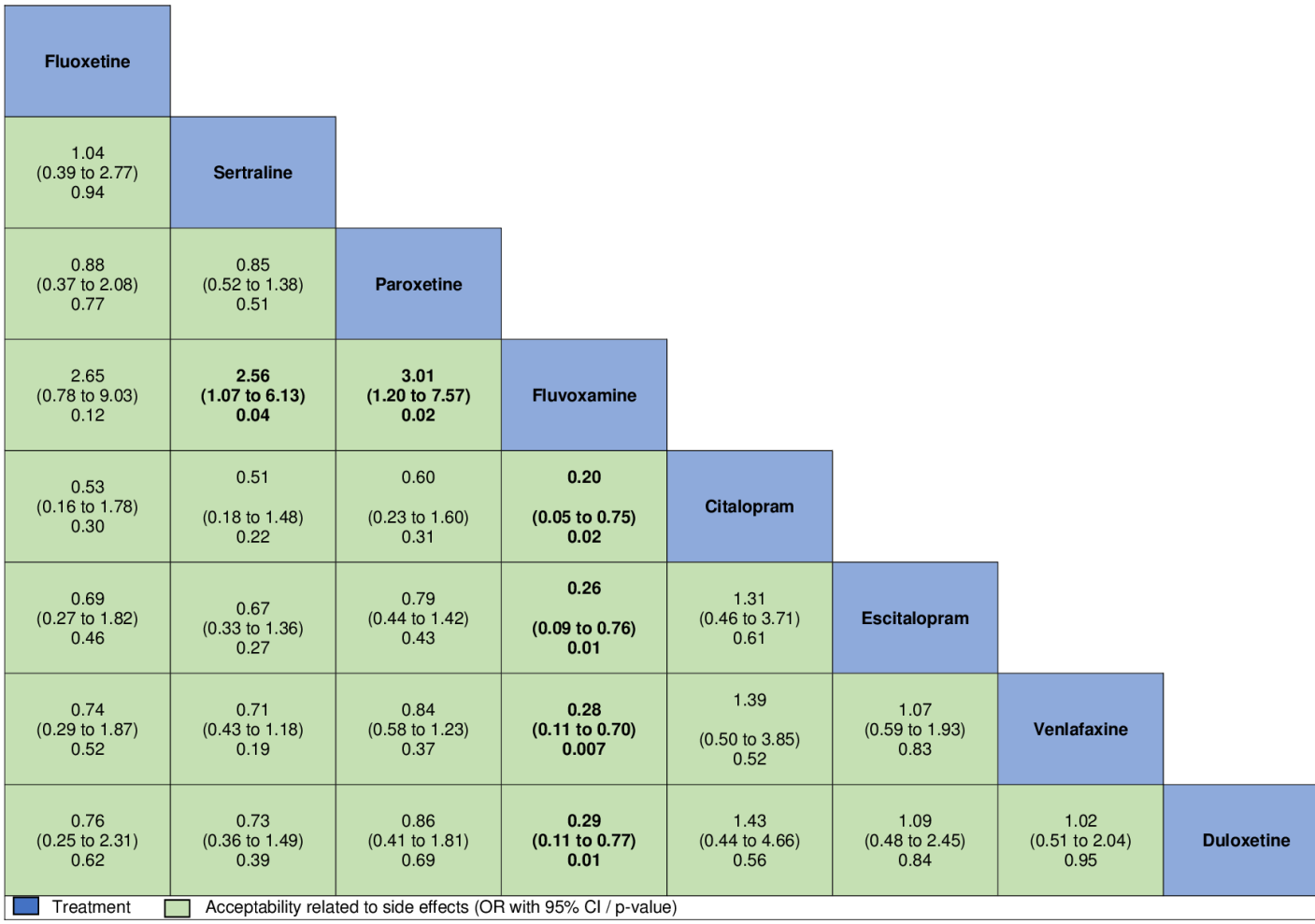
Legend: Efficacy measured as standardized mean differences between medication and placebo for the primary outcome (aggregate measure of mental health related symptoms). Standardized mean differences less than 0 favour medication and greater than 0 favour placebo. Horizontal lines indicate 95% confidence intervals for each included outcome measure; horizontal points of the diamond are the limits of 95% confidence interval of the overall summary measure

Fig 4. Comparisons of efficacy and discontinuations rates of all SSRIs and SNRIs, considering three-level multiple meta-regression models

Fluoxetine	0.17 (-0.14 to 0.47) 0.29	-0.14 (-0.41 to 0.13) 0.31	0.05 (-0.28 to 0.38) 0.77	-0.07 (-0.43 to 0.30) 0.42	-0.14 (-0.47 to 0.20) 0.42	-0.03 (-0.33 to 0.28) 0.87	-0.03 (-0.45 to 0.38) 0.87
0.68 (0.37 to 1.27) 0.23	**Sertraline**	**-0.32 (-0.53 to -0.11) 0.003**	-0.11 (-0.36 to 0.13) 0.36	-0.27 (-0.61 to 0.07) 0.13	**-0.32 (-0.61 to -0.03) 0.03**	-0.20 (-0.44 to 0.03) 0.09	-0.16 (-0.48 to 0.15) 0.32
0.72 (0.41 to 1.28) 0.26	1.06 (0.76 to 1.46) 0.73	**Paroxetine**	0.21 (-0.06 to 0.47) 0.13	0.05 (-0.23 to 0.34) 0.71	0.00 (-0.22 to 0.22) 0.98	0.12 (-0.05 to 0.29) 0.16	0.16 (-0.15 to 0.47) 0.41
0.85 (0.40 to 1.78) 0.66	1.24 (0.72 to 2.13) 0.43	1.17 (0.66 to 2.09) 0.59	**Fluvoxamine**	-0.15 (-0.52 to 0.22) 0.43	-0.20 (-0.53 to 0.12) 0.22	-0.09 (-0.36 to 0.19) 0.54	-0.05 (-0.39 to 0.29) 0.79
0.71 (0.33 to 1.51) 0.38	1.04 (0.54 to 2.01) 0.90	0.99 (0.55 to 1.77) 0.96	0.84 (0.37 to 1.90) 0.67	**Citalopram**	-0.05 (-0.31 to 0.21) 0.69	0.06 (-0.24 to 0.37) 0.67	0.10 (-0.29 to 0.50) 0.60
0.71 (0.36 to 1.38) 0.31	1.04 (0.64 to 1.69) 0.89	0.98 (0.67 to 1.44) 0.91	0.83 (0.42 to 1.65) 0.60	0.99 (0.54 to 1.82) 0.98	**Escitalopram**	0.12 (-0.11 to 0.34) 0.31	0.16 (-0.18 to 0.50) 0.36
0.67 (0.36 to 1.25) 0.21	0.98 (0.69 to 1.40) 0.93	0.93 (0.70 to 1.23) 0.61	0.79 (0.45 to 1.40) 0.42	0.94 (0.50 to 1.76) 0.85	0.95 (0.63 to 1.43) 0.80	**Venlafaxine**	0.04 (-0.26 to 0.34) 0.79
0.87 (0.42 to 1.83) 0.71	1.28 (0.75 to 2.17) 0.37	1.21 (0.73 to 2.00) 0.47	1.03 (0.55 to 1.91) 0.93	1.22 (0.58 to 1.24) 0.60	1.23 (0.71 to 2.14) 0.46	1.30 (0.82 to 2.06) 0.27	**Duloxetine**
Treatment	Efficacy (SMD with 95% CI / p-value)			Acceptability (OR with 95% CI / p-value)			

Legend: SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; OR, odds ratio; CI, Confidence Interval. 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. For efficacy, SMD below 0 favour the column-defining treatment. For safety, ORs above 1 favour the column-defining treatment

Fig 5. Comparisons of discontinuation rates due to adverse events of all SSRIs and SNRIs, considering three-level multiple meta-regression models



Legend: SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; OR, odds ratio; CI, Confidence Interval. 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 favour the column-defining treatment

Selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors for anxiety, obsessive-compulsive and stress disorders: a three-level network meta-analysis

S1 Appendix

Contents

S1Table A: Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses checklist

Section/Topic	Item #	Checklist Item	Section (paragraph)
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	Introduction (paragraphs 1-2)
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction (paragraph 3)
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Methods (paragraph 1)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	Inclusion criteria (Methods; paragraph 1)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Search strategy (Methods; paragraph 1)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	(S1 Text A)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Data extraction and data synthesis (Methods; paragraph 1)

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Data extraction and data synthesis (Methods; paragraph 1)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Data extraction and data synthesis (Methods; paragraph 4)
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	Statistical analysis (Methods; paragraph 1)
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Assessment of bias (Methods; paragraph 1)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	Statistical analysis (Methods; paragraph 1)
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	Statistical analysis (Methods; paragraphs 1-2)
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	Statistical analysis (Methods; paragraph 2)
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Assessment of bias (Methods; paragraph 1)
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	Meta-regression analysis; Subgroup and sensitivity analyses (Methods)
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage,	(S1 Fig. A)

		ideally with a flow diagram.	
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Fig. 2
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	(S1 Table 6)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	(S3 App.)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	(S3 App.)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger network*	(S3 App.)
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	Outcomes (Results; paragraph 1)
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	(S1 Table 6)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	(S1 Figs B-H)
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses*, and so forth).	Univariate and multiple meta-regression analyses; Subgroup and sensitivity analyses (Results)
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	Discussion (paragraphs 1-8)
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	Strengths and limitations of the study (Discussion; paragraph 2)
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusions (Discussion; paragraph 1)
FUNDING			Abstract

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	

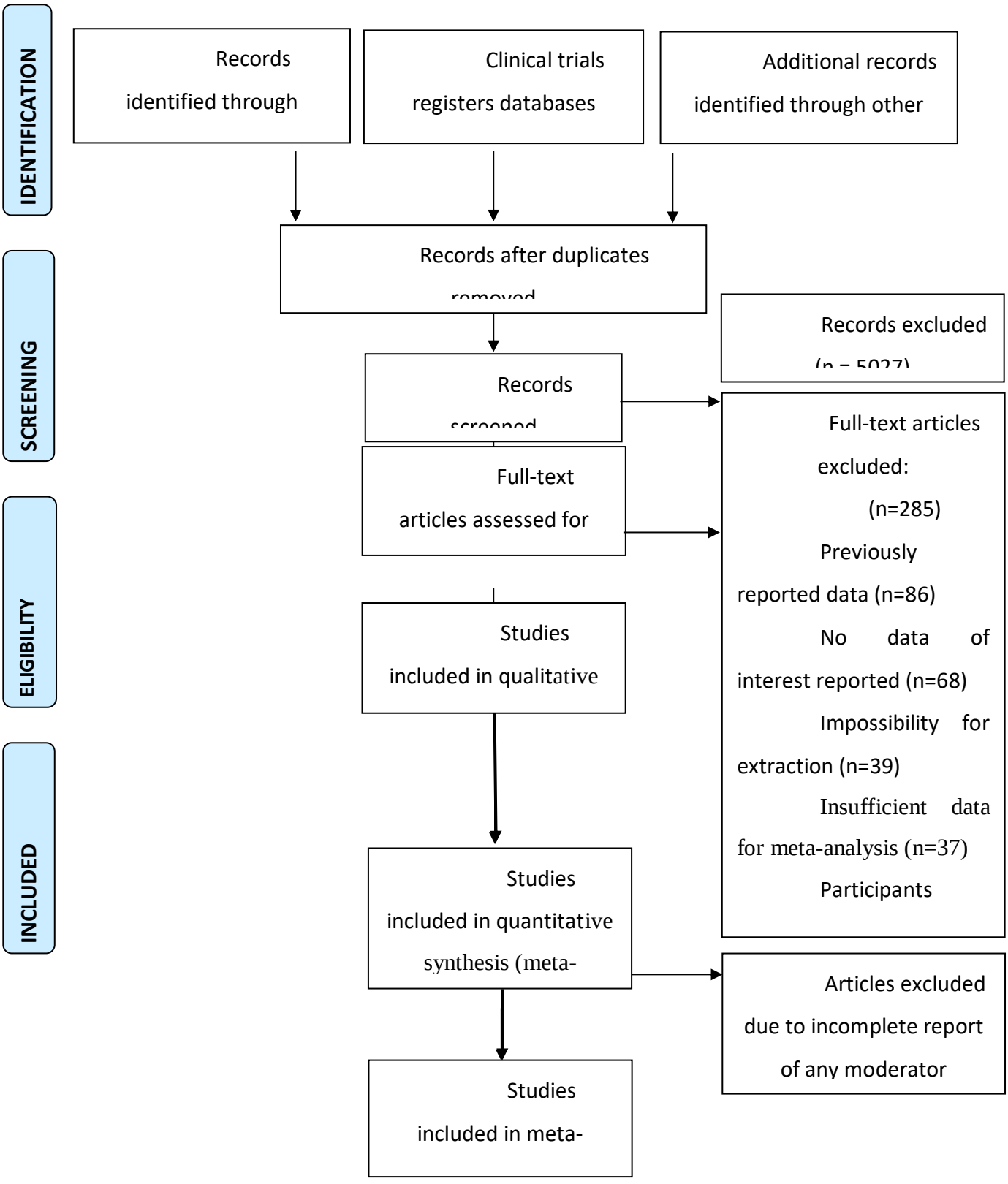
S1Text A: Search terms

(anxi* OR GAD OR phobi* OR “social anxiety” OR panic* OR obsessi* OR compulsi* OR traumatic* OR posttrauma* OR post-trauma* OR "post trauma*” OR "combat disorder*" OR "stress disorder*" OR OCD OR ptsd) AND ("selective serotonin reuptake" OR “selective serotonin re-uptake inhibitors” OR “serotonin-specific reuptake inhibitors” OR ssri OR fluoxetine OR fluvoxamine OR sertraline OR paroxetine OR citalopram OR escitalopram OR dapoxetine OR “serotonin-norepinephrine reuptake" OR SNRI* OR venlafaxine OR desvenlafaxine OR duloxetine OR milnacipran OR Levomilnacipran) AND ((randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] OR randomised[Title/Abstract]) AND controlled[Title/Abstract] AND trial[Title/Abstract]) OR (meta-analysis OR metaanalysis OR "systematic review" OR metaanalyses OR meta-analyses OR "systematic-review"))

S1Text B: Three-level model description

```
model1<-rma.mv(yi=yi,
    V=V,
    data=data,
    random = list(~instrument|study, ~medication|study),
    slab=paste(author, instrument, sep=", "))
```

S1Fig. A: Flowchart of included and excluded studies



S1Table B: Standardized mean change from baseline to endpoint for placebo, medication class and medications within the same class for primary outcome (aggregate measure of mental health related symptoms) retrieved from the included studies

Intervention	o/k (n)	Estimated SMC (95%CI)	SE	p value	τ^2	Heterogeneity I^2 (%)
Placebo	469/135 (12 474)	-1.11 (-1.22 to -1.00)	0.06	<.001	0.531	94.65
SSRIs and SNRIs	469/135 (17 763)	-1.70 (-1.83 to -1.57)	0.07	<.001	0.507	89.20
SSRIs	396/111 (12 923)	-1.65 (-1.79 to -1.50)	0.07	<.001	0.551	95.07
Fluoxetine	64/16 (1168)	-1.56 (-1.91 to -1.20)	0.18	<.001	1.01	96.17
Sertraline	98/25 (2218)	-1.53 (-1.86 to -1.19)	0.17	<.001	0.926	96.94
Paroxetine	132/36 (5122)	-1.71 (-1.96 to -1.46)	0.13	<.001	0.680	96.73
Fluvoxamine	50/19 (1067)	-1.33 (-1.55 to -1.11)	0.11	<.001	0.437	91.34
Citalopram	19/6 (1113)	-1.80 (-2.34 to -1.26)	0.28	<.001	0.632	95.21
Escitalopram	33/13 (2135)	-2.33 (-2.80 to -1.86)	0.24	<.001	0.900	97.18
SNRIs	77/29 (4848)	-1.87 (-2.13 to -1.60)	0.14	<.001	0.745	96.87
Venlafaxine	56/22 (3358)	-1.78 (-2.07 to -1.48)	0.15	<.001	0.829	97.13
Duloxetine	19/8 (1460)	-2.15 (-2.69 to -1.62)	0.27	<.001	0.736	97.15
Desvenlafaxine	2/1 (30)	-1.62 (-2.40 to -0.85)	0.39	<.001	0.342	77.31

k, number of studies; n, sample size; o, number of outcomes; SMC, standardized mean change; SE, standard error; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors

S1Table C: Direct and indirect standardized mean differences between available head-to-head medications comparisons for the primary outcome (aggregate measure of mental health related symptoms)

Medication comparison	Number of trials	Direct SMD (95%CI)	p value	Indirect SMD (95%CI)	p value
Sertraline vs citalopram	1	-0.18 (-0.92 to 0.56)	0.63	-0.28 (-0.18 to 0.74)	0.23
Paroxetine vs escitalopram	2	-0.23 (-0.54 to 0.08)	0.14	0.01 (-0.20 to 0.22)	0.11
Paroxetine vs venlafaxine	3	0.17 (-0.10 to 0.43)	0.21	-0.07 (-0.27 to 0.13)	0.10
Citalopram vs escitalopram	1	-0.12 (-0.30 to 0.06)	0.20	-0.28 (-0.70 to 0.14)	0.21
Venlafaxine vs duloxetine	2	0.20 (-0.06 to 0.46)	0.13	0.01 (-0.23 to 0.25)	0.12

SMD, standardized mean difference; CI, confidence interval

S1Table D: Univariate meta-regression according to medication versus placebo for each symptomatic domain in included studies

		o/k (n)	Estimated SMD (95%CI)	SE	p value	Test of moderators (QM)	p value	Test for residual heterogeneity (QE)	p value
GAD	Fluoxetine	15/8 (900)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Sertraline	16/10 (1196)	0.16 (-0.21 to 0.53)	0.19	0.40	10.3253	0.24	263.8103	<.001
	Paroxetine	27/11 (2102)	-0.01 (-0.36 to 0.35)	0.18	0.98				
	Fluvoxamine	12/9 (333)	-0.44 (-0.86 to -0.02)	0.22	**0.04**				
	Citalopram	5/3 (417)	0.08 (-0.43 to 0.59)	0.26	0.76				
	Escitalopram	15/10 (1330)	-0.11 (-0.48 to 0.27)	0.19	0.57				
	Venlafaxine	21/13 (1645)	-0.10 (-0.45 to 0.26)	0.18	0.60				
	Duloxetine	18/8 (1460)	-0.06 (-0.43 to 0.30)	0.19	0.74				
	Desvenlafaxine	1/1 (30)	-0.11 (-1.08 to 0.85)	0.49	0.82				

		o/k (n)	Estimated SMD (95%CI)	SE	p value	Test of moderators (QM)	p value	Test for residual heterogeneity (QE)	p value
Social Anxiety	Fluoxetine	2/1 (57)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Sertraline	9/3 (352)	-0.30 (-0.85 to 0.25)	0.28	0.29	5.7650	0.45	52.4378	0.38
	Paroxetine	24/12 (1312)	-0.27 (-0.77 to 0.24)	0.26	0.30				
	Fluvoxamine	8/5 (527)	-0.26 (-0.79 to 0.28)	0.27	0.34				
	Escitalopram	3/2 (573)	0.05 (-0.53 to 0.62)	0.29	0.87				
	Venlafaxine	10/6 (919)	-0.33 (-0.85 to 0.19)	0.26	0.21				
	Desvenlafaxine	1/1 (30)	-0.10 (-1.19 to 0.99)	0.56	0.86				
OCD	Fluoxetine	17/5 (269)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Sertraline	15/5 (414)	0.05 (-0.26 to 0.36)	0.16	0.75	8.2625	0.14	72.4962	0.08
	Paroxetine	13/6 (854)	-0.11 (-0.41 to 0.19)	0.15	0.47				
	Fluvoxamine	8/5 (299)	-0.21 (-0.55 to 0.12)	0.17	0.21				
	Citalopram	6/1 (390)	-0.33 (-0.77 to 0.10)	0.22	0.13				
	Escitalopram	4/1 (232)	-0.47 (-0.93 to 0.001)	0.24	0.05				

		o/k (n)	Estimated SMD (95%CI)	SE	p value	Test of moderators (QM)	p value	Test for residual heterogeneity (QE)	p value
Panic	Fluoxetine	4/2 (255)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Sertraline	16/4 (404)	0.08 (-0.31 to 0.48)	0.20	0.68	2.3882	0.88	72.3849	0.01
	Paroxetine	18/4 (842)	0.02 (-0.37 to 0.41)	0.20	0.91				
	Fluvoxamine	8/4 (184)	-0.07 (-0.49 to 0.34)	0.21	0.72				
	Citalopram	2/1 (119)	0.06 (-0.47 to 0.59)	0.27	0.83				
	Escitalopram	2/1 (128)	-0.02 (-0.55 to 0.52)	0.27	0.95				
	Venlafaxine	5/3 (504)	-0.17 (-0.66 to 0.33)	0.25	0.51				
Specific Phobias	Paroxetine	9/3 (691)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Sertraline	1/1 (6)	-0.24 (-1.75 to 1.26)	0.77	0.75	19.1619	<.001	95.3315	<.001
	Fluvoxamine	2/2 (40)	-0.23 (-0.97 to 0.50)	0.37	0.53				
	Citalopram	3/1 (281)	-1.06 (-1.61 to -0.52)	0.28	<.001				
	Venlafaxine	8/4 (527)	0.13 (-0.13 to 0.39)	0.13	0.33				

		o/k (n)	Estimated SMD (95%CI)	SE	p value	Test of moderators (QM)	p value	Test for residual heterogeneity (QE)	p value
PTSD	Fluoxetine	15/5 (496)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Sertraline	19/8 (464)	0.23 (-0.33 to 0.78)	0.33	0.48	2.0467	0.73	113.9119	<.001
	Paroxetine	12/6 567)	-0.14 (-0.71 to 0.54)	0.36	0.69				
	Citalopram	2/1 (25)	0.76 (-0.93 to 2.45)	0.91	0.41				
	Venlafaxine	1/1 (161)	-0.17 (-1.21 to 0.86)	0.63	0.79				

k, number of studies; n, sample size; o, number of outcomes; SMD, standardized mean difference; SE, standard error; QM, Cochran's Q test of moderators; QE, Cochran's Q test for residual heterogeneity; GAD, generalized anxiety disorder; PTSD, post-traumatic stress disorder; OCD, obsessive-compulsive disorder

S1Table E: Univariate meta-regressions for the primary outcome (aggregate measure of mental health related symptoms) comparing medication versus placebo

		o/k (n)	Estimated SMD (95%CI)	SE	p value	Test of moderators (QM)	p value	Test for residual heterogeneity (QE)	p value
Medication class	SSRI	284/75 (16 151)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	SNRI	62/23 (6893)	0.06 (-0.08 to 0.19)	0.07	0.40	0.7067	0.40	823.1743	<.001
Medication	Fluoxetine	61/15 (1609)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Sertraline	86/21 (3231)	0.16 (-0.06 to 0.37)	0.11	0.16	10.0751	0.18	794.6615	<.001
	Paroxetine	72/21 (6527)	-0.11 (-0.32 to 0.10)	0.11	0.30				
	Fluvoxamine	33/12 (1733)	-0.05 (-0.30 to 0.20)	0.13	0.69				
	Citalopram	12/3 (699)	0.03 (-0.31 to 0.36)	0.17	0.87				
	Escitalopram	20/7 (2352)	-0.09 (-0.35 to 0.18)	0.14	0.53				
	Venlafaxine	48/19 (5116)	0.04 (-0.18 to 0.25)	0.11	0.73				
	Duloxetine	14/6 (1777)	0.03 (-0.25 to 0.32)	0.14	0.81				

		o/k (n)	Estimated SMD (95%CI)	SE	p value	Test of moderators (QM)	p value	Test for residual heterogeneity (QE)	p value
Comparator	Head-to-head	40/12 (4503)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Different dose	98/14 (5152)	-0.03 (-0.28 to 0.22)	0.13	0.81	0.0771	0.96	822.8887	<.001
	Placebo	208/68 (13 389)	-0.03 (-0.24 to 0.18)	0.11	0.79				
Equivalent dose	1 – 1.99	120/44 (9011)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	2 – 2.99	146/47 (9520)	0.05 (-0.04 to 0.10)	0.05	0.27	3.5660	0.31	753.2485	<.001
	3 – 3.99	52/19 (3137)	0.08 (-0.06 to 0.22)	0.07	0.26				
	>= 4	28/11 (1376)	-0.08 (-0.26 to 0.10)	0.09	0.40				

		o/k (n)	Estimated SMD (95%CI)	SE	p value	Test of moderators (QM)	p value	Test for residual heterogeneity (QE)	p value
Main diagnosis	GAD	59/21 (6916)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Social anxiety	58/20 (5719)	-0.02 (-0.19 to 0.15)	0.09	0.82	20.0673	**0.001**	656.2081	<.001
	Panic	93/17 (4430)	0.31 (0.13 to 0.48)	0.09	**<.001**				
	PTSD	104/17 (3030)	0.23 (0.04 to 0.41)	0.10	**0.02**				
	OCD	9/2 (95)	0.11 (-0.08 to 0.29)	0.09	0.26				
	More than 1 diagnosis	57/21 (6916)	-0.05 (-0.63 to 0.52)	0.29	0.86				
Time to outcome	12-14 weeks	159/44 (12 061)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	6-8 weeks	64/20 (4107)	0.02 (-0.15 to 0.18)	0.08	0.84	9.4382	0.09	720.8498	<.001
	9-11 weeks	110/28 (6021)	0.17 (0.03 to 0.31)	0.07	**0.02**				
	15-17 weeks	4/1 (322)	-0.29 (-0.79 to 0.22)	0.26	0.27				
	18-20 weeks	6/1 (204)	-0.28 (-0.78 to 0.22)	0.26	0.27				
	21-26 weeks	3/1 (329)	0.07 (-0.48 to 0.62)	0.28	0.81				

		o/k (n)	Estimated SMD (95%CI)	SE	p value	Test of moderators (QM)	p value	Test for residual heterogeneity (QE)	p value
Sample age	Adults/Elderly	306/80 (21 193)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Children/Adolescents	40/14 (1851)	-0.04 (-0.23 to 0.16)	0.10	0.71	0.1385	0.71	816.4079	<.001
Sampling	Outpatients	247/70 (17 651)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Community	10/5 (701)	-0.21 (-0.55 to 0.13)	0.17	0.22	1.5568	0.67	799.3650	<.001
	Mixed	11/4 (877)	-0.04 (-0.34 to 0.26)	0.15	0.81				
	Unclear	78/15 (3815)	0.00 (-0.17 to 0.18)	0.09	0.95				
Benzodiazepine use	No	184/51 (15 040)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Yes	58/11 (1598)	0.13 (-0.07 to 0.34)	0.10	0.21	5.7484	0.12	801.4178	<.001
	Not informed	99/30 (5869)	-0.12 (-0.26 to 0.02)	0.07	0.10				
	Unclear	5/2 (537)	0.07 (-0.36 to 0.51)	0.22	0.74				

	o/k (n)	Estimated SMD (95%CI)	SE	p value	Test of moderators (QM)	p value	Test for residual heterogeneity (QE)	p value
Placebo lead-in No	105/35 (6492)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
Yes	200/43 (13 336)	0.05 (-0.09 to 0.19)	0.07	0.47	3.3673	0.34	799.5166	<.001
Not informed	34/14 (2666)	-0.14 (-0.36 to 0.08)	0.11	0.21				
Unclear	7/2 (550)	0.03 (-0.37 to 0.42)	0.20	0.89				
Publication year	346/94 (23 044)	0.01 (-0.01 to 0.02)	0.01	0.37	0.7890	0.37	818.0060	<.001
Analysis Mix/Hierarchic/Random	22/5 (856)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
LOCF	291/78 (21 478)	-0.33 (-0.58 to -0.07)	0.13	**0.01**	9.2512	**0.03**	774.5552	<.001
Completers	4/2 (65)	0.05 (-0.60 to 0.70)	0.33	0.87				
Unclear	29/9 (645)	-0.47 (-0.83 to -0.12)	0.18	**0.009**				

		o/k (n)	Estimated SMD (95%CI)	SE	p value	Test of moderators (QM)	p value	Test for residual heterogeneity (QE)	p value
Funding	Academic	17/8 (415)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Governmental or non-profit	21/7 (366)	0.24 (-0.17 to 0.65)	0.21	0.26	4.1129	0.25	812.6459	<.001
	Industry	273/71 (20 460)	0.30 (0.003 to 0.60)	0.15	**0.047**				
	Unclear	35/8 (1803)	0.32 (-0.04 to 0.67)	0.18	0.08				

o, number of outcomes; k, number of studies; n, sample size; SMD, standardized mean difference; SE, standard error; QM, Cochran's Q test of moderators; QE, Cochran's Q test for residual heterogeneity; SSRI, Selective Serotonin Reuptake Inhibitor; SNRI, Serotonin and Norepinephrine Reuptake Inhibitor; GAD, generalized anxiety disorder; PTSD, post-traumatic stress disorder; OCD, obsessive-compulsive disorder; LOCF, last observation carried forward

S1Table F: Multiple meta-regression for primary outcome (aggregate measure of mental health related symptoms) comparing medication versus placebo

		o/k (n)	Estimated SMD (95%CI)	SE	p value	Test of moderators (QM)	p value
Publication year		346/94 (23 044)	0.03 (0.01 to 0.05)	0.01	**0.002**	9.7947	**0.002**
Medication	Fluoxetine	61/15 (1609)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Sertraline	86/21 (3231)	0.17 (-0.14 to 0.47)	0.16	0.29	8.5882	0.28
	Paroxetine	72/21 (6527)	-0.14 (-0.41 to 0.13)	0.14	0.31		
	Fluvoxamine	33/12 (1733)	0.05 (-0.28 to 0.38)	0.17	0.77		
	Citalopram	12/3 (699)	-0.07 (-0.43 to 0.30)	0.19	0.72		
	Escitalopram	20/7 (2352)	-0.14 (-0.47 to 0.20)	0.17	0.42		
	Venlafaxine	48/19 (5116)	-0.03 (-0.33 to 0.28)	0.16	0.87		
	Duloxetine	14/6 (1777)	-0.03 (-0.45 to 0.38)	0.21	0.87		
Comparator	Head-to-head	40/12 (4503)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Different dose	98/14 (5152)	0.05 (-0.19 to 0.29)	0.12	0.67	1.3188	0.52
	Placebo	208/68 (13 389)	-0.05 (-0.27 to 0.18)	0.11	0.69		

		o/k (n)	Estimated SMD (95%CI)	SE	p value	Test of moderators (QM)	p value
Equivalent dose	1 – 1.99	120/44 (9011)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	2 – 2.99	146/47 (9520)	-0.04 (-0.15 to 0.07)	0.06	0.49	1.2131	0.75
	3 – 3.99	52/19 (3137)	0.00 (-0.16 to 0.16)	0.08	0.99		
	>= 4	28/11 (1376)	-0.10 (-0.33 to 0.12)	0.11	0.37		
Time to outcome weeks	12-14	159/44 (12 061)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	6-8 weeks	64/20 (4107)	0.39 (0.16 to 0.63)	0.12	**<.001**	18.3588	**0.002**
	9-11 weeks	110/28 (6021)	0.31 (0.14 to 0.49)	0.09	**<.001**		
	15-17 weeks	4/1 (322)	-0.02 (-0.51 to 0.47)	0.25	0.93		
	18-20 weeks	6/1 (204)	-0.33 (-0.77 to 0.11)	0.22	0.14		
	21-26 weeks	3/1 (329)	-0.21 (-1.15 to 0.73)	0.48	0.66		

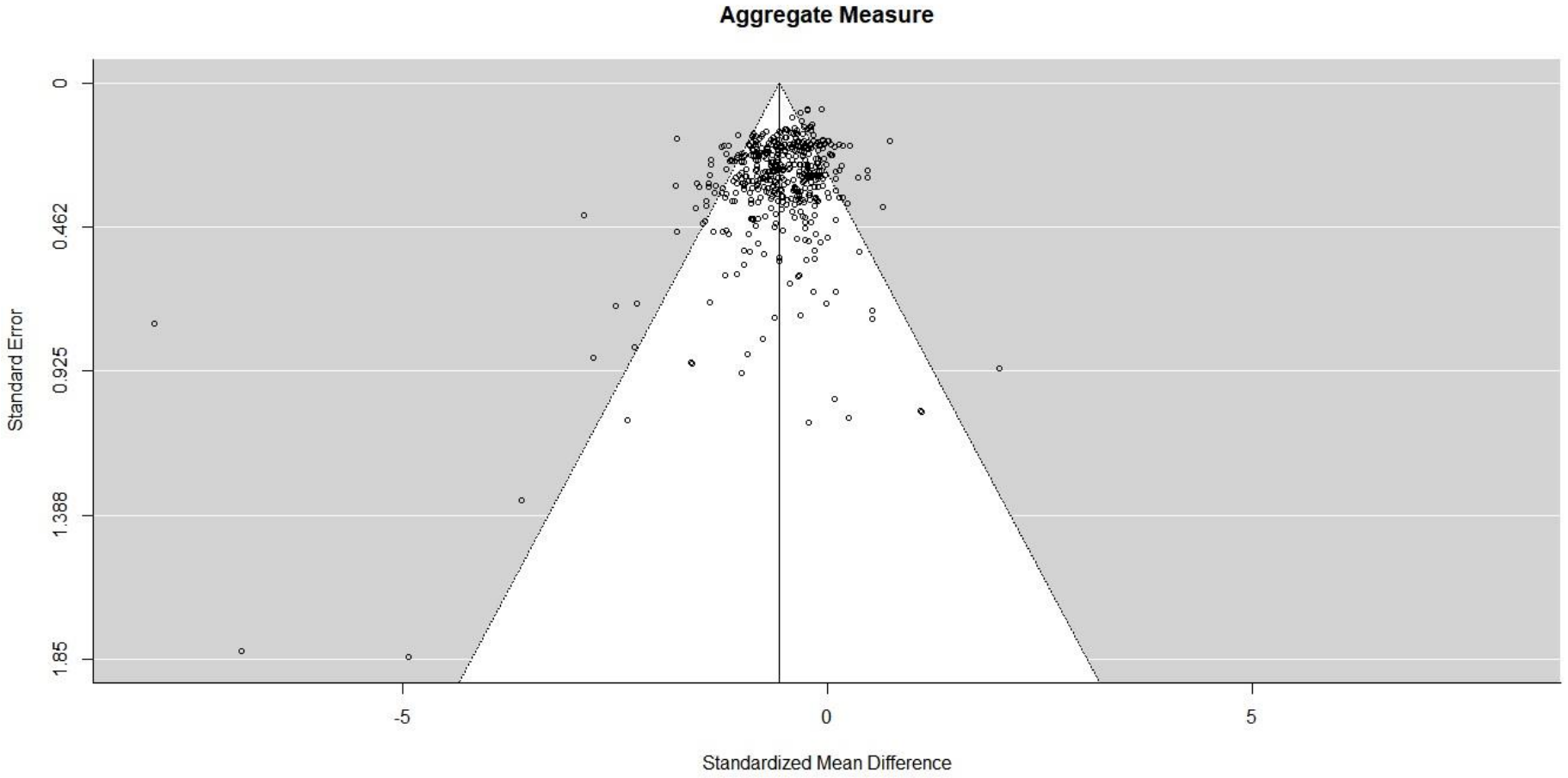
		o/k (n)	Estimated SMD (95%CI)	SE	p value	Test of moderators (QM)	p value
Main diagnosis	GAD	59/21 (6916)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Social anxiety	58/20 (5719)	0.32 (0.07 to 0.56)	0.13	**0.01**	17.0862	**0.004**
	Panic	93/17 (4430)	0.42 (0.20 to 0.64)	0.11	**<.001**		
	PTSD	135/17 (2854)	0.46 (0.21 to 0.72)	0.13	**<.001**		
	OCD	104/17 (3030)	0.40 (0.11 to 0.69)	0.15	**0.006**		
	More than 1 diagnosis	9/2 (95)	0.84 (0.01 to 1.68)	0.42	**0.047**		
Sampling	Outpatients	247/70 (17 651)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Community	10/5 (701)	0.03 (-0.29 to 0.35)	0.16	0.87	1.5610	0.67
	Mixed	11/4 (877)	0.13 (-0.17 to 0.42)	0.15	0.41		
	Unclear	78/15 (3815)	-0.09 (-0.29 to 0.11)	0.10	0.38		
Sample age	Adults/Elderly	306/80 (21 193)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Children/Adolescents	40/14 (1851)	-0.08 (-0.32 to 0.16)	0.12	0.50	0.4525	0.50

		o/k (n)	Estimated SMD (95%CI)	SE	p value	Test of moderators (QM)	p value
Benzodiazepine use	No	184/51 (15 040)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Yes	58/11 (1598)	0.04 (-0.16 to 0.25)	0.11	0.67	0.8825	0.83
	Not informed	99/30 (5869)	-0.03 (-0.19 to 0.13)	0.08	0.74		
	Unclear	5/2 (537)	0.28 (-0.47 to 1.02)	0.38	0.46		
Placebo lead-in	No	105/35 (6492)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	Yes	200/43 (13 336)	0.03 (-0.15 to 0.22)	0.09	0.72	2.2593	0.52
	Not informed	34/14 (2666)	-0.13 (-0.37 to 0.10)	0.12	0.27		
	Unclear	7/2 (550)	0.18 (-0.20 to 0.55)	0.19	0.35		
Analysis	Mixed/Hierarchical/Random	22/5 (856)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
	LOCF	291/78 (21 478)	-0.16 (-0.42 to 0.11)	0.14	0.25	3.5848	0.31
	Completers	4/2 (65)	0.29 (-0.39 to 0.97)	0.35	0.40		
	Unclear	29/9 (645)	0.01 (-0.42 to 0.44)	0.22	0.97		

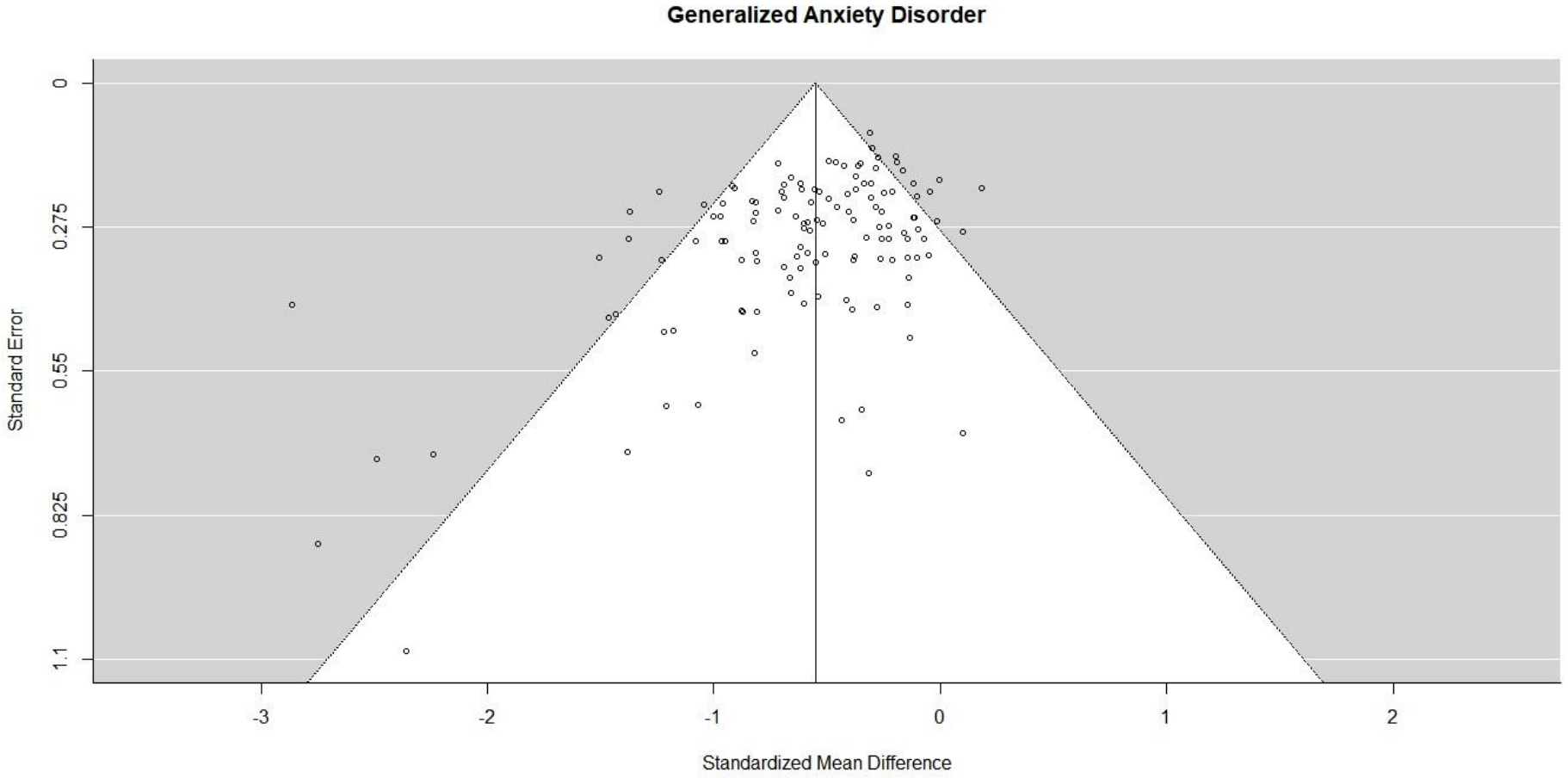
	o/k (n)	Estimated SMD (95%CI)	SE	p value	Test of moderators (QM)	p value
Funding Academic	17/8 (415)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
Governmental or non-profit	21/7 (366)	0.54 (0.05 to 1.04)	0.25	**0.03**	8.7110	**0.03**
Industry	273/71 (20 460)	0.61 (0.20 to 1.02)	0.21	**0.003**		
Unclear	35/8 (1803)	0.56 (0.10 to 1.02)	0.23	**0.01**		

o, number of outcomes; k, number of studies; n, sample size; SMD, standardized mean difference; SE, standard error; QM, Cochran's Q test of moderators; GAD, generalized anxiety disorder; PTSD, post-traumatic stress disorder; OCD, obsessive-compulsive disorder; LOCF, last observation carried forward; QE, Cochran's Q test for residual heterogeneity; test of moderators of the multiple meta-regression model [QM]=98.1922, p value<.001; test for residual heterogeneity of the multiple meta-regression model [QE]=454.9043, p value<.001

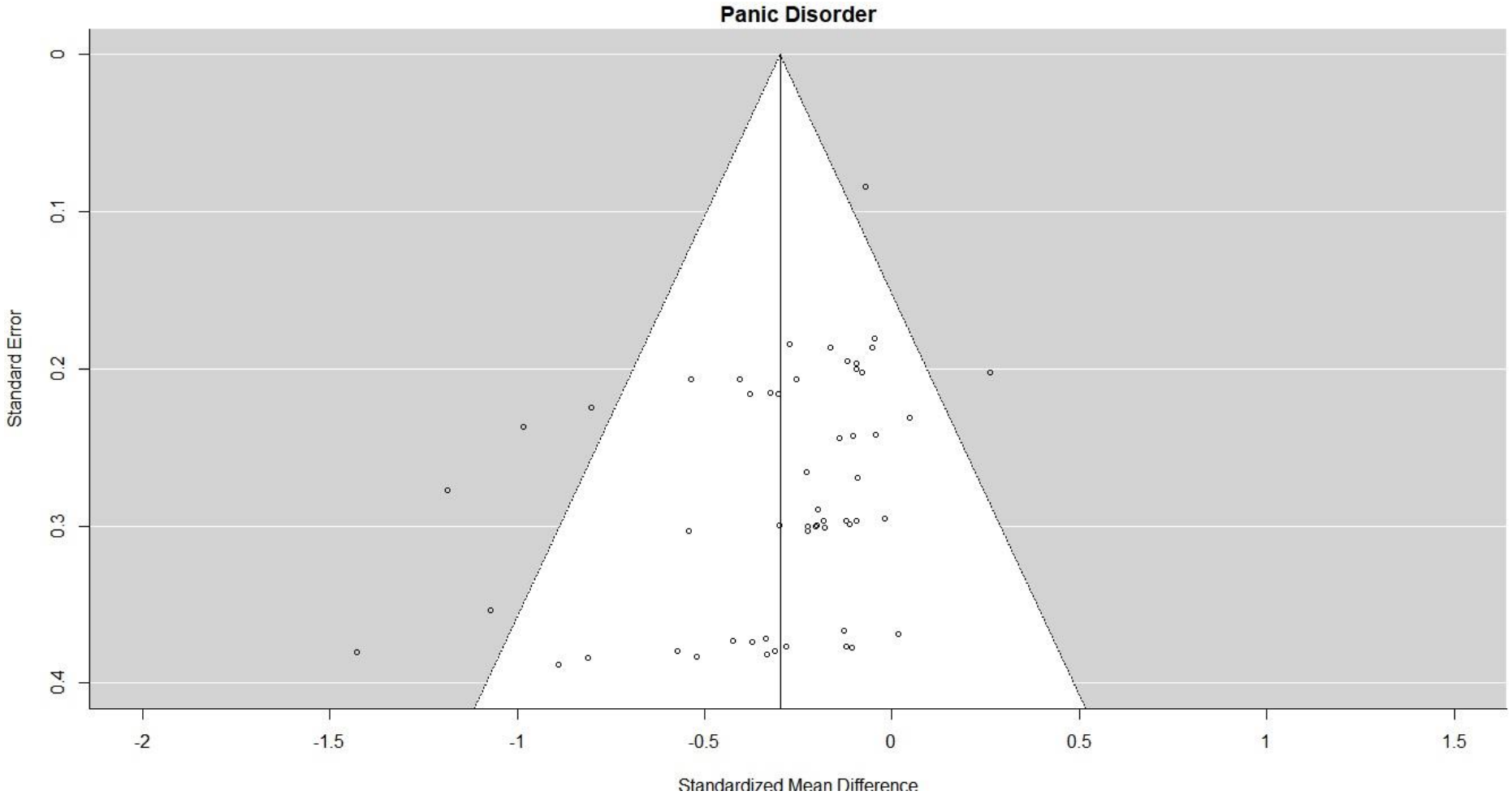
S1 Fig. B: Funnel plot for all internalizing symptoms



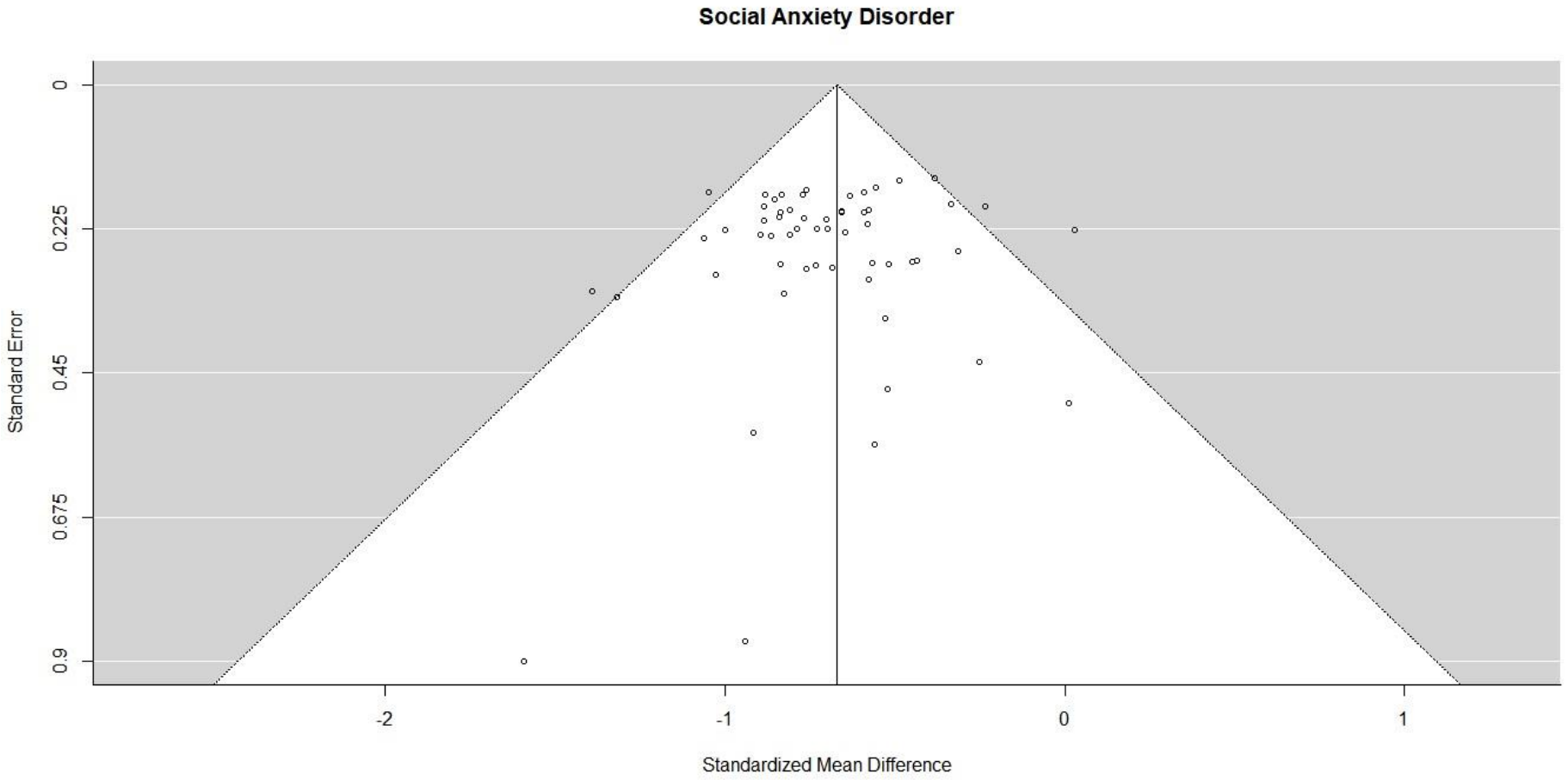
S1 Fig. C: Funnel plot for the generalized anxiety disorder domain



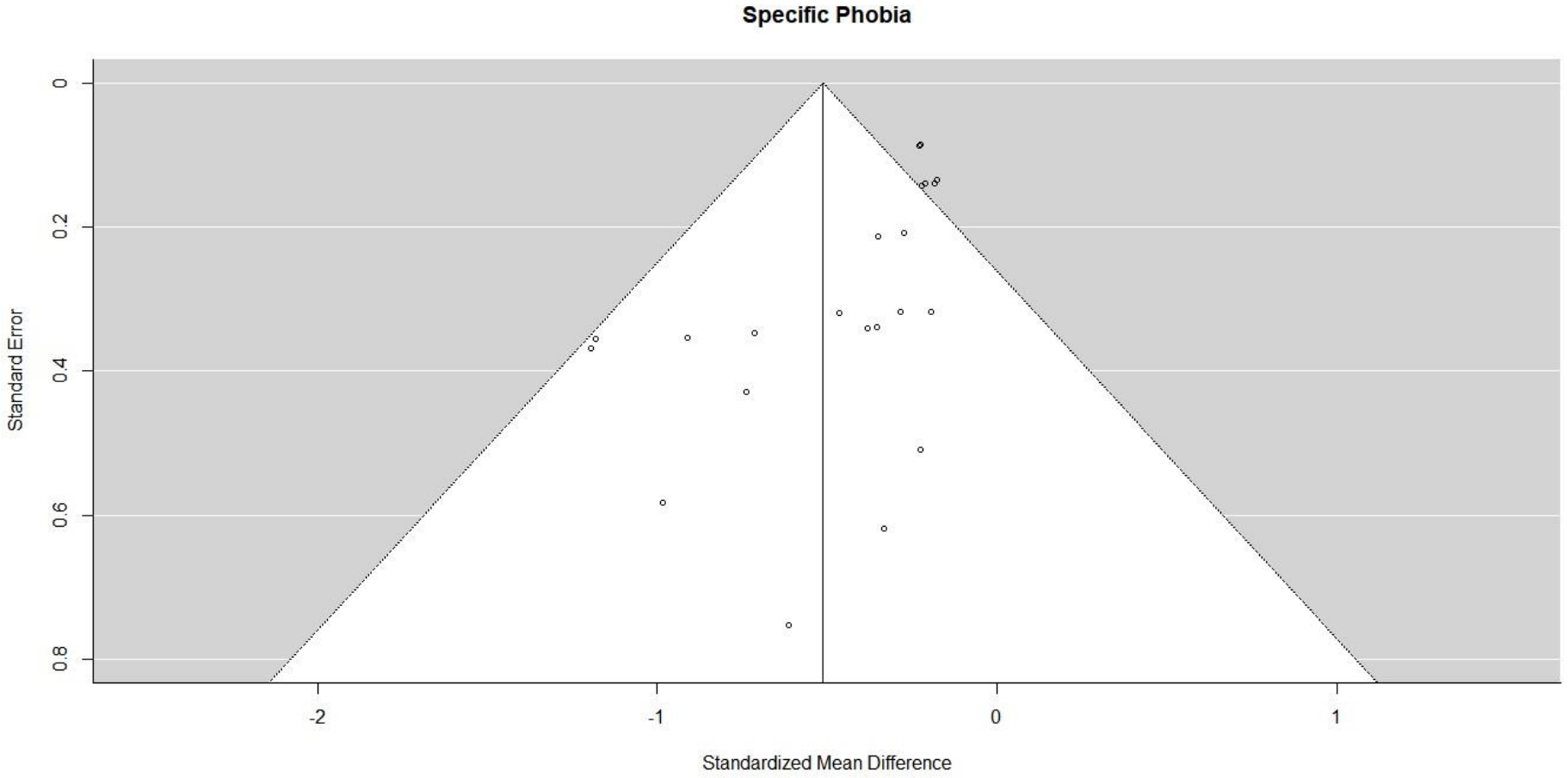
S1 Fig. D: Funnel plot for the panic disorder



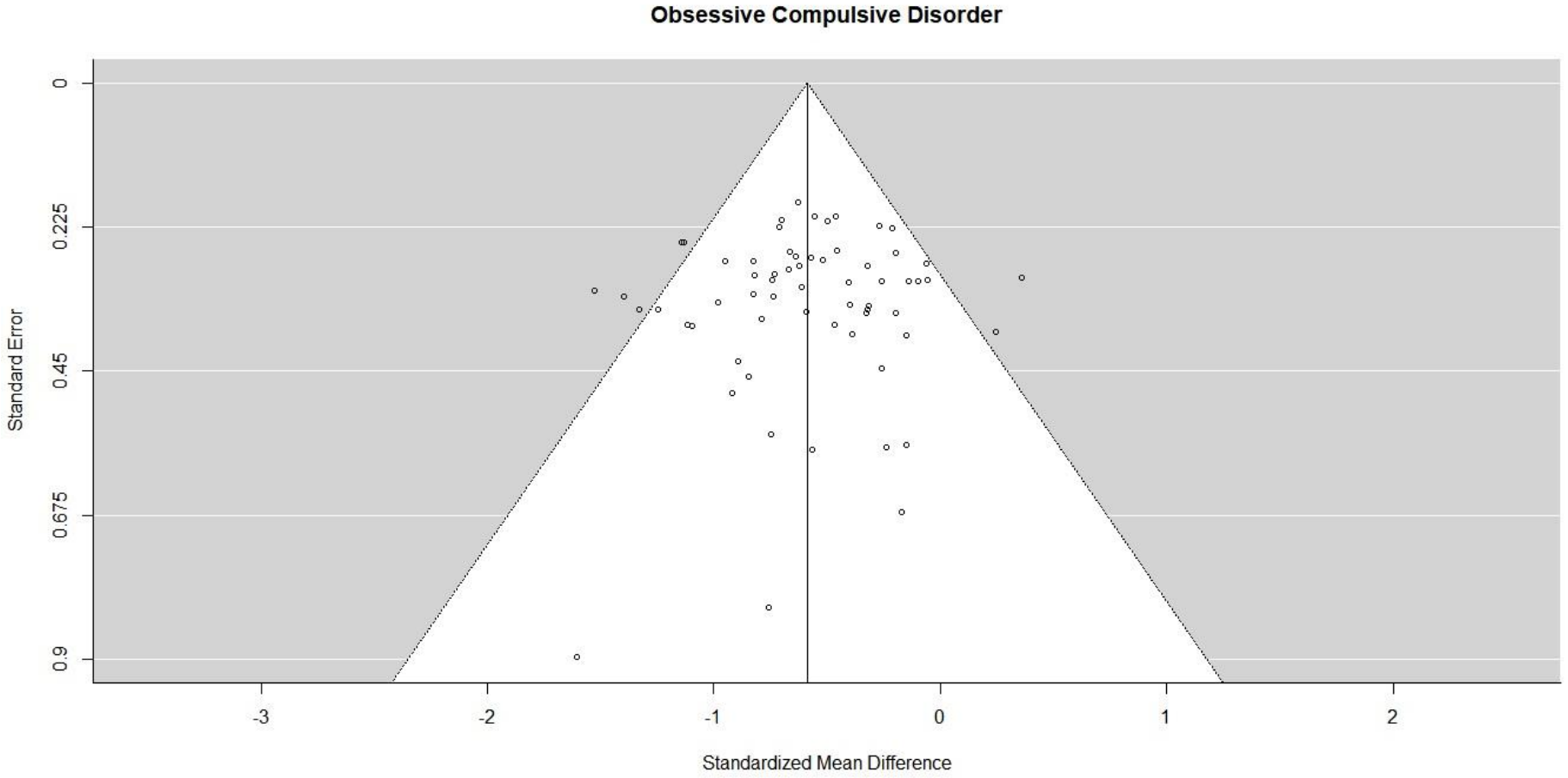
S1 Fig. E: Funnel plot for the social anxiety disorder



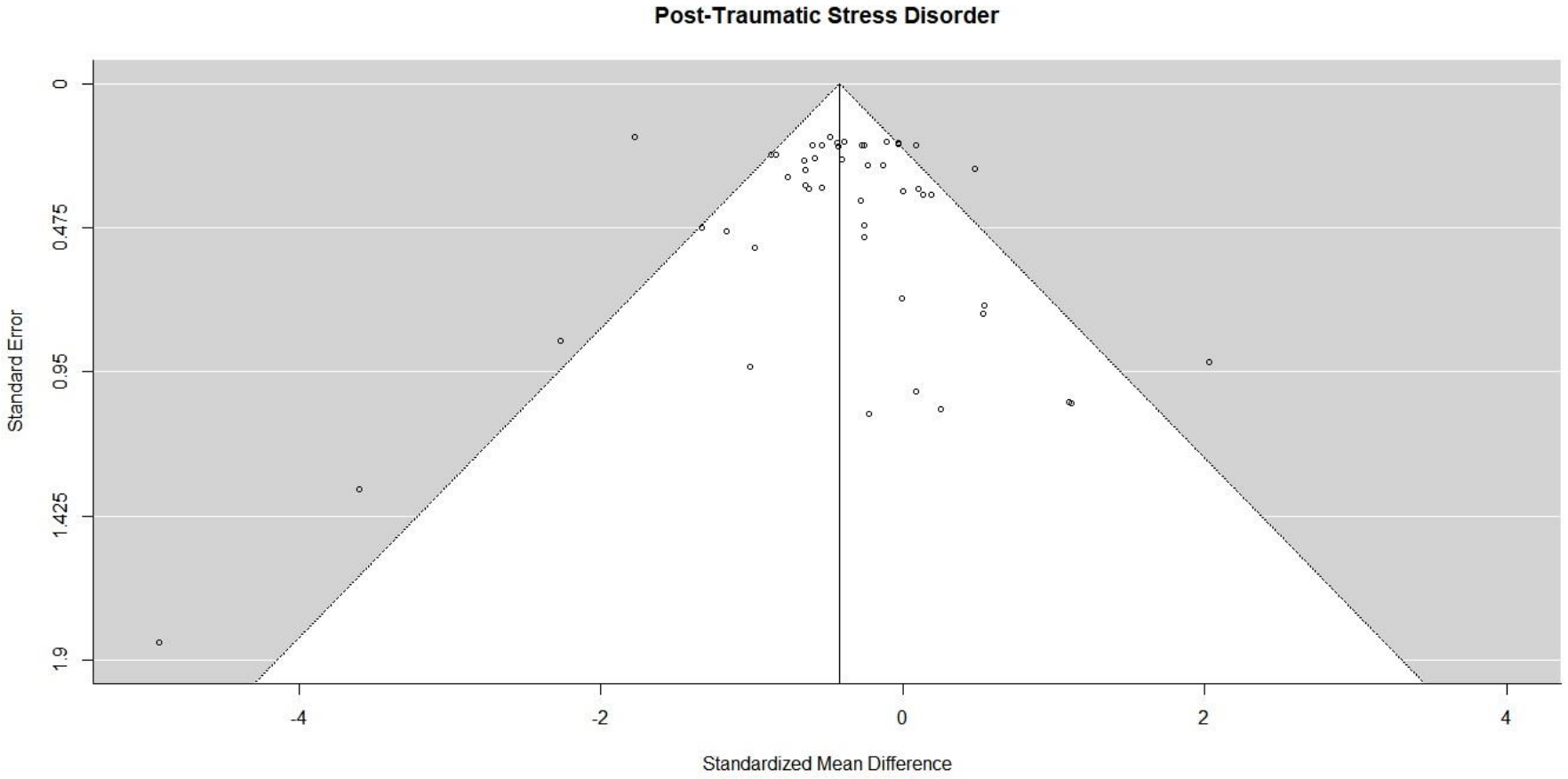
S1 Fig. F: Funnel plot for the specific phobia



S1 Fig. G: Funnel plot for the obsessive compulsive disorder



S1 Fig. H: Funnel plot for the post. Traumatic stress disorder



S2 Appendix. PROSPERO registration and review protocol

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) and placebo for anxiety, obsessive-compulsive and stress-related disorders: a systematic review and multilevel meta-analysis over the lifespan

22 words remaining

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

50 words remaining

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

01/03/2016

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

28/02/2018

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	No

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Professor Salum

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

7. * Named contact email.

Give the electronic mail address of the named contact.
gsalumjr@gmail.com

8. Named contact address

Give the full postal address for the named contact.
R. Ramiro Barcelos, 2350 (Centro de Pesquisa Clínica) - Santa Cecilia, Porto Alegre - RS, 90035-903, Brasil.

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.
Federal University of Rio Grande do Sul

Organisation web address:

www.ufrgs.br

11. Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Professor Giovanni Abrahão Salum. Federal University of Rio Grande do Sul
Dr Natan Pereira Gosmann. Federal University of Rio Grande do Sul
Dr Marianna de Abreu Costa. Federal University of Rio Grande do Sul
Dr Marianna de Barros Jaeger. Federal University of Rio Grande do Sul
Dr Júlia Frozi. Pontifical Catholic University of Rio Grande do Sul

Dr Luis Sousa Motta. Pontifical Catholic University of Rio Grande do Sul
Professor Lucas Spanemberg. Pontifical Catholic University of Rio Grande do Sul
Professor Daniel Samuel Pine. National Institute of Mental Health

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

None

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

Do studies including patients with anxiety, obsessive and stress-related disorders receiving all types of SSRIs/SNRIs if compared to a comparison medication (e.g., Fluoxetine) show differences in efficacy regarding levels of overall symptoms?
Do studies including patients with anxiety, obsessive and stress-related disorders receiving all types of SSRIs/SNRIs if compared to a comparison medication (e.g. Fluoxetine) show differences in levels of side effects?
Do studies including patients with anxiety, obsessive and stress-related disorders receiving SNRI if compared to SSRIs show differences in efficacy regarding levels of overall symptoms?
Do studies including patients with anxiety, obsessive and stress-related disorders being treated with either SSRIs and SNRIs or placebo higher than 18 years of age if compared to those lower than 18 years of age show differences in efficacy regarding levels of overall symptoms?
Do studies including patients with anxiety, obsessive and stress-related disorders being treated with either SSRIs and SNRIs or placebo with high industry influence if compared to those with low industry influence show differences in efficacy regarding levels of overall symptoms?
Do studies including patients with anxiety, obsessive and stress-related disorders being treated with either SSRIs and SNRIs or placebo with a diagnosis of distress disorders, i.e., PTSD, GAD if compared to fear disorders, i.e., Panic, Phobias, and OCD, show differences in efficacy regarding levels of overall symptoms?
Do studies including patients with anxiety, obsessive and stress-related disorders being treated with either SSRIs and SNRIs or placebo with a diagnosis of Panic, OCD, PTSD, Phobias if compared to GAD show differences in efficacy regarding levels of overall symptoms?
Do studies including patients with anxiety, obsessive and stress-related disorders being treated with either SSRIs and SNRIs or placebo with high levels of comorbidity with Major Depression if compared to those with low levels of comorbidity with Major Depression show differences in efficacy regarding levels of overall symptoms?
Do studies including patients with anxiety, obsessive and stress-related disorders being treated with either SSRIs and SNRIs or placebo show difference in efficacy regarding levels of symptoms from the fear domain versus symptoms from the distress domain?
Do studies including patients with anxiety, obsessive and stress-related disorders being treated with either SSRIs and SNRIs or placebo show difference in efficacy regarding levels of Social Phobia symptoms, GAD symptoms, Panic symptoms, OCD symptoms, and PTSD symptoms?

Do studies including patients with anxiety, obsessive and stress-related disorders receiving all types of SSRIs/SNRIs if compared to Fluoxetine show differences in time to respond to medication?
148 words over

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
We will search the following electronic bibliographic databases: PubMed, EMBASE, PsycINFO and Cochrane. The search terms will be adapted for use in all databases considered in combination with database-specific filters for controlled trials, where these are available. There will be no language or publication period restrictions. The searches will be re-run just before the final analyses and further studies retrieved for inclusion.
238 words remaining

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
Anxiety, obsessive and stress-related disorders and its symptom dimensions.
191 words remaining

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Patients with an anxiety, obsessive or stress-related disorder diagnosis using any recognised diagnostic criteria.
186 words remaining

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.
Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin–norepinephrine Reuptake Inhibitors (SNRI).
190 words remaining

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.
Selective Serotonin Reuptake Inhibitors (SSRI), Serotonin–norepinephrine Reuptake Inhibitors (SNRI), different doses of these medications or placebo
184 words remaining

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.
Randomized controlled trials of SSRI and SNRI in the treatment of anxiety, obsessive or stress-related disorders.
134 words remaining

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.
250 words remaining

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.
Overall symptoms of anxiety, obsessive or stress-related disorders.
192 words remaining

Timing and effect measures
200 words remaining

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review
Anxiety, obsessive or stress-related disorders remission or partial response rates, side effects profile and dropout rates.
Any mental health related factors.
280 words remaining

Timing and effect measures
300 words remaining

26. Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.
Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by four review authors (all psychiatrists) to identify studies that potentially meet the inclusion criteria. The full text of these potentially eligible studies will be retrieved and independently assessed for eligibility by four review team members (all psychiatrists). Any disagreement between them over the eligibility of particular studies will be resolved through discussion with all review team members.
A standardised, pre-piloted form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: publication data; demographic data; inclusion and exclusion criteria of the study population; diagnostic system; intervention regime; control regime; population comorbidities; potential biases; items related to industry influence; data analysis method; remission and response; adverse effects; dropouts; symptomatic outcomes reported in the study. Four review authors (all psychiatrists) will extract data independently, discrepancies will be identified and resolved through discussion (with all review members team). Missing data will be requested from study authors.
126 words remaining

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.
Four review authors will independently assess the risk of bias in included studies using Cochrane Collaboration's tool for assessing risk of bias.
Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion with all review members team.
156 words remaining

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.
First, we will conduct a multilevel meta-analysis for the primary and secondary outcomes. After, we will conduct meta-regression analyses investigating the role of moderators in the primary outcome.
272 words remaining

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

If the necessary data are available, subgroup analyses by age and diagnosis will be done.

235 words remaining

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
Yes

Methodology
Yes

Narrative synthesis
No

Network meta-analysis
Yes

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
Yes

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health

No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

United States of America
Brazil

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository

(SRDR), details and a link should be included here. If none, leave blank.
50 words remaining

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Anxiety
Selective Serotonin Reuptake Inhibitors
Serotonin–norepinephrine Reuptake Inhibitors
mental health

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.
50 words remaining

38. * Current review status.

Review status should be updated when the review is completed and when it is published.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.

Selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors for anxiety, obsessive-compulsive and stress disorders: a three-level network meta-analysis

S3 Appendix

Contents

S3 Table A: Studies general information

id	PMID / Other ID	Author	Title	Pub. Status	Year of Publication	Funding
JF10	2004379131	Allgulander	Efficacy of venlafaxine ER in patients with social anxiety disorder: A double-blind, placebo-controlled, parallel-group comparison with paroxetine [1]	published	2004	Industry
JF11	1999304629	Allgulander C.	Paroxetine in social anxiety disorder: A randomized placebo-controlled study [2]	published	1999	Industry
JF15	2007092774	Asakura S.	Fluvoxamine treatment of generalized social anxiety disorder in Japan: A randomized double-blind, placebo-controlled study [3]	published	2006	Industry
JF16	11472786	Asnis	Fluvoxamine in the treatment of panic disorder: a multi-center, double-blind, placebo-controlled study in outpatients [4]	published	2001	Industry
JF20	10665629	Bakker	Paroxetine, clomipramine, and cognitive therapy in the treatment of panic disorder [5]	published	1999	academic
JF22	2006434703	Baldwin	Escitalopram and paroxetine in the treatment of generalised anxiety disorder: Randomised, placebo-controlled, double-blind study [6]	published	2006	Industry
JF25	1999268351	Baldwin D.	Paroxetine in social phobia/social anxiety disorder: Randomised, double- blind, placebo-controlled study [7]	published	1999	Industry
JF28	1998025805	Ballenger	Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder [8]	published	1998	Industry
JF29	2010331033	Bandelow	Extended-release quetiapine fumarate (quetiapine XR): A once-daily monotherapy effective in generalized anxiety disorder. Data from a randomized, double-blind, placebo-and active-controlled study [9]	published	2010	Industry
JF3	24644106	Alaka	Efficacy and safety of duloxetine in the treatment of older adult patients with generalized anxiety disorder: a randomized, double-blind, placebo-controlled trial [10]	published	2014	Industry
JF34	2007567996	Beidel D.C.	SET-C versus fluoxetine in the treatment of childhood social phobia [11]	published	2007	Industry
JF42	12649628	Birmaher	Fluoxetine for the treatment of childhood anxiety disorders [12]	published	2003	governmental or non-profit

JF45	8422221	Black	A comparison of fluvoxamine, cognitive therapy, and placebo in the treatment of panic disorder [13]	published	1993	academic
JF56	2005461776	Bradwejn	Venlafaxine extended-release capsules in panic disorder: Flexible-dose, double-blind, placebo-controlled study [14]	published	2005	academic
JF59	2000137979	Brady	Efficacy and safety of sertraline treatment of posttraumatic stress disorder: A randomized controlled trial [15]	published	2000	Unclear
JF61	2006335133	Brawman-Mintzer O.	Sertraline treatment for generalized anxiety disorder: A randomized, double-blind, placebo-controlled study [16]	published	2006	Industry
JF7	2004388355	Allgulander	Efficacy of sertraline in a 12-week trial for generalized anxiety disorder [17]	published	2004	Industry
JF72	2274626	Chouinard	Results of a double-blind placebo controlled trial of a new serotonin uptake inhibitor, sertraline, in the treatment of obsessive-compulsive disorder [18]	published	1990	Industry
JF78	1999231913	Connor K.M.	Fluoxetine in post-traumatic stress disorder. Randomised, double-blind study [19]	published	1999	Unclear
JF80	20455246	Coric	Multicenter, randomized, double-blind, active comparator and placebo-controlled trial of a corticotropin-releasing factor receptor-1 antagonist in generalized anxiety disorder [20]	published	2010	governmental or non-profit
JF82	2013806668	Da Costa	Comparison among clomipramine, fluoxetine, and placebo for the treatment of anxiety disorders in children and adolescents [21]	published	2013	Industry
JF83	15877709	Dahl	Sertraline in generalized anxiety disorder: efficacy in treating the psychic and somatic anxiety factors [22]	published	2005	academic
JF87	1999307984	Davidson	Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder [23]	published	1999	academic
JF88	2004332730	Davidson	Escitalopram in the treatment of generalized anxiety disorder: Double-blind, placebo controlled, flexible-dose study [24]	published	2004	Industry
JF89	15206657	Davidson	Fluvoxamine-controlled release formulation for the treatment of generalized socialanxiety disorder [25]	published	2004	Industry

JF9	17559726	Koponen	Efficacy of Duloxetine for the Treatment of GeneralizedAnxiety Disorder: Implications for Primary Care Physicians [26]	published	2007	Industry
JF94	NA	Asakura S.	A randomized, double-blind, placebo-controlled study of escitalopram in patients with social anxiety disorder in Japan [27]	published	2016	Industry
LM10	1697419	Den Boer	Serotonin function in panic disorder: a double blind placebo controlled study with fluvoxamine and ritanserin [28]	published	1990	Industry
LM23	2011102179	Fani N.	Increased neural response to trauma scripts in posttraumatic stress disorder following paroxetine treatment: A pilot study [29]	published	2011	Industry
LM24	2009487779	Fani N.	Neuropsychological functioning in patients with posttraumatic stress disorder following short-term paroxetine treatment [30]	published	2009	Industry
LM34	2007265412	Friedman M.J.	Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a department of veterans affairs setting [31]	published	2007	Industry
LM37	2000217510	Gelenberg	Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder a 6-month randomized controlled trial [32]	published	2000	Industry
LM39	2001231890	Geller D.A.	Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: A placebo-controlled clinical trial [33]	published	2001	Industry
LM4	2006486251	Davidson J.	Treatment of posttraumatic stress disorder with venlafaxine extended release: A 6-month randomized controlled trial [34]	published	2006	Industry
LM40	2004455208	Geller D.A.	Paroxetine treatment in children and adolescents with obsessive-compulsive disorder: A randomized, multicenter, double-blind, placebo-controlled trial [35]	published	2004	Industry
LM42	2014038390	Gimenez M.	Functional effects of chronic paroxetine versus placebo on the fear, stress and anxiety brain circuit in Social Anxiety Disorder: Initial validation of an imaging protocol for drug discovery [36]	published	2013	Industry
LM48	1996126650	Goodman W.K.	Treatment of obsessive-compulsive disorder with fluvoxamine: A multicentre, double-blind, placebo-controlled trial [37]	published	1996	Industry

LM5	2004433622	Davidson J.R.T.	Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia [38]	published	2004	governmental or non-profit
LM50	1995114731	Greist	Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder [39]	published	1995	Industry
LM54	2007173305	Hartford	Duloxetine as an SNRI treatment for generalized anxiety disorder: Results from a placebo and active-controlled trial [40]	published	2007	Industry
LM57	10907802	Hertzberg	Lack of efficacy for fluoxetine in PTSD: a placebo controlled trial in combat veterans [41]	published	2000	Industry
LM59	8227490	Hoehn-Saric	Effect of fluvoxamine on panic disorder [42]	published	1993	academic
LM6	2001168539	Davidson J.R.T.	Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder [43]	published	2001	Industry
LM60	2003250843	Hollander	A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder [44]	published	2003	Industry
LM67	2143637	Jenike	A controlled trial of fluvoxamine in obsessive-compulsive disorder: implications for a serotonergic theory [45]	published	1990	academic
LM69	1997265747	Jenike M.A.	Placebo-controlled trial of fluoxetine and phenelzine for obsessive- compulsive disorder [46]	published	1997	governmental or non-profit
LM71	2004359161	Kamijima K.	Paroxetine in the treatment of obsessive-compulsive disorder: Randomized, double-blind, placebo-controlled study in Japanese patients [47]	published	2004	academic
LM72	2009168154	Kasper	Efficacy of pregabalin and venlafaxine-XR in generalized anxiety disorder: Results of a double-blind, placebo-controlled 8-week trial [48]	published	2009	Industry
LM73	2005116331	Kasper	Escitalopram in the treatment of social anxiety disorder: Randomised, placebo-controlled, flexible-dosage study [49]	published	2005	Industry
LM74	2014307110	Kasper S.	Lavender oil preparation Silexan is effective in generalized anxiety disorder - A randomized, double-blind comparison to placebo and paroxetine [50]	published	2014	academic
LM76	1995265890	Katzelnick D.J.	Sertraline for social phobia: A double-blind, placebo-controlled crossover study [51]	published	1995	Industry

LM86	20462466	Koszycki	A randomized trial of sertraline, self-administered cognitive behavior therapy, and their combination for panic disorder [52]	published	2011	Industry
LM95	28266242	Li	Effect and safety of sertraline for treat posttraumatic stress disorder: a multicenter randomised controlled study [53]	published	2017	academic
MC1	16175565	Ledley	Impact of depressive symptoms on the treatment of generalized social anxiety disorder [54]	published	2005	governmental or non-profit
MC10	15003077	Lepola	Controlled-release paroxetine in the treatment of patients with social anxiety disorder [55]	published	2004	Industry
MC12	2009266799	Liebowitz	A double-blind, placebo-controlled, parallel-group, flexible-dose study of venlafaxine extended release capsules in adult outpatients with panic disorder [56]	published	2009	Industry
MC13	2002049438	Liebowitz	A randomized, double-blind, fixed-dose comparison of paroxetine and placebo in the treatment of generalized social anxiety disorder [57]	published	2002	Industry
MC14	2005105216	Liebowitz	A randomized controlled trial of venlafaxine extended release in generalized social anxiety disorder [58]	published	2005	Industry
MC15	2003299727	Liebowitz	Efficacy of sertraline in severe generalized social anxiety disorder: Results of a double-blind, placebo-controlled study [59]	published	2003	Industry
MC16	12447029	Liebowitz	Fluoxetine in children and adolescents with OCD: a placebo-controlled trial [60]	published	2002	Industry
MC17	2005062649	Liebowitz M.R.	Venlafaxine extended release vs placebo and paroxetine in social anxiety disorder [61]	published	2005	Industry
MC2	2000096828	Leinonen	Citalopram controls phobic symptoms in patients with panic disorder: Randomized controlled trial [62]	published	2000	academic
MC20a	1998228027	Londborg P.D.	Sertraline in the treatment of panic disorder. A multi-site, double- blind, placebo-controlled, fixed-dose investigation [63]	published	1998	Industry
MC20b	1998228027	Londborg P.D.	Sertraline in the treatment of panic disorder. A multi-site, double- blind, placebo-controlled, fixed-dose investigation [63]	published	1998	Industry

MC22	2013802284	Mahableshwarkar	A randomised, double-blind, placebo-controlled, duloxetine-referenced study of the efficacy and tolerability of vortioxetine in the acute treatment of adults with generalised anxiety disorder [64]	published	2013	Industry
MC25	2007528912	March	A Randomized Controlled Trial of Venlafaxine ER Versus Placebo in Pediatric Social Anxiety Disorder [65]	published	2007	Industry
MC26	2004455374	March	Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: The pediatric OCD treatment study (POTS) randomized controlled trial [66]	published	2004	governmental or non-profit
MC28	1998400055	March J.S.	Sertraline in children and adolescents with obsessive-compulsive disorder: A multicenter randomized controlled trial [67]	published	1998	Industry
MC3	2003412218	Lenox-Smith	A double-blind, randomised, placebo controlled study of venlafaxine XL in patients with generalised anxiety disorder in primary care [68]	published	2003	Industry
MC31	2001420732	Marshall	Efficacy and safety of paroxetine treatment for chronic PTSD: A fixed-dose, placebo-controlled study [69]	published	2001	Industry
MC32	2007163092	Marshall	A controlled trial of paroxetine for chronic PTSD, dissociation, and interpersonal problems in mostly minority adults [70]	published	2007	Unclear
MC33	17414240	Martenyi	Failed efficacy of fluoxetine in the treatment of posttraumatic stress disorder: results of a fixed-dose, placebo-controlled study [71]	published	2007	Industry
MC34	2006287406	Martenyi	Fluoxetine in the acute treatment and relapse prevention of combat-related post-traumatic stress disorder: Analysis of the veteran group of a placebo-controlled, randomized clinical trial [72]	published	2006	Unclear
MC38	2011677266	Merideth	Efficacy and tolerability of extended release quetiapine fumarate monotherapy in the acute treatment of generalized anxiety disorder: A randomized, placebo controlled and active-controlled study [73]	published	2011	Industry

MC39	9812120	Michelson	Outcome assessment and clinical improvement in panic disorder: evidence from a randomized controlled trial of fluoxetine and placebo. The Fluoxetine Panic Disorder Study Group [74]	published	1998	Industry
MC4	2005031032	Lenze	Efficacy and tolerability of citalopram in the treatment of late-life anxiety disorders: Results from an 8-week randomized, placebo-controlled trial [75]	published	2005	academic
MC40	2002013536	Michelson D.	Efficacy of usual antidepressant dosing regimens of fluoxetine in panic disorder. Randomised, placebo-controlled trial [76]	published	2001	Industry
MC42	1994091030	Montgomery	A double-blind, placebo-controlled study of fluoxetine in patients with DSM-III-R obsessive-compulsive disorder [77]	published	1993	Unclear
MC44	2006302530	Montgomery	Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: A 6-week, multicenter, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine [78]	published	2006	Industry
MC45	2001077435	Montgomery	Citalopram 20 mg, 40 mg and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder [79]	published	2001	Industry
MC51	9160622	Nair	Comparison of fluvoxamine, imipramine, and placebo in the treatment of outpatients with panic disorder [80]	published	1996	Industry
MC55	18485261	Nicolini	Improvement of psychic and somatic symptoms in adult patients with generalized anxiety disorder: examination from a duloxetine, venlafaxine extended-release and placebo-controlled trial [81]	published	2008	Unclear
MC56	2004493169	Nimatoudis I.	Remission rates with venlafaxine extended release in Greek outpatients with generalized anxiety disorder. A double-blind, randomized, placebo [82]	published	2004	Unclear
MC6	2009047569	Lenze	Escitalopram for older adults with generalized anxiety disorder: A randomized controlled trial [83]	published	2009	governmental or non-profit
MC62	21349225	Panahi	A randomized, double-blind, placebo-controlled trial on the efficacy and tolerability of sertraline in Iranian veterans with post-traumatic stress disorder [84]	published	2011	academic

MC73	2007466592	Pollack	A randomized controlled trial of venlafaxine ER and paroxetine in the treatment of outpatients with panic disorder [85]	published	2007	Industry
MC77	11411817	Pollack	Paroxetine in the treatment of generalized anxiety disorder: results of a placebo-controlled, flexible-dosage trial [86]	published	2001	Industry
MC79	2007096532	Pollack	A double-blind study of the efficacy of venlafaxine extended-release, paroxetine, and placebo in the treatment of panic disorder [87]	published	2006	Industry
MC81	1997005505	Pollack	Venlafaxine for panic disorder: Results from a double-blind, placebo- controlled study [88]	published	1996	Unclear
MC82	1998374883	Pollack M.H.	Sertraline in the treatment of panic disorder: A flexible-dose multicenter trial [89]	published	1998	Industry
MJ1	2004408566	Rickels	A double-blind, placebo-controlled study of a flexible dose of venlafaxine ER in adult outpatients with generalized social anxiety disorder [90]	published	2004	Unclear
MJ14	2008171568	Rynn	Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: A flexible-dose, progressive-titration, placebo-controlled trial [91]	published	2007	Industry
MJ16	2001420736	Rynn M.A.	Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder [92]	published	2001	governmental or non-profit
MJ17	1998292538	Sandmann J.	Fluvoxamine or placebo in the treatment of panic disorder and relationship to blood concentrations of fluvoxamine [93]	published	1998	academic
MJ2	2000222191	Rickels	Efficacy of extended-release Venlafaxine in nondepressed outpatients with generalized anxiety disorder [94]	published	2000	Industry
MJ22	1996223201	Sharp D.M.	Global measures of outcome in a controlled comparison of pharmacological and psychological treatment of panic disorder and agoraphobia in primary care [95]	published	1997	Industry
MJ25	15669886	Sheehan	Efficacy and tolerability of controlled-release paroxetine in the treatment of panic disorder [96]	published	2005	Industry
MJ3	2005347556	Rickels K.	Paroxetine treatment of generalized anxiety disorder: A double-blind, placebo-controlled study [97]	published	2003	Industry

MJ36	2003496184	Stahl	Escitalopram in the Treatment of Panic Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial [98]	published	2003	Industry
MJ4	1429406	Riddle	Double-blind, crossover trial of fluoxetine and placebo in children and adolescents with obsessive-compulsive disorder [99]	published	1992	governmental or non-profit
MJ42	2005044275	Stein	Efficacy of low and higher dose extended-release venlafaxine in generalized social anxiety disorder: A 6-month randomized controlled trial [100]	published	2004	Industry
MJ44	2007198511	Stein	Escitalopram in obsessive-compulsive disorder: A randomized, placebo-controlled, paroxetine-referenced, fixed-dose, 24-week study [101]	published	2007	Industry
MJ5	2001046511	Riddle M.A.	Fluvoxamine for children and adolescents with obsessive-compulsive disorder: A randomized, controlled, multicenter trial [102]	published	2001	Industry
MJ53	1999166603	Stein M.B.	Fluvoxamine treatment of social phobia (social anxiety disorder): A double-blind, placebo-controlled study [103]	published	1999	Industry
MJ54	1998297625	Stein M.B.	Paroxetine treatment of generalized social phobia (social anxiety disorder): A randomized controlled trial [104]	published	1998	Industry
MJ56	2015802599	Strawn	A randomized, placebo-controlled study of duloxetine for the treatment of children and adolescents with generalized anxiety disorder [105]	published	2015	Industry
MJ6	2011001857	Robb A.S.	Sertraline treatment of children and adolescents with posttraumatic stress disorder: A double-blind, placebo-controlled trial [106]	published	2010	Industry
MJ64	14608246	Tucker	Can physiologic assessment and side effects tease out differences in PTSD trials? A double-blind comparison of citalopram, sertraline, and placebo [107]	published	2003	Industry
MJ66	2001431494	Tucker P.	Paroxetine in the treatment of chronic posttraumatic stress disorder: Results of a placebo-controlled, flexible-dosage trial [108]	published	2001	Unclear
MJ7	2000093467	Rolland P.D.	Treatment of generalised anxiety disorder with venlafaxine XR. A randomised, double-blind trial in comparison with buspirone and placebo [109]	published	2000	Industry
MJ70	2001050465	Van Ameringen M.A.	Sertraline treatment of generalized social phobia: A 20-week, double-blind, placebo-controlled study [110]	published	2001	Industry

MJ71	2007077920	Van Der Kolk	A Randomized clinical trial of eye movement desensitization and reprocessing (EMDR), fluoxetine, and pill placebo in the treatment of posttraumatic stress disorder: treatment effects and long-term maintenance [111]	published	2007	Industry
MJ73	1994203727	Van Vliet I.M.	Psychopharmacological treatment of social phobia; a double blind placebo controlled study with fluvoxamine [112]	published	1993	governmental or non-profit
MJ77	9330022	Wade	The effect of citalopram in panic disorder [113]	published	1997	Unclear
MJ78	2004471921	Wagner	A multicenter, randomized, double-blind, placebo-controlled trial of paroxetine in children and adolescents with social anxiety disorder [114]	published	2004	Unclear
MJ79	18974308	Walkup	Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety [115]	published	2008	Industry
MJ80	11323729	Walkup	Fluvoxamine for the treatment of anxiety disorders in children and adolescents. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group [116]	published	2001	governmental or non-profit
MJ84	2004049533	Westenberg	A Double-Blind Placebo-Controlled Study of Controlled Release Fluvoxamine for the Treatment of Generalized Social Anxiety Disorder [117]	published	2004	Industry
MJ85	2528158	Westenberg	Selective monoamine uptake inhibitors and a serotonin antagonist in the treatment of panic disorder [118]	published	1989	Industry
MJ89	2011586428	Wu	Duloxetine versus placebo in the treatment of patients with generalized anxiety disorder in China [119]	published	2011	academic
MJ93	2002132412	Zohar	Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder [120]	published	2002	Industry
MJ94	1996302206	Zohar	Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder [121]	published	1996	Industry
MJ96a	2192564	Jenike	Sertraline in Obsessive-Compulsive Disorder: A double-Blind Comparison With Placebo [122]	published	1990	Industry
MJ96b	2192564	Jenike	Sertraline in Obsessive-Compulsive Disorder: A double-Blind Comparison With Placebo [122]	published	1990	Industry

UNG9	NKF100110	Unknown	A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Forced-Dose Titration Study Evaluating the Efficacy and Safety of a New Chemical Entity (NCE) and Paroxetine in Subjects with Social Anxiety Disorder.	unpublished	unpublished	Industry
UNG1	SCT-MD-05	Unknown	Escitalopram in the treatment of generalized anxiety disorder: Double-blind, placebo controlled, flexible-dose study	unpublished	unpublished	Industry
UNG10	NKP102280	Unknown	A double-blind, double dummy, placebo-controlled, randomised, parallel group positron emission tomography (PET) study to investigate the effects of a 8 week administration of a new compound and Paroxetine in combination or Paroxetine alone (7.5 mg) on regional cerebral blood flow (rCBF) during a Public Speaking test in subjects affected by social anxiety disorder (SAD).	unpublished	unpublished	Industry
UNG11	BRL-029060/CPMS-116	Unknown	Paroxetine versus Placebo in the Treatment of Obsessive-Compulsive Disorder	unpublished	unpublished	Industry
UNG12	MY- 1028/BRL-029060/1/CPMS-118	Unknown	Paroxetine versus Clomipramine and Placebo in the Treatment of Obsessive-Compulsive Disorder	unpublished	unpublished	Industry
UNG17	NKP103401	Unknown	A randomized, double-blind, parallel group, placebo-controlled fixed dose study comparing the efficacy and safety of New Chemical Entity (NCE))/Paroxetine combination of Paroxetine monotherapy to placebo in subjects with Social Anxiety Disorder (SAD)	unpublished	unpublished	Industry
UNG2	SCT-MD-06	Unknown	Flexible-dose comparison of the safety and efficacy of Escitalopram and placebo in the treatment of generalized anxiety disorder	unpublished	unpublished	Industry
UNG3	NCT01933919	Unknown	A phase 3 study of fluvoxamine (SME3110) in pediatric/adolescent patients with obsessive compulsive disorder	unpublished	unpublished	Industry

UNG6	GSK 637	Hewett	A double-blind, placebo controlled study to evaluate the efficacy and tolerability of paroxetine in patients with generalized anxiety disorder (GAD)	unpublished	unpublished	Industry
UNG7	GSK 791	Unknown	A randomized, double-blind, placebo-controlled, flexible dosage trial to evaluate the efficacy and tolerability of Paroxetine CR in patients with generalized anxiety disorder (GAD)	unpublished	unpublished	Industry
UNG8	Sonne draft	Sonne	The effect of Paroxetine in the treatment of comorbid PTSD and substance dependence	unpublished	unpublished	Industry
UPD3	10.4172/2167-1044.S1-014	Liebowitz MR	A 12-Week Double-Blind, Placebo-Controlled, Flexible-Dose Trial of Desvenlafaxine Extended-Release Tablets in Generalized Social Anxiety Disorder	published	2015	Industry
UPD8	32857933	Strawn JR	Escitalopram in Adolescents With Generalized Anxiety Disorder: A Double-Blind, Randomized, Placebo-Controlled Study	published	2015	governmental or non-profit

S3 Table B: Studies demographic information

id	Country	Number of Sites	Population	Sampling	Main Disorder	n Placebo Arm (Baseline)	n Drug(s) Arm(s) (Baseline)	Number of Drug(s) Arms
JF10	Unclear	Several	Adults/Elderly	Outpatients	SAD	132	257	2
JF11	Sweden	1	Adults/Elderly	Outpatients	SAD	48	44	1
JF15	Japan	54	Adults/Elderly	Unclear	SAD	89	176	1
JF16	USA	1	Adults/Elderly	Unclear	Panic	95	93	1
JF20	Netherlands	2	Adults/Elderly	Outpatients	Panic	39	38	1
JF22	Several	63	Adults/Elderly	Outpatients	GAD	139	407	3
JF25	Several	39	Adults/Elderly	Community	SAD	151	139	1
JF28	USA and Canada	20	Adults/Elderly	Unclear	Panic	69	209	3
JF29	Several	112	Adults/Elderly	Outpatients	GAD	217	217	1
JF3	Several	47	Adults/Elderly	Outpatients	GAD	140	151	1
JF34	USA	2	Children/Adolescents	Community	SAD	32	33	1
JF42	Unclear	Unclear	Children/Adolescents	Mixed	More than 1 AnxDis	37	37	1
JF45	Unclear	Several	Adults/Elderly	Community	Panic	25	25	1
JF56	Several	50	Adults/Elderly	Outpatients	Panic	180	181	1
JF59	Unclear	14	Adults/Elderly	Outpatients	PTSD	93	94	1
JF61	USA	9	Adults/Elderly	Outpatients	GAD	170	68	1
JF7	Several	21	Adults/Elderly	Outpatients	GAD	190	188	1
JF72	Unclear	6	Adults/Elderly	Unclear	OCD	44	43	1
JF78	Unclear	Unclear	Adults/Elderly	Community	PTSD	27	27	1
JF80	USA	50	Adults/Elderly	Outpatients	GAD	104	53	1

JF82	Brazil	1	Children/Adolescents	Unclear	More than 1 AnxDis	11	10	1
JF83	Several	21	Adults/Elderly	Outpatients	GAD	189	184	1
JF87	USA	17	Adults/Elderly	Outpatients	GAD	98	174	2
JF88	USA	NA	Adults/Elderly	Outpatients	GAD	157	158	1
JF89	USA	23	Adults/Elderly	Mixed	GAD	140	139	1
JF9	Several	42	Adults/Elderly	Outpatients	GAD	175	338	2
JF94	Japan	86	Adults/Elderly	Outpatients	SAD	196	392	2
LM10	Netherlands	1	Adults/Elderly	Outpatients	Panic	19	20	1
LM23	US	1	Adults/Elderly	Outpatients	PTSD	6	7	1
LM24	US	1	Adults/Elderly	Outpatients	PTSD	10	8	1
LM34	USA	10	Adults/Elderly	Outpatients	PTSD	83	86	1
LM37	USA	14	Adults/Elderly	Outpatients	GAD	127	124	1
LM39	USA	21	Children/Adolescents	Unclear	OCD	32	69	1
LM4	Several	56	Adults/Elderly	Outpatients	PTSD	168	161	1
LM40	Several	36	Children/Adolescents	Outpatients	OCD	105	98	1
LM42	Spain	1	Adults/Elderly	Outpatients	SAD	16	17	1
LM48	USA	4	Adults/Elderly	Outpatients	OCD	78	78	1
LM5	USA	2	Adults/Elderly	Outpatients	SAD	60	57	1
LM50	USA	11	Adults/Elderly	Outpatients	OCD	84	241	3
LM54	USA	42	Adults/Elderly	Outpatients	GAD	161	326	2
LM57	USA	1	Adults/Elderly	Outpatients	PTSD	6	6	1
LM59	USA	NA	Adults/Elderly	Community	Panic	36	18	1
LM6	USA	12	Adults/Elderly	Outpatients	PTSD	108	100	1

LM60	USA	several	Adults/Elderly	Unclear	OCD	126	127	1
LM67	USA	NA	Adults/Elderly	Outpatients	OCD	20	18	1
LM69	USA	NA	Adults/Elderly	Outpatients	OCD	21	23	1
LM71	Japan	56	Adults/Elderly	Outpatients	OCD	94	94	1
LM72	Several	47	Adults/Elderly	Mixed	GAD	128	125	1
LM73	Several	41	Adults/Elderly	Outpatients	SAD	177	181	1
LM74	Germany	57	Adults/Elderly	Outpatients	GAD	136	137	1
LM76	USA	1	Adults/Elderly	Outpatients	SAD	6	6	1
LM86	Canada	15	Adults/Elderly	Outpatients	Panic	62	62	1
LM95	China	1	Adults/Elderly	Outpatients	PTSD	36	36	1
MC1	USA	2	Adults/Elderly	Unclear	SAD	55	54	1
MC10	Several	NA	Adults/Elderly	Outpatients	SAD	184	186	1
MC12	Several	56	Adults/Elderly	Outpatients	Panic	168	175	1
MC13	Several	22	Adults/Elderly	Outpatients	SAD	94	289	3
MC14	Several	19	Adults/Elderly	Mixed	SAD	138	133	1
MC15	USA	20	Adults/Elderly	Outpatients	SAD	204	211	1
MC16	USA	2	Children/Adolescents	Unclear	OCD	22	21	1
MC17	USA	26	Adults/Elderly	Outpatients	SAD	144	269	2
MC2	Several	22	Adults/Elderly	Unclear	Panic	64	192	2
MC20a	USA	7	Adults/Elderly	Outpatients	Panic	44	127	1
MC20b	USA	7	Adults/Elderly	Outpatients	Panic	43	127	3
MC22	USA	72	Adults/Elderly	Unclear	GAD	52	156	1
MC25	USA	48	Children/Adolescents	Outpatients	SAD	148	137	1

MC26	USA	3	Children/Adolescents	Outpatients	OCD	28	28	1
MC28	USA	12	Children/Adolescents	Outpatients	OCD	95	92	1
MC3	UK	31	Adults/Elderly	Community	GAD	122	122	1
MC31	USA	59	Adults/Elderly	Outpatients	PTSD	186	365	2
MC32	USA	NA	Adults/Elderly	Unclear	PTSD	27	25	1
MC33	USA	43	Adults/Elderly	Unclear	PTSD	88	323	2
MC34	Several	8	Adults/Elderly	Unclear	PTSD	34	110	1
MC38	USA	64	Adults/Elderly	Unclear	GAD	212	203	1
MC39	Unclear	Several	Adults/Elderly	Unclear	Panic	78	165	2
MC4	USA	1	Adults/Elderly	Mixed	More than 1 AnxDis	17	17	1
MC40	Several	9	Adults/Elderly	Outpatients	Panic	90	90	1
MC42	Several	13	Adults/Elderly	Unclear	OCD	55	158	3
MC44	Several	76	Adults/Elderly	Outpatients	GAD	101	113	1
MC45	Several	53	Adults/Elderly	Unclear	OCD	100	390	3
MC51	Canada	3	Adults/Elderly	Outpatients	Panic	47	43	1
MC55	Several	33	Adults/Elderly	Outpatients	GAD	169	411	3
MC56	Greece	4	Adults/Elderly	Outpatients	GAD	22	24	1
MC6	USA	1	Adults/Elderly	Mixed	GAD	93	86	1
MC62	Iran	1	Adults/Elderly	Outpatients	PTSD	35	35	1
MC73	Several	39	Adults/Elderly	Outpatients	Panic	157	467	3
MC77	Several	35	Adults/Elderly	Outpatients	GAD	163	161	1
MC79	Several	71	Adults/Elderly	Outpatients	Panic	156	478	3
MC81	USA	1	Adults/Elderly	Outpatients	Panic	12	13	1

MC82	USA	10	Adults/Elderly	Outpatients	Panic	88	88	1
MJ1	Unclear	17	Adults/Elderly	Outpatients	SAD	135	126	1
MJ14	USA	27	Adults/Elderly	Outpatients	GAD	159	168	1
MJ16	USA	1	Children/Adolescents	Outpatients	GAD	11	11	1
MJ17	Germany	2	Adults/Elderly	Outpatients	Panic	23	23	1
MJ2	USA	15	Adults/Elderly	Outpatients	GAD	96	253	3
MJ22	Scotland	NA	Adults/Elderly	Outpatients	Panic	37	36	1
MJ25	United States, Canada	Several	Adults/Elderly	Unclear	Panic	445	444	1
MJ3	USA, Canada	50	Adults/Elderly	Outpatients	GAD	180	386	2
MJ36	USA	Several	Adults/Elderly	Outpatients	Panic	119	247	2
MJ4	USA	1	Children/Adolescents	Outpatients	OCD	7	7	1
MJ42	USA	19	Adults/Elderly	Outpatients	SAD	134	261	2
MJ44	Canada, Finland, France, Germany, South Africa, Sweden	58	Adults/Elderly	Outpatients	OCD	115	351	3
MJ5	USA	17	Children/Adolescents	Outpatients	OCD	63	57	1
MJ53	USA	4	Adults/Elderly	Outpatients	SAD	44	48	1
MJ54	USA, Canada	13	Adults/Elderly	Outpatients	SAD	93	94	1
MJ56	USA, Mexico, South Africa	32	Children/Adolescents	Outpatients	GAD	137	135	1

MJ6	USA	21	Children/Adolescents	Outpatients	PTSD	62	67	1
MJ64	USA	1	Adults/Elderly	Outpatients	PTSD	10	48	2
MJ66	USA, Canada	37	Adults/Elderly	Outpatients	PTSD	156	151	1
MJ7	USA	1	Adults/Elderly	Outpatients	GAD	62	67	1
MJ70	Canada	10	Adults/Elderly	Outpatients	SAD	69	135	1
MJ71	USA	NA	Adults/Elderly	Community	PTSD	29	30	1
MJ73	Netherlands	1	Adults/Elderly	Outpatients	SAD	13	15	1
MJ77	Finland, Sweden, Netherlands, UK	22	Adults/Elderly	Outpatients	Panic	96	281	3
MJ78	USA, South Africa Canda, Belgium	38	Children/Adolescents	Outpatients	SAD	157	165	1
MJ79	USA	6	Children/Adolescents	Outpatients	More than 1 AnxDis	76	133	1
MJ80	USA	5	children/Adolescents	Outpatients	more than 1 AnxDis	65	63	1
MJ84	France, Germany, UK, Ireland, Netherlands, South Africa, USA	42	Adults/Elderly	Outpatients	SAD	151	149	1
MJ85	Netherlands	NA	adults/Elderly	Outpatients	Panic	20	20	1
MJ89	China	9	Adults/Elderly	Outpatients	GAD	102	108	1
MJ93	Israel	3	Adults/Elderly	Outpatients	PTSD	19	23	1
MJ94	Several	Several	Adults/Elderly	Outpatients	OCD	99	201	1
MJ96	USA	NA	Adults/Elderly	Outpatients	OCD	9	10	1
MJ97	USA	NA	Adults/Elderly	Outpatients	OCD	9	10	1

UNG09	Several	27	Adults/Elderly	Outpatients	SAD	71	36	1
UNG1	USA	25	Adults/Elderly	Outpatients	GAD	128	124	1
UNG10	Sweden	1	Adults/Elderly	Outpatients	SAD	12	12	1
UNG11	USA	15	Adults/Elderly	Outpatients	OCD	88	260	3
UNG12	USA	13	Adults/Elderly	Outpatients	OCD	77	82	1
UNG17	Several	16	Adults/Elderly	Outpatients	SAD	62	66	1
UNG2	USA	19	Adults/Elderly	Outpatients	GAD	138	143	1
UNG3	Japan	34	Children/Adolescents	Unclear	OCD	18	19	1
UNG6	Several	50	Adults/Elderly	Outpatients	GAD	183	181	1
UNG7	USA	32	Adults/Elderly	Unclear	GAD	163	164	1
UNG8	USA	1	Adults/Elderly	Outpatients	PTSD	11	11	1
UPD3	USA	1	Adults/Elderly	Outpatients	SAD	30	30	1
UPD8	USA	1	Children/Adolescents	Outpatients	GAD	25	26	1

GAD, generalized anxiety disorder; PTSD, post-traumatic stress disorder; OCD, obsessive-compulsive disorder

S3 Table C: Intervention information

id	Drug(s) mean dose or min. to max. dose	Drug(s) Class	Comparator	Number of Visits	Outcome Week	Concomitant use of Benzodiazepines	Placebo (led in) exclusion
JF10	venlafaxine - 192mg paroxetine - 44mg	SNRI,SSRI	placebo	9	12-14 week	not informed	no
JF11	paroxetine - 20 to 50mg	SSRI	placebo	7	12-14 week	no	no
JF15	fluvoxamine - 180mg	SSRI	placebo	9	9-11 week	yes	not informed
JF16	fluvoxamine - 100 to 300mg	SSRI	placebo	9	6-8 week	yes	yes
JF20	paroxetine - 20 to 60mg	SSRI	placebo	not informed	12-14 week	no	yes
JF22	escitalopram - 5mg escitalopram - 20mg paroxetine - 20mg	SSRI	head-to-head	10	12-14 week	no	yes
JF25	paroxetine - 35mg	SSRI	placebo	8	12-14 week	no	yes
JF28	paroxetine - 10mg paroxetine - 20mg paroxetine - 40mg	SSRI	different dose	8	9-11 week	yes	yes
JF29	paroxetine - 20mg	SSRI	placebo	9	6-8 week	no	not informed
JF3	duloxetine - 30 to 120mg	SNRI	placebo	5	9-11 week	no	no
JF34	fluoxetine - 10 to 40mg	SSRI	placebo	13	12-14 week	not informed	not informed
JF42	fluoxetine - 20mg	SSRI	placebo	13	12-14 week	not informed	not informed

JF45	fluvoxamine - 50 to 300mg	SSRI	placebo	not informed	6-8 week	not informed	yes
JF56	venlafaxine - 163mg	SNRI	placebo	9	9-11 week	not informed	yes
JF59	sertraline - 133mg	SSRI	placebo	9	12-14 week	not informed	yes
JF61	sertraline - 149mg	SSRI	placebo	9	9-11 week	no	no
JF7	sertraline - 95mg	SSRI	placebo	7	12-14 week	no	yes
JF72	sertraline - 50 to 200mg	SSRI	placebo	6	6-8 week	yes	yes
JF78	fluoxetine - 30mg	SSRI	placebo	9	12-14 week	not informed	not informed
JF80	escitalopram - 10 to 20mg	SSRI	placebo	not informed	6-8 week	no	not informed
JF82	fluoxetine - 35mg	SSRI	placebo	not informed	12-14 week	not informed	not informed
JF83	sertraline - 50 to 100mg	SSRI	placebo	7	12-14 week	no	yes
JF87	venlafaxine - 75mg venlafaxine - 150mg	SNRI	placebo	7	6-8 week	no	yes
JF88	escitalopram - 12mg	SSRI	placebo	6	6-8 week	no	yes
JF89	fluvoxamine - 174mg	SSRI	placebo	10	12-14 week	not informed	yes
JF9	duloxetine - 60mg duloxetine - 120mg	SNRI	different dose	6	9-11 week	no	yes
JF94	escitalopram - 10mg escitalopram - 20mg	SSRI	different dose	7	12-14 week	not informed	not informed
LM10	fluvoxamine - 75 to 150mg	SSRI	placebo	6	6-8 week	not informed	no
LM23	paroxetine – 12,5 to 62,5mg	SSRI	placebo	NA	12-14 week	not informed	not informed

LM24	paroxetine – 12,5 to 62,5mg	SSRI	placebo	4	6-8 week	not informed	not informed
LM34	sertraline - 135mg	SSRI	placebo	8	12-14 week	no	yes
LM37	venlafaxine - 75 to 225mg	SNRI	placebo	12	12-14 week	no	no
LM39	fluoxetine - 25mg	SSRI	placebo	10	12-14 week	not informed	no
LM4	venlafaxine - 182mg	SNRI	placebo	8	21-26 week	unclear	no
LM40	paroxetine - 25mg	SSRI	placebo	7	9-11 week	not informed	no
LM42	paroxetine - 20mg	SSRI	placebo	4	6-8 week	unclear	no
LM48	fluvoxamine - 230mg	SSRI	placebo	5	9-11 week	yes	no
LM5	fluoxetine - 44mg	SSRI	placebo	4	12-14 week	not informed	no
LM50	sertraline - 50mg sertraline - 100mg sertraline - 2000mg	SSRI	different dose	8	12-14 week	no	yes
LM54	duloxetine - 107mg venlafaxine - 184mg	SNRI	head-to-head	7	9-11 week	not informed	not informed
LM57	fluoxetine - 48mg	SSRI	placebo	8	12-14 week	no	no
LM59	fluvoxamine - 205mg	SSRI	placebo	9	6-8 week	no	no
LM6	sertraline - 146mg	SSRI	placebo	9	12-14 week	no	yes
LM60	fluvoxamine - 271mg	SSRI	placebo	7	12-14 week	no	no
LM67	fluvoxamine - 294mg	SSRI	placebo	6	9-11 week	no	no
LM69	fluoxetine - 78mg	SSRI	placebo	6	9-11 week	no	no
LM71	paroxetine - 40 to 50mg	SSRI	placebo	6	12-14 week	not informed	no
LM72	venlafaxine - 155mg	SNRI	placebo	7	6-8 week	not informed	no
LM73	escitalopram - 18mg	SSRI	placebo	8	12-14 week	no	yes
LM74	paroxetine - 20mg	SSRI	placebo	6	9-11 week	no	no

LM76	sertraline - 134mg	SSRI	placebo	4	9-11 week	not informed	not informed
LM86	sertraline - 116mg	SSRI	placebo	8	12-14 week	yes	no
LM95	sertraline - 135mg	SSRI	placebo	not informed	12-14 week	not informed	not informed
MC1	fluoxetine - 10 to 40mg	SSRI	placebo	10	12-14 week	unclear	no
MC10	paroxetine - 32mg	SSRI	placebo	8	12-14 week	no	unclear
MC12	venlafaxine - 188mg	SNRI	placebo	8	9-11 week	no	yes
MC13	paroxetine - 20mg paroxetine - 40mg paroxetine - 60mg	SSRI	different dose	8	12-14 week	no	yes
MC14	venlafaxine - 165mg	SNRI	placebo	9	12-14 week	no	yes
MC15	sertraline - 159mg	SSRI	placebo	8	12-14 week	no	yes
MC16	fluoxetine - 65mg	SSRI	placebo	9	6-8 week	no	no
MC17	venlafaxine - 202mg paroxetine - 46mg	SNRI,SSRI	head-to-head	not informed	12-14 week	no	yes
MC2	citalopram - 10 to 15mg citalopram - 20 to 40mg	SSRI	different dose	not informed	12-14 week	yes	yes
MC20a	sertraline - 50 to 200mg	SSRI	different dose	9	12-14 week	no	yes
MC20b	sertraline - 50mg sertraline - 100mg sertraline - 2000mg	SSRI	different dose	9	12-14 week	no	yes
MC22	duloxetine - 60mg	SNRI	head-to-head	6	6-8 week	unclear	not informed
MC25	venlafaxine - 142mg	SNRI	different dose	9	12-14 week	no	not informed
MC26	sertraline - 170mg	SSRI	placebo	9	12-14 week	no	not informed
MC28	sertraline - 167mg	SSRI	placebo	8	12-14 week	no	yes
MC3	venlafaxine - 110mg	SNRI	placebo	6	6-8 week	no	no

MC31	paroxetine - 20mg paroxetine - 40mg	SSRI	different dose	7	12-14 week	no	yes
MC32	paroxetine - 40mg	SSRI	placebo	3	9-11 week	no	yes
MC33	fluoxetine - 20mg fluoxetine - 40mg	SSRI	different dose	not informed	12-14 week	not informed	no
MC34	fluoxetine - 65mg	SSRI	placebo	not informed	12-14 week	not informed	no
MC38	escitalopram - 10mg	SSRI	placebo	not informed	6-8 week	not informed	no
MC39	fluoxetine - 10mg fluoxetine - 20mg	SSRI	different dose	6	9-11 week	no	no
MC4	citalopram - 10 to 30mg	SSRI	placebo	7	6-8 week	yes	no
MC40	fluoxetine - 30mg	SSRI	placebo	7	12-14 week	not informed	unclear
MC42	fluoxetine - 20mg fluoxetine - 40mg fluoxetine - 60mg	SSRI	different dose	7	6-8 week 9-11 week	yes	yes
MC44	venlafaxine - 75mg	SNRI	placebo	6	6-8 week	no	no
MC45	citalopram - 20mg citalopram - 40mg citalopram - 60mg	SSRI	different dose	6	12-14 week	no	yes
MC51	fluvoxamine - 171mg	SSRI	placebo	9	6-8 week	yes	yes
MC55	duloxetine - 20mg duloxetine - 90mg venlafaxine - 151mg	SNRI	head-to-head	not informed	9-11 week	no	no
MC56	venlafaxine - 75 to 150mg	SNRI	placebo	7	9-11 week	no	yes

MC6	escitalopram - 10 to 20mg	SSRI	placebo	9	12-14 week	yes	no
MC62	sertraline - 140mg	SSRI	placebo	7	9-11 week	yes	not informed
MC73	venlafaxine - 75mg venlafaxine - 225mg paroxetine - 40mg	SNRI,SSRI	head-to-head	9	12-14 week	no	yes
MC77	paroxetine - 27mg	SSRI	placebo	4	6-8 week	no	yes
MC79	venlafaxine - 75mg venlafaxine - 150mg paroxetine - 40mg	SNRI,SSRI	head-to-head	9	12-14 week	no	yes
MC81	venlafaxine - 166mg	SNRI	placebo	9	6-8 week	not informed	yes
MC82	sertraline - 131mg	SSRI	placebo	8	9-11 week	no	yes
MJ1	venlafaxine - 165mg	SNRI	placebo	9	12-14 week	no	yes
MJ14	duloxetine - 102mg	SNRI	placebo	6	9-11 week	no	yes
MJ16	sertraline - 50mg	SSRI	placebo	10	9-11 week	not informed	no
MJ17	fluvoxamine - 160mg	SSRI	placebo	7	6-8 week	not informed	no
MJ2	venlafaxine - 75mg venlafaxine - 150mg venlafaxine - 225mg	SNRI	different dose	8	6-8 week	no	no
MJ22	fluvoxamine - 100 to 150mg	SSRI	placebo	8	12-14 week	not informed	yes
MJ25	paroxetine - 50mg	SSRI	placebo	11	9-11 week	no	yes
MJ3	paroxetine - 20mg paroxetine - 40mg	SSRI	different dose	7	6-8 week	no	yes
MJ36	escitalopram - 11mg citalopram - 21mg	SSRI	head-to-head	7	9-11 week	no	yes

MJ4	fluoxetine - 20mg	SSRI	placebo	3	6-8 week	not informed	no
MJ42	venlafaxine - 72mg venlafaxine - 214mg	SNRI	different dose	12	12-14 week	not informed	yes
MJ44	escitalopram - 10mg escitalopram - 20mg paroxetine - 40mg	SSRI	head-to-head	11	12-14 week	no	no
MJ5	fluvoxamine - 165mg	SSRI	placebo	8	9-11 week	no	yes
MJ53	fluvoxamine - 202mg	SSRI	placebo	9	12-14 week	yes	no
MJ54	paroxetine - 37mg	SSRI	placebo	8	12-14 week	not informed	yes
MJ56	duloxetine - 54mg	SNRI	placebo	6	9-11 week	no	no
MJ6	sertraline - 106mg	SSRI	placebo	6	9-11 week	no	no
MJ64	citalopram - 36mg sertraline - 134mg	SSRI	head-to-head	8	9-11 week	yes	no
MJ66	paroxetine - 28mg	SSRI	placebo	7	12-14 week	not informed	yes
MJ7	venlafaxine - 75mg venlafaxine - 150mg	SNRI	different dose	9	6-8 week	no	unclear
MJ70	sertraline - 147mg	SSRI	placebo	9	18-20 week	no	yes
MJ71	fluoxetine - 30mg	SSRI	placebo	not informed	6-8 week	not informed	no
MJ73	fluvoxamine - 50 to 150mg	SSRI	placebo	6	12-14 week	yes	no
MJ77	citalopram - 10 to 15mg citalopram - 20 to 40mg citalopram - 40 to 60mg	SSRI	different dose	9	6-8 week	yes	yes
MJ78	paroxetine - 33mg	SSRI	placebo	10	15-17 week	not informed	no
MJ79	sertraline - 25 to 200mg	SSRI	placebo	9	12-14 week	not informed	no
MJ80	fluvoxamine - 300mg	SSRI	placebo	8	6-8 week	no	no

MJ84	fluvoxamine - 209mg	SSRI	placebo	7	12-14 week	not informed	no
MJ85	fluvoxamine - 300mg	SSRI	placebo	7	6-8 week	not informed	not informed
MJ89	duloxetine - 60 to 120mg	SNRI	placebo	not informed	15-17 week	yes	no
MJ93	sertraline - 120mg	SSRI	placebo	6	9-11 week	yes	yes
MJ94	paroxetine - 38mg	SSRI	placebo	4	12-14 week	yes	yes
MJ96	sertraline - 200mg	SSRI	placebo	7	9-11 week	no	no
MJ97	Sertraline - 200mg	SSRI	placebo	7	9-11 week	no	no
UNG09	paroxetine - 20 to 30mg	SSRI	placebo	not informed	12-14 week	not informed	not informed
UNG1	escitalopram - 10 to 20mg	SSRI	placebo	6	6-8 week	no	yes
UNG10	paroxetine - 8mg	SSRI	placebo	not informed	12-14 week 6-8 week	not informed	not informed
UNG11	paroxetine - 20mg paroxetine - 40mg paroxetine - 60mg	SSRI	placebo	8	12-14 week	no	yes
UNG12	paroxetine - 20 to 60mg	SSRI	placebo	not informed	12-14 week	no	not informed
UNG17	paroxetine - 8mg	SSRI	placebo	not informed	12-14 week	not informed	not informed
UNG2	escitalopram - 10 to 20mg	SSRI	Placebo	6	6-8 week	no	yes
UNG3	fluvoxamine - 50 to 150mg	SSRI	Placebo	5	9-11 week	not informed	not informed
UNG6	paroxetine - 20 to 50mg	SSRI	Placebo	8	6-8 week	no	yes

UNG7	paroxetine - 12 to 38mg	SSRI	Placebo	8	6-8 week	no	yes
UNG8	paroxetine - 42mg	SSRI	Placebo	12	12-14 week	no	not informed
UPD3	desvenlafaxine - 79mg	SNRI	Placebo	8	12-14 week	no	no
UPD8	escitalopram - 15 to 20mg	SSRI	Placebo	6	12-14 week	no	not informed

SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors

S3 Table D: Outcomes assessment information

id	Scale Abbreviation[a]	Scale[b]	Associated Factors	DSM Factors	Type of Analysis	Effect Size (yi)	Variance (vi)
JF10	LSAS	Liebowitz social anxiety scale (LSAS)	social anxiety	social anxiety	LOCF	-0.896097744888929	0.0543638718430562
JF10	LSAS	Liebowitz social anxiety scale (LSAS)	social anxiety	social anxiety	LOCF	-1.0622091785337	0.0570595968681807
JF10	SPIN	social phobia inventory (SPIN)	social anxiety	social anxiety	LOCF	-0.886115099349378	0.0451309430827813
JF11	BSPS	Brief Social Phobia Scale (BSPS) total score	social anxiety	social anxiety	LOCF	-1.31923006693011	0.109599705867586
JF11	FNE	Fear of Negative Evaluation Scale (FONE)	fear of negative evaluation	social anxiety	LOCF	-1.02837524517162	0.0882808067241331
JF11	LSAS	Liebowitz Social Anxiety Scale (LSAS) total score	social anxiety	social anxiety	LOCF	-1.39140574069214	0.103957872435007
JF15	LSAS	Liebowitz Social Anxiety Scale – Japanese Version. Total score	social anxiety	social anxiety	LOCF	-0.579099136052946	0.0381189720175578
JF16	CAS	Clinical Anxiety Scale (CAS) 1-6 items	anxiety (general)	GAD	LOCF	-0.373684718613133	0.0411059226358366
JF16	CAS_P	Estimate of Panic Attack frequency and severity (item 7 of the CAS)	panic	panic	LOCF	-1.18640405043006	0.0766811424809354
JF16	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-1.00933663443424	0.0627586450654598
JF16	PAAS_PAF_WK_N	No. of full panic attacks week	panic attack (full)	panic	LOCF	-0.274175947317793	0.03395420085955
JF16	PAAS_PAL_WK_N	No. of limited symptom attacks week	panic attack (limited)	panic	LOCF	-0.0453216696070832	0.0326123759990558
JF16	PANICSS	Panic disorder severity DSM-III-R derived	panic attack	panic	LOCF	-0.802753826624984	0.0504146864766325
JF20	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-1.42806339398136	0.156104371270559

JF20	HAM_A	Hamilton Rating Scale For Anxiety (HAM-A)	anxiety (general)	GAD	LOCF	-0.81494602179861	0.104941377899764
JF20	MSPRS_A	Marks- Sheehan Phobia Scale (MSPS)/ anxiety	anxiety (general)	GAD	LOCF	-0.618789538971025	0.0982220055055598
JF20	MSPRS_AGO	Marks- Sheehan Phobia Scale (MSPS)/ agoraphobia	agoraphobia	agoraphobia	LOCF	-0.786910217198722	0.0933422824065059
JF20	OPS	Overall Phobia score	phobia	phobia	LOCF	-1.18076179823524	0.125766033250536
JF20	PAAS_AA	Antecipatory anxiety score	anticipatory anxiety	GAD	LOCF	-1.23276667821622	0.114194493164258
JF20	PAAS_PA_WK_N	Panic frequency (mean number of panic attacks per week)	panic attack	panic	LOCF	-0.197524880314345	0.0835319997865033
JF20	PGI	Patient global evaluation	patient impression (general)	psychiatric symptoms (general)	LOCF	-0.979297653406917	0.109421987324686
JF22	HAM_A	Hamilton Rating Scale for Anxiety (HAMA)	anxiety (general)	GAD	LOCF	-0.387597104456079	0.187650018186041
JF22	HAM_A	Hamilton Rating Scale for Anxiety (HAMA)	anxiety (general)	GAD	LOCF	-0.281429608063417	0.182650139736394
JF22	HAM_A	Hamilton Rating Scale for Anxiety (HAMA)	anxiety (general)	GAD	LOCF	-0.145363921185109	0.179584177715256
JF25	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.792960296177988	0.0318012552867151
JF25	LSAS	Liebowitz Social Anxiety Scale (LSAS)	social anxiety	social anxiety	LOCF	-0.853337315451156	0.0318630218740182
JF25	SADS	Social Avoidance and Distress Scalse (SADS)	social anxiety	social anxiety	LOCF	-0.634179328979538	0.0298975626103604
JF28	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	0.0949560700020937	0.193811627865147
JF28	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.188564987759888	0.19978439550452

JF28	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.613252188812093	0.212051885612085
JF28	FQ	Fear score	fear	phobia	LOCF	-0.355057905474546	0.115198178816713
JF28	FQ	Fear score	fear	phobia	LOCF	-0.713629248409826	0.12094762891597
JF28	FQ	Fear score	fear	phobia	LOCF	-0.912001861563782	0.124488919151157
JF28	HAM_A	Hamilton Anxiety Rating Scale total score	anxiety (general)	GAD	LOCF	-0.102353435230698	0.111266174972579
JF28	HAM_A	Hamilton Anxiety Rating Scale total score	anxiety (general)	GAD	LOCF	-0.143685640684603	0.110590542395451
JF28	HAM_A	Hamilton Anxiety Rating Scale total score	anxiety (general)	GAD	LOCF	-0.550226365719823	0.116677908563761
JF28	MSPRS_AV	Marks-Sheehan Phobia Scale Avoidance score	avoidance (phobia)	phobia	LOCF	-0.194465319213568	0.100693393227033
JF28	MSPRS_AV	Marks-Sheehan Phobia Scale Avoidance score	avoidance (phobia)	phobia	LOCF	-0.28478983152039	0.100626629750824
JF28	MSPRS_AV	Marks-Sheehan Phobia Scale Avoidance score	avoidance (phobia)	phobia	LOCF	-0.464960159239507	0.102346446502004
JF28	PA_INT	Intensity of full panic attacks (0=completely at ease, 10=completely in panic)	panic attack (full)	panic	LOCF	-0.572295326728247	0.143895965054973
JF28	PA_INT	Intensity of full panic attacks (0=completely at ease, 10=completely in panic)	panic attack (full)	panic	LOCF	-0.890529833464921	0.15077896407188
JF28	PA_INT	Intensity of full panic attacks (0=completely at ease, 10=completely in panic)	panic attack (full)	panic	LOCF	-0.811342756280216	0.147023207308763
JF28	PAAS_SIPA_WK_N	Number of situational panic attacks	situational panic attack	panic	LOCF	-0.112654774394894	0.0893577278611116

JF28	PAAS_SPA_WK_N	Number of spontaneous panic attacks	panic attack	panic	LOCF	-0.201768491464134	0.0897052206179256
JF28	PAAS_SIPA_WK_N	Number of situational panic attacks	situational panic attack	panic	LOCF	-0.542395688066405	0.0916719679637843
JF28	PAAS_SPA_WK_N	Number of spontaneous panic attacks	panic attack	panic	LOCF	-0.094989324194495	0.088159587992807
JF28	PAAS_SIPA_WK_N	Number of situational panic attacks	situational panic attack	panic	LOCF	-0.183018953885395	0.088099521990374
JF28	PAAS_SPA_WK_N	Number of spontaneous panic attacks	panic attack	panic	LOCF	-0.0197699437446626	0.0872761788862923
JF28	PAAS_AA_T_P	Anticipatory anxiety (% time worrying)	anticipatory anxiety	GAD	LOCF	-0.0733761203613051	0.0886510027064458
JF28	PAAS_AA_T_P	Anticipatory anxiety (% time worrying)	anticipatory anxiety	GAD	LOCF	-0.260368712007974	0.0885667842932907
JF28	PAAS_AA_T_P	Anticipatory anxiety (% time worrying)	anticipatory anxiety	GAD	LOCF	-0.229542839775623	0.0877584898908462
JF28	PAAS_PA_WK_N	Total number of panic attacks (full and limited)	panic attack	panic	LOCF	-0.224492650470099	0.0917174337325355
JF28	PAAS_PA_WK_N	Total number of panic attacks (full and limited)	panic attack	panic	LOCF	-0.179431076203721	0.0903420460150124
JF28	PAAS_PA_WK_N	Total number of panic attacks (full and limited)	panic attack	panic	LOCF	-0.223865298012914	0.0900128682332348
JF28	PAAS_PAF_WK_N	Number of full panic attacks	panic attack (full)	panic	LOCF	-0.203872731158078	0.0900786053439796
JF28	PAAS_PAF_WK_N	Number of full panic attacks	panic attack (full)	panic	LOCF	-0.301896267678868	0.0897294882243462
JF28	PAAS_PAF_WK_N	Number of full panic attacks	panic attack (full)	panic	LOCF	-0.122965403722179	0.087992087670391
JF29	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.597913849345459	0.0425127154810276
JF29	HAM_A	Hamilton Rating Scale for Anxiety total score	anxiety (general)	GAD	LOCF	-0.814204654695805	0.0615665547258891

JF3	HADS_A	HADS-A	anxiety (general)	GAD	LOCF	-0.815729743980988	0.0515755546649122
JF3	HAM_A	Hamilton Anxiety Rating Scale total score	anxiety (general)	GAD	LOCF	-0.83295177435592	0.0504750170373928
JF34	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.335467830712653	0.120360693897177
JF42	PARS	Pediatric Anxiety Rating Scale (PARS)	anxiety (general)(child)	GAD	Unclear	-0.811168436727752	0.19062696027017
JF42	SCARED	Screen for Child Anxiety Related Emotional Disorders child-rated (SCARED-C)	anxiety (general)(child)	GAD	Unclear	-0.377703332496096	0.110036987652575
JF42	SCARED_P	Screen for Child Anxiety Related Emotional Disorders parent-rated (SCARED-P)	anxiety (general)(child)	GAD	Unclear	-0.667198379499194	0.137859058888984
JF45	CAS	Clinical Anxiety Scale	anxiety (general)	GAD	Unclear	-1.18093321152161	0.222508917293493
JF45	PASS	Panic Attack Severity Score	panic attack	panic	Unclear	-0.128709499427317	0.134259036509213
JF56	CAS	Covi	anxiety (general)	GAD	LOCF	-0.284485742148074	0.0265302112310064
JF56	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	0.736489675754226	0.0350413260960901
JF56	FQ_F	Phobia scale fear	fear (phobia)	phobia	LOCF	-0.210084705830164	0.0193541062188335
JF56	FQ_AV	Phobia scale avoidance	avoidance (phobia)	phobia	LOCF	-0.178120651442753	0.0181512657273323
JF59	CAPS	Clinician Administred Posttraumatic Stress Disorder (PTSD) Scale Part 2 (CAPS-2)	PTSD	PTSD	LOCF	-0.581780035902446	0.0600086326822387
JF59	CAPS_AF	CAPS-2 Associated features	PTSD	PTSD	LOCF	-0.430924232532928	0.0425065356956058
JF59	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.528512834923249	0.0527575839621797

JF59	DTS	Davidson PTSD scale total score	PTSD	PTSD	LOCF	-0.599701487634021	0.0413265961127933
JF59	IES	Impact of event Scale (IES)	PTSD	PTSD	LOCF	-0.26936006159537	0.0413270189140937
JF61	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	Mixed/Hierarchical/Random	-0.534807016075285	0.133603683930225
JF61	HAM_A	Hamilton Anxiety Scale (HAMA) total score	anxiety (general)	GAD	Mixed/Hierarchical/Random	-0.137045277320874	0.236392476763627
JF7	CGI-S	CGI Severity	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-1.2093049466451	0.0406422779202736
JF7	HADS_A	Hospital Anxiety and Depreesion scale/ Anxiety	anxiety (general)	GAD	LOCF	-0.495802169270289	0.0218552514401096
JF7	HAM_A	Hamilton anxiety scale	anxiety (general)	GAD	LOCF	-0.907096942581445	0.0399000205084083
JF72	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.613645405759402	0.0788870048149041
JF72	MOCI	Maudsley Obsessive compulsive Inventory	OCD	OCD	LOCF	-0.19667102723797	0.070175700642075
JF72	NIMH_GOCS	NIMH Global Obsessive-Compulsive (NIMHOC)	OCD	OCD	LOCF	-0.625477245439855	0.0814310908902494
JF72	YBOCS	Yale-Brown Obsessive-Compulsive Scale (YBOCS) total score	OCD	OCD	LOCF	-0.52119855280954	0.0763287912706237
JF78	DTS	Davidson Trauma Scale (DTS)	PTSD	PTSD	LOCF	-1.16469101721478	0.236421907923942
JF78	DUKE	Duke Global Severity Rating for PTSD (Duke)	PTSD	PTSD	LOCF	-1.33488618844004	0.227015072365685
JF78	SIP	Structured Intreview for PTSD (SIP)	PTSD	PTSD	LOCF	-0.979167675818037	0.290729525727433
JF78	SVS	Vulnerability to the Effects of Stress (VS)	stress vulnerability	stress	LOCF	-0.902698156138078	0.14089909856066

JF80	CGI-S	CGI-S endpoint	clinical impression (severity)	psychiatric symptoms (general)	Mixed/Hierarchical/Random	-0.665637301078418	0.0898537882204157
JF80	HAM_A	Hamilton					
Anxiety scale (HAM-A) total score	anxiety (general)	GAD	Mixed/Hierarchical/ Random	-0.588183354363679	0.105647356899362		
JF82	MASC	Multidimensional Anxiety Scale for Children (MASC) total score	anxiety (general)(child)	GAD	Unclear	-1.38026136930563	0.49619908701048
JF83	CGI-S	CGI-severity	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-1.16171359788262	0.0411589450906771
JF83	HAM_A	Hamilton Anxiety scale (HAM-A) total score	anxiety (general)	GAD	LOCF	-0.90690783090784	0.0405197197025528
JF87	HAM_A	Hamilton Anxiety scale (HAM-A) total score	anxiety (general)	GAD	LOCF	-0.688665942108189	0.123083291465255
JF87	HAM_A	Hamilton Anxiety scale (HAM-A) total score	anxiety (general)	GAD	LOCF	-0.381620401531615	0.114495205280633
JF88	CAS	Covi Anxiety Scale	anxiety (general)	GAD	LOCF	-0.65700571072329	0.0328937747271865
JF88	CGI-S	CGI Severity score	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-1.1943060234367	0.0516955407771696
JF88	HADS_A	Hospital Anxiety and Depression Scale (HAD) Anxiety Subscale	anxiety (general)	GAD	LOCF	-0.718555246796547	0.023849383270864
JF88	HAM_A	Hamilton Anxiety scale (HAM-A) total score	anxiety (general)	GAD	LOCF	-0.691346721425004	0.0477532968296333
JF89	CGI-S	CGI Severity of Illness	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.846554404574765	0.0342681449342716
JF89	LSAS	Liebowitz Social Anxiety Scale (LSAS)	social anxiety	social anxiety	LOCF	-0.834995617665281	0.0292088822766303

JF9	HADS	Hospital Anxiety and Depression Scale	anxiety/depression (general)	GAD	LOCF	-0.691265815584649	0.0377600911901718
JF9	HADS	Hospital Anxiety and Depression Scale	anxiety/depression (general)	GAD	LOCF	-0.616335615414626	0.0366548505253204
JF9	HAM_A	Hamilton Anxiety Scale	anxiety (general)	GAD	LOCF	-0.701723378336957	0.0426217562151912
JF9	HAM_A	Hamilton Anxiety Scale	anxiety (general)	GAD	LOCF	-0.611622385053353	0.0412051625865182
JF94	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	0.022743702824878	0.0344742289878599
JF94	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.502883293274385	0.0387185732004275
JF94	LSAS	Liebowitz Social Anxiety Scale Japanese version (LSAS-J)	social anxiety	social anxiety	LOCF	-0.233421623090585	0.0361882394298545
JF94	LSAS	Liebowitz Social Anxiety Scale Japanese version (LSAS-J)	social anxiety	social anxiety	LOCF	-0.590963915422649	0.039500404269173
LM10	FQ	FQ (Fear Questionarie)	fear	phobia	Mixed/Hierarchical/Random	-0.334029437663238	0.381783676447242
LM10	STAI_STA	A-STATE (State-Anxiety Inventory)	state anxiety (general)	GAD	Mixed/Hierarchical/Random	-1.4663202343883	0.201522097132981
LM23	CAPS	CAPS Total	PTSD	PTSD	Completers	-4.92606466181063	3.39206465299058
LM24	CAPS	CAPS Total	PTSD	PTSD	Completers	-3.59830312716196	1.7909862795776
LM34	CAPS	CAPS-2 = Clinician-Administered PTSD Scale	PTSD	PTSD	Mixed/Hierarchical/Random	0.0908472643721259	0.0417784848506463
LM34	CGI-S	CGI-S = Clinical Global Impressions-Severity of Illness Scale	clinical impression (severity)	psychiatric symptoms (general)	Mixed/Hierarchical/Random	0.0438558883435708	0.0394059897818265
LM34	DESNOS	DES = Disorders of Extreme Stress–Not Otherwise Specified Scale	stress disorders	stress	Mixed/Hierarchical/Random	0.141771189402752	0.0396029516228681

LM34	DTS	DTS = Davidson Trauma Scale	PTSD	PTSD	Mixed/Hierarchical/Random	-0.0269776671736612	0.0373834663567825
LM34	HAM_A	HAM-A = Hamilton Rating Scale for Anxiety	anxiety (general)	GAD	Mixed/Hierarchical/Random	0.180321304688063	0.0399599095296002
LM34	IES	IES = Impact of Event Scale	PTSD	PTSD	Mixed/Hierarchical/Random	-0.0312929021066191	0.0388402654473661
LM34	MISS	MISS = Mississippi Rating Scale for Combat-Related PTSD–Civilian Trauma Version	PTSD	PTSD	Mixed/Hierarchical/Random	-0.104333957737645	0.0361108446909316
LM37	HAM_A	HAM-A total	anxiety (general)	GAD	Completers	-0.973759299220289	0.064453406622245
LM39	CGI-S	CGI-Severity	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-1.10547923852035	0.100135498435691
LM39	COIS	OCD-impact = Obsessive Compulsive Disorder Impact Scale	OCD	OCD	LOCF	-0.32432446218064	0.0816422117678798
LM39	CYBOCS	CY-BOCS total	OCD (child)	OCD	LOCF	-0.739877971551536	0.110917635029375
LM39	NIMH_GOCS	NIMH-OCD = National Institute of Mental Health Global OCD Scale	OCD	OCD	LOCF	-1.39780601733035	0.111608602517328
LM4	CAPS	CAPS-SX17 (Clinician-administered PTSD Scale) TOTAL	PTSD	PTSD	LOCF	-0.649133701057857	0.0815058420688498
LM4	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.590614803724663	0.0638728683135084
LM4	SVS	SVS (Sheehan Vulnerability to the Effects of Stress Scale)	stress vulnerability	stress	LOCF	-0.399342216268594	0.0263528311796011
LM40	CYBOCS	CY-BOCS total	OCD (child)	OCD	LOCF	-0.71020291155133	0.0506433732429119
LM42	LSAS	LSAS: liebowitz social anxiety scale	social anxiety	social anxiety	Mixed/Hierarchical/Random	-0.253617510887107	0.187754350387284
LM48	NIMH_GOCS	NIMH-OCD = National Institute of Mental Health Global OCD Scale	OCD	OCD	LOCF	-0.553980710910298	0.0432566438612353

LM48	YBOCS	Y-BOCS total	OCD	OCD	LOCF	-0.461292179918487	0.0434170925526235
LM5	BSPS	BSPS (Brief Social Phobia Scale)	social anxiety	social anxiety	Mixed/Hierarchical/Random	-0.577523559869115	0.09264131903487
LM5	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	Mixed/Hierarchical/Random	-6.8988793022798	3.33078077515911
LM5	SPAI	SPAI (Social Phobia and Anxiety Inventory)	social anxiety	social anxiety	Mixed/Hierarchical/Random	-0.31320378165083	0.067802863571517
LM50	CGI-S	CGI-S = Clinical Global Impression severity scale	clinical impression (severity)	psychiatric symptoms (general)	Unclear	-0.266170281385921	0.0987701482803267
LM50	CGI-S	CGI-S = Clinical Global Impression severity scale	clinical impression (severity)	psychiatric symptoms (general)	Unclear	0.105151791359413	0.0935958260009241
LM50	CGI-S	CGI-S = Clinical Global Impression severity scale	clinical impression (severity)	psychiatric symptoms (general)	Unclear	-0.266170281385921	0.0987701482803267
LM50	NIMH_GOCS	NIMH-OCD = National Institute of Mental Health Global OCD Scale	OCD	OCD	Unclear	-0.258136097301266	0.0955020536024788
LM50	NIMH_GOCS	NIMH-OCD = National Institute of Mental Health Global OCD Scale	OCD	OCD	Unclear	-0.403951841275587	0.097394744313816
LM50	NIMH_GOCS	NIMH-OCD = National Institute of Mental Health Global OCD Scale	OCD	OCD	Unclear	-0.611598346116329	0.101431344322544
LM50	YBOCS	Y-BOCS total	OCD	OCD	Unclear	-0.139113449783697	0.0959502132032371
LM50	YBOCS	Y-BOCS total	OCD	OCD	Unclear	-0.0561962377330943	0.0945522709125012
LM50	YBOCS	Y-BOCS total	OCD	OCD	Unclear	-0.82672174156386	0.108284196915934
LM54	HADS_A	HADS-A	anxiety (general)	GAD	LOCF	-0.960591707293092	0.0528710938123652
LM54	HADS_A	HADS-A	anxiety (general)	GAD	LOCF	-1.04588739825831	0.0533986180789742
LM54	HAM_A	HAM-A total	anxiety (general)	GAD	LOCF	-0.455603711911817	0.0560589081346431

LM54	HAM_A	HAM-A total	anxiety (general)	GAD	LOCF	-0.716137713375574	0.0588003181696513
LM57	DTS	DTS Davidson Trauma Scale	PTSD	PTSD	Unclear	0.537144991571468	0.533861205539994
LM57	SIP	SIP Structured Interview for PTSD	PTSD	PTSD	Unclear	-0.00934165202732988	0.501316269144212
LM59	CAS	CAS = Clinical Anxiety Scale	anxiety (general)	GAD	Unclear	-1.22264105790017	0.226572101647125
LM6	CAPS	CAPS-2 total	PTSD	PTSD	Mixed/Hierarchical/Random	-0.405667832387109	0.0614108499952165
LM6	CAPS_AF	CAPS-2 Associated Features	PTSD	PTSD	Mixed/Hierarchical/Random	-0.386467949901448	0.0363075256866828
LM6	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	Mixed/Hierarchical/Random	-0.186820750269397	0.0428464983057364
LM6	DTS	Davidson PTSD Scale total	PTSD	PTSD	Mixed/Hierarchical/Random	-0.433626562334422	0.0386486537324069
LM6	HAM_A	HAM-A total	anxiety (general)	GAD	Mixed/Hierarchical/Random	-0.121053648367075	0.0371037341651184
LM6	IES	IES total	PTSD	PTSD	Mixed/Hierarchical/Random	-0.255838489329648	0.0406645978532524
LM60	CGI-S	CGI-S = Clinical Global Impression severity scale	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.351099592294512	0.0269748277689889
LM60	YBOCS	Y-BOCS total	OCD	OCD	LOCF	-1.1405848244277	0.0622345602260092
LM67	CGI	CGI	clinical impression (general)	psychiatric symptoms (general)	Unclear	-0.874319168318061	0.194263543895105
LM67	NIMH_GOCS	NIMH-OCD = National Institute of Mental Health Global OCD Scale	OCD	OCD	Unclear	-0.84450023859519	0.210106704115032
LM67	YBOCS	Y-BOCS total	OCD	OCD	Unclear	-0.895352088450134	0.188704887816515
LM69	CPRS_OCD	OCD scale	OCD	OCD	LOCF	0.246242535923511	0.150383046609692

LM69	NIMH_GOCS	NIMH-OCD = National Institute of Mental Health Global OCD Scale	OCD	OCD	LOCF	-0.387582713536209	0.153139335062664
LM69	YBOCS	Y-BOCS total	OCD	OCD	LOCF	-0.469573576468501	0.142116810645409
LM71	YBOCS	Y-BOCS total	OCD	OCD	LOCF	-1.13290194955859	0.0617237984063304
LM72	CGI-S	CGI-S = Clinical Global Impression severity scale	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.193330294161598	0.0396403641963503
LM72	GA_VAS	Global Anxiety VAS	anxiety (general)	GAD	LOCF	-0.165927220918203	0.0277448632340076
LM72	HADS_A	HADS-A	anxiety (general)	GAD	LOCF	-0.338736948143764	0.0363989922454104
LM72	HAM_A	HAM-A total	anxiety (general)	GAD	LOCF	-0.0969576272981456	0.0779721178591617
LM73	LSAS	LSAS - Liebowitz Social Anxiety Scale	social anxiety	social anxiety	LOCF	-0.336563130476382	0.0346512848666479
LM74	CAS	CAS - COVI Anxiety Scale	anxiety (general)	GAD	LOCF	-0.57383724195528	0.0788730042191649
LM74	CGI-S	CGI-S = Clinical Global Impression severity scale	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.49730509661538	0.0490214936766551
LM74	HAM_A	HAM-A total	anxiety (general)	GAD	LOCF	-0.28335456057042	0.0560275142198966
LM76	BSPS	BSPS - Brief Social Phobia Scale	social anxiety	social anxiety	LOCF	-0.941139005461723	0.755503387843023
LM76	FQ	Fear Questionnaire - Total	fear	phobia	LOCF	-0.614738809367854	0.565820271791833
LM76	LSAS	LSAS - Liebowitz Social Anxiety Scale	social anxiety	social anxiety	LOCF	-1.5911838668432	0.808970593516625
LM86	ACQ	Agoraphobic Cognitions Questionarie	panic	panic	Mixed/Hierarchical/Random	-0.0425628318722365	0.0583112491060051
LM86	BSQ	Body Sensations Questionnaire	somatic anxiety	somatic	Mixed/Hierarchical/Random	0.174021324744664	0.07135627783812

LM86	CGI-S	CGI-S = Clinical Global Impression severity scale	clinical impression (severity)	psychiatric symptoms (general)	Mixed/Hierarchical/Random	-1.55279870974033	0.161530717119452
LM86	MI-AAL	avoidance-alone subscale of the Mobility Inventory for Agoraphobia (MI-AAL)	avoidance (panic)	panic	Mixed/Hierarchical/Random	0.0471875226281513	0.0532228394087688
LM95	CGI-S	CGI-S = Clinical Global Impression severity scale	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.652260824999814	0.133559382813197
LM95	IES_R	Impact of Event Scale-Revised: total score	PTSD	PTSD	LOCF	-1.01257366043148	0.868515987667249
MC10	CGI-S	CGI-Severity	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.871485991929581	0.0264459542648743
MC10	LSAS	Liebowitz Social Anxiety Scale (LSAS)	social anxiety	social anxiety	LOCF	-0.487699784207584	0.0220836086510707
MC10	SADS	Social Avoidance and Distress Scale	social anxiety	social anxiety	LOCF	-0.382783741634625	0.0214044226735938
MC12	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.491037457211079	0.0386571850068216
MC12	FQ_F	Phobia Scale – Fear	fear (phobia)	phobia	LOCF	-0.222773886214315	0.0204721725141613
MC12	FQ_AV	Phobia Scale – Avoidance	avoidance (phobia)	phobia	LOCF	-0.183866672013408	0.0192895857627823
MC12	HAM_A	HAM-A	anxiety (general)	GAD	LOCF	-0.371719409706261	0.0319786746120002
MC12	PDSS	Panic Disorder Severity Scale (PDSS)	panic	panic	LOCF	-0.983935919138733	0.0561754489620449
MC13	CGI-S	CGI-Severity	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.888644607980234	0.099728889895995
MC13	CGI-S	CGI-Severity	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.921641798566183	0.0991258329837433
MC13	CGI-S	CGI-Severity	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.714580803597877	0.0964491869685866

MC13	LSAS	Liebowitz Social Anxiety Scale (LSAS)	social anxiety	social anxiety	LOCF	-0.733443475950587	0.0799368459231838
MC13	LSAS	Liebowitz Social Anxiety Scale (LSAS)	social anxiety	social anxiety	LOCF	-0.437165714036319	0.0749681512922611
MC13	LSAS	Liebowitz Social Anxiety Scale (LSAS)	social anxiety	social anxiety	LOCF	-0.449402995163015	0.0763515504478216
MC13	SADS	Social Avoidance and Distress Scale	social anxiety	social anxiety	LOCF	-0.761284925589592	0.0827191001156355
MC13	SADS	Social Avoidance and Distress Scale	social anxiety	social anxiety	LOCF	-0.517129460843719	0.0780992072805873
MC13	SADS	Social Avoidance and Distress Scale	social anxiety	social anxiety	LOCF	-0.686404647477936	0.0816208107862386
MC14	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.498981303189453	0.0299656567097255
MC14	LSAS	Liebowitz Social Anxiety Scale (LSAS)	social anxiety	social anxiety	LOCF	-0.885828939394371	0.0359755911626184
MC15	BSPS	Duke Brief Social Phobia Scale (BSPS)	social anxiety	social anxiety	LOCF	-0.55629706547761	0.0258706534731637
MC15	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.56952606088662	0.0245537820120631
MC15	HAM_A	HAM-A	anxiety (general)	GAD	LOCF	-0.300248152761861	0.0151737182033477
MC15	LSAS	Liebowitz Social Anxiety Scale (LSAS)	social anxiety	social anxiety	LOCF	-0.59148067276381	0.0278804565651736
MC16	CGI-S	CGISeverity (CGI-S)	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.604891340850324	0.204378787540087
MC16	CYBOCS	CY-BOCS	OCD (child)	OCD	LOCF	-0.921068041455426	0.234478225903155
MC16	NIMH_GOCS	NIMH-OC	OCD	OCD	LOCF	-0.260933451040715	0.198659103548488
MC17	LSAS	Liebowitz Social Anxiety Scale (LSAS)	social anxiety	social anxiety	LOCF	-0.64659276697537	0.0530794184275367

MC17	LSAS	Liebowitz Social Anxiety Scale (LSAS)	social anxiety	social anxiety	LOCF	-0.811029225652082	0.0548237270254037
MC17	SPIN	Social Phobia Inventory	social anxiety	social anxiety	LOCF	-0.768145871585536	0.0436527766693333
MC2	FQ	Phobia Scale	phobia	phobia	LOCF	-0.380390999422767	0.115810716039014
MC2	FQ	Phobia Scale	phobia	phobia	LOCF	-1.19643183020022	0.136189350622542
MC2	FQ	Phobia Scale	phobia	phobia	LOCF	-7.91741591784332	0.597336806929123
MC20a	PAAS_AA_T_P	%time worrying	anticipatory anxiety	GAD	LOCF	-0.100923939280427	0.0466205346562094
MC20a	PAAS_PA_WK_N	PAAS - panic attack	panic attack	panic	LOCF	-0.378761385663281	0.0466012750023587
MC20a	PAAS_PAL_WK_N	PAAS - Limited symptom attacks	panic attack (limited)	panic	LOCF	-0.324247238477408	0.0462877783568242
MC20a	PAAS_UA_WK_DN	PAAS - unexpected attack	unexpected panic attack	panic	LOCF	-0.304858305965752	0.0467340134206335
MC20b	PAAS_PA_WK_N	PAAS - panic attack	panic attack	panic	LOCF	-0.522551728759832	0.14662051961541
MC20b	PAAS_PA_WK_N	PAAS - panic attack	panic attack	panic	LOCF	-0.423151022606068	0.139204400915965
MC20b	PAAS_PA_WK_N	PAAS - panic attack	panic attack	panic	LOCF	-0.121250507149682	0.141562228163036
MC20b	PAAS_PAL_WK_N	PAAS - Limited symptom attacks	panic attack (limited)	panic	LOCF	-0.311263192155349	0.143932633690107
MC20b	PAAS_PAL_WK_N	PAAS - Limited symptom attacks	panic attack (limited)	panic	LOCF	-0.335910734638967	0.137874010852535
MC20b	PAAS_PAL_WK_N	PAAS - Limited symptom attacks	panic attack (limited)	panic	LOCF	-0.283579258723304	0.142080581300147
MC20b	PAAS_UA_WK_DN	PAAS - unexpected attack	unexpected panic attack	panic	LOCF	-0.332548766866426	0.145587122585403

MC20b	PAAS_UA_WK_DN	PAAS - unexpected attack	unexpected panic attack	panic	LOCF	-0.371890986306236	0.139795024444299
MC20b	PAAS_UA_WK_DN	PAAS - unexpected attack	unexpected panic attack	panic	LOCF	-0.106396729938198	0.142174679399488
MC22	HADS_A	HAD-Anxiety Subscale	anxiety (general)	GAD	LOCF	-0.258526786952658	0.0601605114616971
MC22	HAM_A	HAM-A	anxiety (general)	GAD	LOCF	-0.538274520038385	0.165198171674461
MC25	SAS_CA	Social Anxiety Scale for Children and Adolescent (SAS-CA)	social anxiety (child)	social anxiety	LOCF	-0.581372319704758	0.0474840267738051
MC26	CYBOCS	CYBOCS	OCD (child)	OCD	LOCF	-0.151020239937988	0.1558385439182
MC28	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.339922905154325	0.0422634797071146
MC28	CYBOCS	CY-BOCS	OCD (child)	OCD	LOCF	-0.700825861250215	0.0454088490344553
MC28	NIMH_GOCS	NIMH GOCS	OCD	OCD	LOCF	-0.499087823020904	0.0463462452130454
MC3	HAM_A	HAM-A	anxiety (general)	GAD	LOCF	-0.307633851572878	0.048116193846123
MC31	CAPS	Clinician-Administered PTSD Scale, part 2	PTSD	PTSD	LOCF	-0.871293226979787	0.0541096386928722
MC31	CAPS	Clinician-Administered PTSD Scale, part 2	PTSD	PTSD	LOCF	-0.841221989504018	0.0538425142862902
MC32	CAPS	Clinician Administered PTSD Scale (1-17)	PTSD	PTSD	LOCF	-0.278999173114065	0.147643995260599
MC32	CAPS_AF	Clinician Administered PTSD Scale - Associated Features	PTSD	PTSD	LOCF	0.00156558065016693	0.124262483841618
MC32	HAM_A	HAM-A	anxiety (general)	GAD	LOCF	-0.138174104223465	0.13819855417039
MC33	CAPS	Clinician Administered PTSD Scale	PTSD	PTSD	LOCF	-0.535523103205238	0.117729273552964

MC33	CAPS	Clinician Administered PTSD Scale	PTSD	PTSD	LOCF	-0.621182041492074	0.119774512347
MC33	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.524612198835786	0.145091714967783
MC33	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.204658327930409	0.140002997179906
MC33	DTS	Davidson Trauma Scale	PTSD	PTSD	LOCF	-0.233742922398243	0.0726520951202202
MC33	DTS	Davidson Trauma Scale	PTSD	PTSD	LOCF	-0.130644903505671	0.0719708169129591
MC33	HAM_A	HAM-A	anxiety (general)	GAD	LOCF	-0.1195891730282	0.0661181492544698
MC33	HAM_A	HAM-A	anxiety (general)	GAD	LOCF	-0.113388659267244	0.0663434191979346
MC33	TOP8	TOP-8	PTSD	PTSD	LOCF	0.137177792530268	0.134590865096738
MC33	TOP8	TOP-8	PTSD	PTSD	LOCF	0.187753307522724	0.134343798679577
MC34	CAPS	Clinician Administered PTSD Scale	PTSD	PTSD	LOCF	-0.759826304127986	0.0949044378054871
MC34	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-1.78103578440608	0.109957978400773
MC34	DTS	Davidson Trauma Scale	PTSD	PTSD	LOCF	-0.655668031222213	0.0637580906001894
MC34	HAM_A	HAM-A	anxiety (general)	GAD	LOCF	-0.824854613472736	0.0696369373439422
MC34	TOP8	TOP-8	PTSD	PTSD	LOCF	-0.645553534993528	0.111407445508915
MC38	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.866423672792104	0.0475865810537489
MC38	HAM_A	HAM-A	anxiety (general)	GAD	LOCF	-0.571944765492951	0.0520230945354241
MC39	HAM_A	Hamilton anxiety scale score	anxiety (general)	GAD	LOCF	-0.384077351551397	0.0680807191851527

MC39	HAM_A	Hamilton anxiety scale score	anxiety (general)	GAD	LOCF	-1.37902921093569	0.0877818267245112
MC39	PAAS_PA_WK_N	Total number of panic attacks/week	panic attack	panic	LOCF	-0.105260643106419	0.0587399838029328
MC39	PAAS_PA_WK_N	Total number of panic attacks/week	panic attack	panic	LOCF	-0.140728569123994	0.0596367103399871
MC4	HAM_A	Hamilton Anxiety Rating Scale	anxiety (general)	GAD	LOCF	-0.435814112038605	0.413880262569642
MC40	HAM_A	HAM-A	anxiety (general)	GAD	LOCF	-0.543920688638513	0.0682560167918013
MC40	PAAS_PAF_WK_N	Full Panic Attacks per week	panic attack (full)	panic	LOCF	-0.0944328874263338	0.0400205201629529
MC40	PDSS	Panic Disorder Severity Scale (PDSS)	panic	panic	LOCF	-1.07019730843988	0.124790678415017
MC40	STAI_STA	State Anxiety Inventory (SAI)	state anxiety (general)	GAD	LOCF	-0.536049073426506	0.0425923570768259
MC42	CAS	Covi Anxiety Scale (CAS)	anxiety (general)	GAD	LOCF	-0.210484202232828	0.113698196214172
MC42	CAS	Covi Anxiety Scale (CAS)	anxiety (general)	GAD	LOCF	-0.0510236640920367	0.108507791378836
MC42	CAS	Covi Anxiety Scale (CAS)	anxiety (general)	GAD	LOCF	-0.262424355026377	0.112937538228438
MC42	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.361099376901288	0.133015582883766
MC42	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.206034325578929	0.125376620757144
MC42	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.223392265810162	0.129223579249366
MC42	CPRS_OCD	CPRS-OCD subscale	OCD (child)	OCD	LOCF	-0.198009324495876	0.128374797757531
MC42	CPRS_OCD	CPRS-OCD subscale	OCD (child)	OCD	LOCF	-0.323967332909595	0.125628084529934
MC42	CPRS_OCD	CPRS-OCD subscale	OCD (child)	OCD	LOCF	-0.328140768930346	0.129162230181122

MC42	YBOCS	Y-BOCS	OCD	OCD	LOCF	-0.589389395262429	0.12774453840455
MC42	YBOCS	Y-BOCS	OCD	OCD	LOCF	-0.397794558404583	0.119681777699323
MC42	YBOCS	Y-BOCS	OCD	OCD	LOCF	-0.317326428860534	0.121798086521847
MC44	HADS_A	HADS anxiety subscale	anxiety (general)	GAD	LOCF	-0.4950942258834	0.0484548584120231
MC44	HAM_A	HAMA	anxiety (general)	GAD	LOCF	-0.951411332771208	0.0908337944630801
MC45	NIMH_GOCS	NIMH-OC	OCD	OCD	LOCF	-0.573091249535557	0.0739622470143186
MC45	NIMH_GOCS	NIMH-OC	OCD	OCD	LOCF	-0.821373622734619	0.0899650067367786
MC45	NIMH_GOCS	NIMH-OC	OCD	OCD	LOCF	-0.732789760984332	0.0895035109175915
MC45	YBOCS	Y-BOCS	OCD	OCD	LOCF	-0.743441896260542	0.0950321458731142
MC45	YBOCS	Y-BOCS	OCD	OCD	LOCF	-0.983778603425426	0.117433994055235
MC45	YBOCS	Y-BOCS	OCD	OCD	LOCF	-1.24447112652959	0.125250907661653
MC51	CAS	Clinical Anxiety Scale (CAS)	anxiety (general)	GAD	LOCF	-0.14594221041741	0.088482680938531
MC51	CGI-S	CGI severity	clinical impression (severity)	psychiatric symptoms (general)	LOCF	0.479003388896702	0.0909886236236609
MC51	CGI_E	CGI efficacy	clinical impression (efficacy)	psychiatric symptoms (general)	LOCF	-0.487554814981119	0.151572672307464
MC51	PAAS_AA	Anticipatory intensity	anticipatory anxiety	GAD	LOCF	-0.227030103316042	0.0737279493029697
MC51	PAAS_AA_T_P	Anticipatory anxiety (%)	anticipatory anxiety	GAD	LOCF	-0.0132022462440178	0.0692413825911932
MC51	PAAS_PAF_WK_N	Full panic attacks/weekb	panic attack (full)	panic	LOCF	-0.227894991425983	0.0706884461528982

MC51	PAAS_PAL_WK_N	Limited panic attacks/week	panic attack (limited)	panic	LOCF	-0.0926199502432197	0.0723393736237974
MC55	HAM_A	HAMA	anxiety (general)	GAD	LOCF	-0.329024818127338	0.0872977108467122
MC55	HAM_A	HAMA	anxiety (general)	GAD	LOCF	-0.599891286427086	0.071679562060493
MC55	HAM_A	HAMA	anxiety (general)	GAD	LOCF	-0.587321015778156	0.070778780822593
MC56	HAM_A	HAM-A	anxiety (general)	GAD	Unclear	-2.24150593386951	0.502476547420537
MC6	HAM_A	HAMA	anxiety (general)	GAD	LOCF	-0.41211079312799	0.0450434554565327
MC6	PSWQ	PSWQ	worry (GAD)	GAD	LOCF	-0.306937304863669	0.0363850693412463
MC62	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.698392985897364	0.112749724563892
MC62	IES_R	Event Scale – Revised (IES-R)	PTSD	PTSD	LOCF	-2.26888182854349	0.715692996243586
MC73	PAAS_PAF_WK_N	Full-symptom panic attacks at baseline	panic attack (full)	panic	LOCF	0.262057841160195	0.0408106777635585
MC73	PAAS_PAF_WK_N	Full-symptom panic attacks at baseline	panic attack (full)	panic	LOCF	-0.0809318455487767	0.0408136166412
MC73	PAAS_PAF_WK_N	Full-symptom panic attacks at baseline	panic attack (full)	panic	LOCF	-0.255910534414473	0.0427640284836731
MC73	PDSS	PDSS	panic	panic	LOCF	-1.42644913175607	0.144793023657791
MC77	HADS_A	HAD - anxiety subscale	anxiety (general)	GAD	LOCF	-0.423292752997891	0.0252001794477692
MC77	HAM_A	HAM-A	anxiety (general)	GAD	LOCF	-1.37080021678031	0.0602717014214067
MC79	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.988990328892815	0.104123731742637
MC79	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.964072260059015	0.103424311254195

MC79	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-1.0680100738446	0.104904108142391
MC79	FQ_F	Phobia Scale (fear)	fear (phobia)	phobia	LOCF	-0.35035638153721	0.0454655422785409
MC79	FQ_AV	Phobia Scale (avoidance)	avoidance (phobia)	phobia	LOCF	-0.273452821661214	0.0432027565564592
MC81	HAM_A	HAM-A	anxiety (general)	GAD	LOCF	-0.818136179659416	0.26579465779166
MC81	MSPRS_F	Marks-Sheehan Phobia Rating Scale (Fear)	fear	phobia	LOCF	-0.985279753136499	0.339745460782456
MC81	MSPRS_AV	Marks-Sheehan Phobia Rating Scale (Avoidance)	avoidance (phobia)	phobia	LOCF	-0.223860726463671	0.258270093731638
MC81	PAAS_PA_WK_N	Panic Frequecy (per week)	panic attack	panic	LOCF	0.377374602185948	0.292858849863363
MC81	SCL61	SCL-61	psychiatric symptoms (general)	psychiatric symptoms (general)	LOCF	-0.351443722454722	0.25074187831987
MC82	CGI-S	CGI-S (change from baseline)	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.644377697147378	0.0647607614520025
MC82	HAM_A	HAM-A	anxiety (general)	GAD	LOCF	0.099961155583119	0.0801222152788349
MC82	PAAS_AA_T_P	Antecipatory Anxiety (% of time worrying)	anticipatory anxiety	GAD	LOCF	-0.00232890233112867	0.0340916708696623
MC82	PAAS_PAF_EB	Full Panic Attack (ratio: em point-baseline)	panic attack (full)	panic	LOCF	-0.0531182581810795	0.0346784711390743
MC82	PDSS	PDSS	panic	panic	LOCF	-0.164490716992607	0.0348270285953204
MJ1	LSAS	Liebowitz Social Anxiety Scale total	social anxiety	social anxiety	LOCF	-0.837669289416128	0.0394553308056188
MJ14	HADS_A	Hospital Anxiety and Depression Scale Anxiety Subscale	anxiety (general)	GAD	LOCF	-0.46323356234108	0.0227732576210231
MJ14	HADS_D	Hospital Anxiety and Depression Scale Depression Subscale	anxiety (general)	GAD	LOCF	-0.198618700022229	0.0197805785467236

MJ14	HAM_A	Hamilton Anxiety Scale total score	anxiety (general)	GAD	LOCF	-0.35033671458723	0.0236453238092626
MJ16	ADIS_C	Anxiety Disorders Interview Schedule for Children - Revised Severity score Rated by the child	anxiety (general)(child)	GAD	Unclear	-0.317568293680607	0.554261854625454
MJ16	ADIS_P	Anxiety Disorders Interview Schedule for Children - Revised Severity score Rated by the parent	anxiety (general)(child)	GAD	Unclear	-2.35812766502456	1.17531252223087
MJ16	HAM_A	Hamilton Anxiety Rating Scale total score	anxiety (general)	GAD	Unclear	-2.75029454844712	0.774801964410262
MJ16	MASC	Multidimensional Anxiety Scale for Children total score	anxiety (general)(child)	GAD	Unclear	-0.345238890484827	0.387730535595439
MJ16	RCMAS	Revised Children's Manifest Anxiety Scale score	anxiety (general)(child)	GAD	Unclear	-1.06829624114402	0.378308139001662
MJ17	PAAS_PA_WK_N	Number of panic attacks	panic attack	panic	Completers	0.0165766413667774	0.135782033825143
MJ2	HAM_A	Hamilton Anxiety Scale Total	anxiety (general)	GAD	LOCF	-0.413673426430391	0.171267094520831
MJ2	HAM_A	Hamilton Anxiety Scale Total	anxiety (general)	GAD	LOCF	-0.872519422970301	0.190253150813982
MJ2	HAM_A	Hamilton Anxiety Scale Total	anxiety (general)	GAD	LOCF	-0.604823027543269	0.177097151362812
MJ22	HAM_A	Hamilton Anxiety Scale	anxiety (general)	GAD	LOCF	-0.660889090697237	0.161418980047947
MJ25	CGI-S	Clinical Global Impression Severity Scale	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.416065969153984	0.0123005035132668
MJ25	HAM_A	Hamilton Rating Scale for Anxiety	anxiety (general)	GAD	LOCF	-0.313680926323419	0.00886875212625279
MJ25	MSPRS_F	Marks-Sheehan Phobia Scale fear total score	fear	phobia	LOCF	-0.230139342379115	0.00760214643170765
MJ25	MSPRS_AV	Marks-Sheehan Phobia Scale avoidance total score	avoidance (phobia)	phobia	LOCF	-0.226116187348384	0.00735365139524046

MJ25	PAAS_PA_WK_N	Number of full panic attacks on week 2	panic attack	panic	LOCF	-0.0702896802139858	0.00708555692362359
MJ3	CGI-S	Clinical Global Impression Severity	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.838178753230043	0.0616240339171956
MJ3	CGI-S	Clinical Global Impression Severity	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-1.36990376769051	0.0684303393331604
MJ3	HADS_A	Hospital Anxiety and Depression Scale anxiety subscale	anxiety (general)	GAD	LOCF	-1.23928015345067	0.0426084266239782
MJ3	HADS_A	Hospital Anxiety and Depression Scale anxiety subscale	anxiety (general)	GAD	LOCF	-0.920639326655617	0.0384585707150832
MJ3	HAM_A	Hamilton Anxiety Scale Total	anxiety (general)	GAD	LOCF	-0.966086189040117	0.0907514777860236
MJ3	HAM_A	Hamilton Anxiety Scale Total	anxiety (general)	GAD	LOCF	-1.08222178020893	0.091217283021375
MJ36	CGI-S	Clinical Global Impression Severity of Illness scale score	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.676875215140103	0.0976153080372486
MJ36	CGI-S	Clinical Global Impression Severity of Illness scale score	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.509620878052931	0.0960190687207329
MJ36	HAM_A	Hamilton Anxiety Rating Scale score	anxiety (general)	GAD	LOCF	-0.247056334713087	0.0440114234824006
MJ36	HAM_A	Hamilton Anxiety Rating Scale score	anxiety (general)	GAD	LOCF	-0.0474701379540722	0.0433067359042321
MJ36	PAAS	Panic and Agoraphobia Scale score	panic	panic	LOCF	-0.535829228828397	0.0427822377748605
MJ36	PAAS	Panic and Agoraphobia Scale score	panic	panic	LOCF	-0.406686677991597	0.0424998834142318
MJ36	PAAS_PA_WK_N	Panic attacks/week	panic attack	panic	LOCF	-0.118779192827091	0.0381121262986934
MJ36	PAAS_PA_WK_N	Panic attacks/week	panic attack	panic	LOCF	-0.0935051946876677	0.0385316380502873
MJ4	CGI_OCD	CGI-OCD	OCD	OCD	LOCF	-0.760048351848986	0.67193533626221

MJ4	LOICV	Leyton Obsessional Inventory-Child Version Symptoms	obsession (child)	OCD	LOCF	-0.168948378227262	0.449857153133028
MJ4	RCMAS	Revised Children's Manifest Anxiety Scale Total	anxiety (general)(child)	GAD	LOCF	0.0972706257365526	0.447714762191992
MJ4	YBOCS	Children's Yale-Brown Obsessive Compulsive Scale Total	OCD	OCD	LOCF	-1.60376312709261	0.804867348022844
MJ42	LSAS	Liebowitz Social Anxiety Scale	social anxiety	social anxiety	LOCF	-0.698339373067568	0.0501658416351428
MJ42	LSAS	Liebowitz Social Anxiety Scale	social anxiety	social anxiety	LOCF	-0.729956068412802	0.0507284400850915
MJ42	SPIN	Social Phobia Inventory	social anxiety	social anxiety	LOCF	-0.842234103213574	0.0425414900290739
MJ44	NIMH_GOCS	National Institute of Mental Health Osessive-Compulsive Scale	OCD	OCD	LOCF	-0.825155331146921	0.0769846504701909
MJ44	NIMH_GOCS	National Institute of Mental Health Osessive-Compulsive Scale	OCD	OCD	LOCF	-0.948013073739099	0.0776243423910562
MJ44	NIMH_GOCS	National Institute of Mental Health Osessive-Compulsive Scale	OCD	OCD	LOCF	-0.640874483810584	0.073752437051275
MJ44	YBOCS	Yale-Brown Obsessive-Compulsive Scale	OCD	OCD	LOCF	-1.09586008769188	0.144229509084286
MJ44	YBOCS	Yale-Brown Obsessive-Compulsive Scale	OCD	OCD	LOCF	-1.11824549659992	0.142582582980571
MJ44	YBOCS	Yale-Brown Obsessive-Compulsive Scale	OCD	OCD	LOCF	-0.787736270308775	0.135332485419693
MJ5	CGI	Clinician Global Impression Scale	clinical impression (general)	psychiatric symptoms (general)	LOCF	-0.375387270679967	0.0553416210696491
MJ5	CYBOCS	Children's Yale-Brown Obsessive Compulsive Scale	OCD (child)	OCD	LOCF	-0.666133572244989	0.0696611166716426
MJ5	NIMH_GOCS	NIMH Global Obsessive Compulsive Scale	OCD	OCD	LOCF	-0.457006504156923	0.0682460900585724

MJ5	PAGI	Parent Global Impression Scale	parent impression (general)	psychiatric symptoms (general)	LOCF	-0.287303610764644	0.0543207353927967
MJ5	PGI	Subject Global Impression Scale	patient impression (general)	psychiatric symptoms (general)	LOCF	0.0554621280520977	0.05374788881016
MJ53	BSPS	Brief Social Phobia Scale	social anxiety	social anxiety	LOCF	-0.827577424016603	0.1061032084092
MJ53	LSAS	Liebowitz Social Anxiety Scale	social anxiety	social anxiety	LOCF	-0.837567889421583	0.0781649129053738
MJ53	SPIN	Social Phobia Inventory	social anxiety	social anxiety	LOCF	-0.565883724849287	0.0774117994407535
MJ54	LSAS	Liebowitz Social Anxiety Scale total	social anxiety	social anxiety	LOCF	-0.703833520178714	0.0441684441435051
MJ56	CGI-S	Clinical Global Impression Severity Scale	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.378622645422273	0.0686924468745009
MJ56	PARS	Pediatric Anxiety Rating Scale Severity total score	anxiety (general)(child)	GAD	LOCF	-1.50643224432366	0.11177124003708
MJ6	CGI-S	Clinician Global Impression Severity	clinical impression (severity)	psychiatric symptoms (general)	LOCF	0.656237028082903	0.157087944631301
MJ6	CSDC	Child Stress Disorder Checklist	PTSD	PTSD	LOCF	0.475437963883579	0.078520584309376
MJ6	UCLA_PTSD	University of California at Los Angeles Post-Traumatic Stress Disorder Index for DSM IV	PTSD	PTSD	LOCF	0.105466226832265	0.119842820542054
MJ64	CAPS	Clinical Administered PTSD Scale	PTSD	PTSD	LOCF	-0.223461252213768	1.1880345833822
MJ64	CAPS	Clinical Administered PTSD Scale	PTSD	PTSD	LOCF	0.251751300526784	1.15381611845229
MJ64	IES_R	Impact of Event Scale Revised	PTSD	PTSD	LOCF	1.10028127231664	1.10485064990112
MJ64	IES_R	Impact of Event Scale Revised	PTSD	PTSD	LOCF	1.11806385138948	1.11301118850104
MJ66	CAPS	Clinical Administered PTSD Scale Part 2 total score	PTSD	PTSD	LOCF	-0.539354388319594	0.040853419444631

MJ66	DTS	Davidson Trauma Scale total score	PTSD	PTSD	LOCF	-0.485783043575366	0.030580077648931
MJ66	TOP8	Treatment Outcome PTSD Scale	PTSD	PTSD	LOCF	-1.77345804597957	0.0313227726369623
MJ70	BSPS	Brief Social Phobia Scale total	social anxiety	social anxiety	LOCF	-0.787521708305041	0.0501733887244773
MJ70	CGI-S	Clinical Global Impression Severity	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-1.11336305962027	0.0635297917474482
MJ70	FNE	Fear of negative evaluation Scale	fear of negative evaluation	social anxiety	LOCF	-0.657737696791917	0.0394613468134167
MJ70	FQ_SA	Marks Fear Questionnaire Social Phobia subscale	social anxiety	social anxiety	LOCF	-0.810242986009049	0.0382902280081083
MJ70	SADS	Social Avoidance and Distress Scale	social anxiety	social anxiety	LOCF	-0.86525202999456	0.0554334409535498
MJ70	SPAI_SA	Social Phobia And anxiety Inventory social phobia subscale	social anxiety	social anxiety	LOCF	-1.00202630374456	0.051505879565903
MJ71	CAPS	Clinician-Administered PTSD Scale total score	PTSD	PTSD	Unclear	-0.253179755422702	0.255590852728322
MJ73	HAM_A	Hamilton Anxiety Scale	anxiety (general)	GAD	Completers	-1.20798767216634	0.379519109564276
MJ73	LSAS_AV	Social Phobia Avoidance Ratings	avoidance (social anxiety)	social anxiety	Completers	0.011060286527261	0.246732059361244
MJ73	SCL90	90 Items Symptom Checklist general symptom index	psychiatric symptoms (general)	psychiatric symptoms (general)	Completers	-0.0755021784627874	0.263034646496896
MJ73	SPAI	Social Phobia Anxiety Ratings	social anxiety	social anxiety	Completers	-0.915681826164285	0.294377709168589
MJ77	HAM_A	Hamilton Anxiety Scale total	anxiety (general)	GAD	LOCF	-0.509141437683167	0.106238045248742
MJ77	HAM_A	Hamilton Anxiety Scale total	anxiety (general)	GAD	LOCF	-0.634773946781073	0.109412284978255
MJ77	HAM_A	Hamilton Anxiety Scale total	anxiety (general)	GAD	LOCF	-0.811468891051762	0.115856672423625

MJ78	K_GSADS_A	Kutcher Generalized Social Anxiety Disorder Scale for Adolescents	social anxiety	social anxiety	LOCF	-0.882302643766843	0.0292469131009751
MJ78	LSAS_C	Liebowitz Social Anxiety Scale for Children and Adolescents total score	social anxiety (child)	social anxiety	LOCF	-0.771829112570867	0.0295705599246609
MJ78	SPAI	Social Phobia and Anxiety Inventory difference score	social anxiety	social anxiety	LOCF	-1.04715849965763	0.0278513641036695
MJ78	SPIN_C	Social Phobia and Anxiety Inventory for Children	social anxiety (child)	social anxiety	LOCF	-0.762111832225882	0.0270852980894693
MJ79	CGI-S	Clinical Globe Impression Severity	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-1.00237423521189	0.083592845910612
MJ79	PARS	Pediatric Anxiety Rating Scale total score	anxiety (general)(child)	GAD	LOCF	-0.517698398392553	0.071579238394674
MJ80	PARS	Pediatric Anxiety Rating Scale total score	anxiety (general)(child)	GAD	LOCF	-2.86433376814367	0.179892442368593
MJ84	CGI-S	Clinical Global Impression - Severity	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.568171678483078	0.033872761668266
MJ84	LSAS	Liebowitz Social Anxiety Scale total score	social anxiety	social anxiety	LOCF	-0.6560624820673	0.0387747434811701
MJ85	FQ	Fear Questionnaire	fear	phobia	Unclear	-0.736939181829259	0.183157326512967
MJ85	HAM_A	Hamilton Anxiety Scale	anxiety (general)	GAD	Unclear	-0.880034168592222	0.18871148904592
MJ85	SCL90	90-Item Symptom Checklist - General symptom index	psychiatric symptoms (general)	psychiatric symptoms (general)	Unclear	-1.76667272118889	0.228028312594824
MJ85	STAI_STA	State Trait Anxiety Inventory - State score	state anxiety (general)	GAD	Unclear	-1.43293729800134	0.195324965807374
MJ89	HADS_A	Hospital Anxiety and Depression Scale - Anxiety Subscale total score	anxiety (general)	GAD	LOCF	-0.638696666636714	0.0651215534544911
MJ89	HAM_A	Hamilton Anxiety Rating Scale total score	anxiety (general)	GAD	LOCF	-0.163136671659654	0.0820156278573843

MJ93	CAPS	Clinician-Administered PTSD Scale Part 2 total score	PTSD	PTSD	LOCF	-0.252461497748821	0.216352993083127
MJ93	CGI-S	Clinical Global Impression Severity	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.315228943150478	0.171987395197936
MJ94	YBOCS	Yale-Brown Obsessive-Compulsive Scale total score	OCD	OCD	LOCF	-0.630492041094105	0.0345696138876144
MJ96	CGI-S	Clinical Global Impression - Severity of Ilness scale	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.829946254844362	0.0774881393981623
MJ96	HADS_A	Hospital Anxiety and Depression Scale anxiety score	anxiety (general)	GAD	LOCF	-1.00508151139845	0.0642652584625322
MJ96	HAM_A	Hamilton Anxiety Rating Scale total score	anxiety (general)	GAD	LOCF	-0.879059112481949	0.114423209177242
MJ97	MOCI	Maudsley Obsessional Compulsive Questionnaire	OCD	OCD	Completers	-0.149403664411349	0.320246044620748
MJ97	NIMH_GOCS	NIMH obsessive-compulsive scale	OCD	OCD	Completers	-0.565352385453409	0.326832207584138
MJ97	YBOCS	Yale-Brown Obsessive-Compulsive Scale	OCD	OCD	Completers	-0.241055863065976	0.322772065930144
UNG1	CGI-S	CGI Severity score	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-1.09604014745262	0.0624962400218862
UNG1	HAM_A	Hamilton Anxiety scale (HAM-A) total score	anxiety (general)	GAD	LOCF	-0.600914741274885	0.0765753764569613
UNG10	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.14350793095119	0.290003174743885
UNG10	LSAS	Liebowitz Social Anxiety Scale	social anxiety	social anxiety	LOCF	-0.560683832454027	0.315735056964934
UNG11	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	0.136474626551991	0.0790250078525717
UNG11	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.249159424903963	0.080470723162884

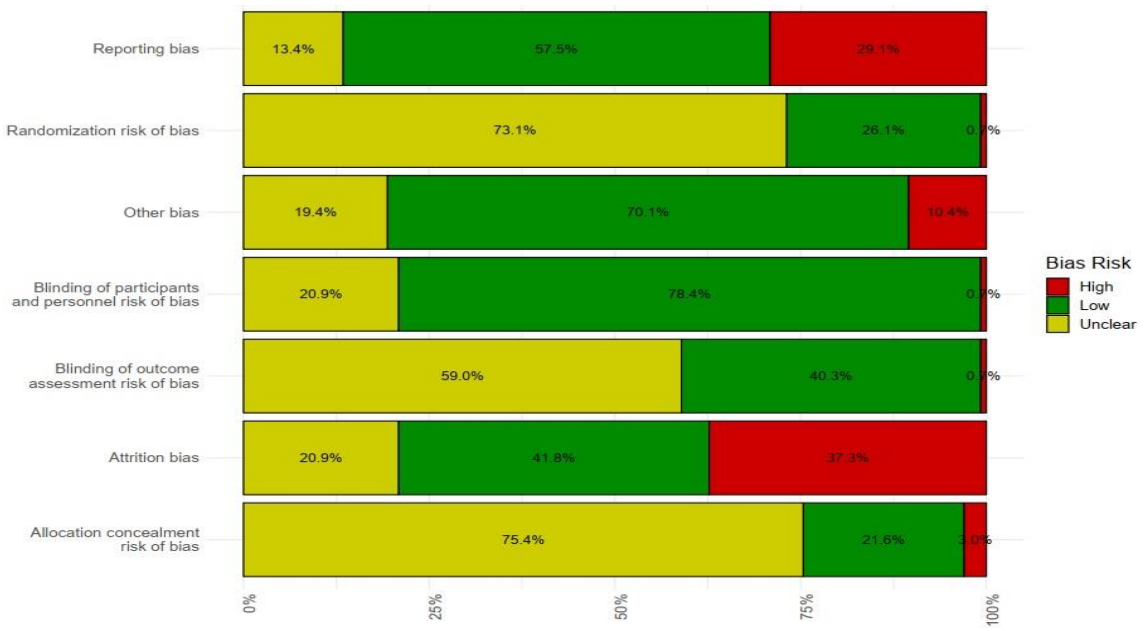
UNG11	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-1.00238144718774	0.0944677593157014
UNG11	NIMH_GOCS	NIMHOCS	OCD	OCD	LOCF	-0.0639938077937108	0.0795557842415643
UNG11	NIMH_GOCS	NIMHOCS	OCD	OCD	LOCF	-0.66762265766928	0.0849091098326264
UNG11	NIMH_GOCS	NIMHOCS	OCD	OCD	LOCF	-1.52825003254428	0.104977956885164
UNG11	SCL90	SCL-90	psychiatric symptoms (general)	psychiatric symptoms (general)	LOCF	-0.229689747345271	0.0694771166375422
UNG11	SCL90	SCL-90	psychiatric symptoms (general)	psychiatric symptoms (general)	LOCF	-0.328337084029851	0.0685685331600441
UNG11	SCL90	SCL-90	psychiatric symptoms (general)	psychiatric symptoms (general)	LOCF	-0.612751400959219	0.0721554134201447
UNG11	YBOCS	YBOCS-tot	OCD	OCD	LOCF	0.358412992122462	0.0929292980141077
UNG11	YBOCS	YBOCS-tot	OCD	OCD	LOCF	-0.100685212146414	0.0952969693774826
UNG11	YBOCS	YBOCS-tot	OCD	OCD	LOCF	-1.32909922144435	0.12458013395512
UNG12	CGI-S	CGI severity of illness	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.227317222480397	0.0446575854014239
UNG12	CGI_E	CGI efficacy index	clinical impression (efficacy)	psychiatric symptoms (general)	LOCF	-0.396623867897827	0.0391141475455638
UNG12	NIMH_GOCS	NIMHOCS	OCD	OCD	LOCF	-0.271504652597824	0.0498436714048574
UNG12	SCL90	SCL-90	psychiatric symptoms (general)	psychiatric symptoms (general)	LOCF	-0.208504438528707	0.0389508828176288
UNG12	YBOCS	YBOCS-tot	OCD	OCD	LOCF	-0.212310723821987	0.0517583248802304
UNG17	LSAS	Liebowitz social anxiety scale (LSAS)	social anxiety	social anxiety	LOCF	0.0276080159182011	0.0517869107852734

UNG2	CGI-S	CGI Severity score	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.590628987759938	0.0562788713170771
UNG2	HAM_A	Hamilton Anxiety scale (HAM-A) total score	anxiety (general)	GAD	LOCF	-0.406217244392494	0.0607766862860209
UNG3	CYBOCS	CYBOCS	OCD (child)	OCD	LOCF	-0.748148243969816	0.301890832516085
UNG6	CAS	CAS - COVI Anxiety Scale	anxiety (general)	GAD	LOCF	-0.190276512200515	0.0226226103031482
UNG6	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.226883923106863	0.0220216206791104
UNG6	HADS	Hospital Anxiety and Depression Scale (HAD) total score	anxiety/depression (general)	GAD	LOCF	-0.275090516176263	0.0202208750889241
UNG6	HAM_A	HAM-A total	anxiety (general)	GAD	LOCF	-0.214914743113866	0.0428458125256215
UNG7	CAS	CAS - COVI Anxiety Scale	anxiety (general)	GAD	LOCF	-0.554192963475487	0.0411470215351861
UNG7	CGI-S	CGI-S	clinical impression (severity)	psychiatric symptoms (general)	LOCF	-0.742914696117978	0.0547405801456653
UNG7	HADS	Hospital Anxiety and Depression Scale (HAD) total score	anxiety/depression (general)	GAD	LOCF	-0.364634968949814	0.0250853784964099
UNG7	HAM_A	HAM-A total	anxiety (general)	GAD	LOCF	-0.272149712524013	0.0758941260167892
UNG8	CAPS	Clinician-Administered PTSD Scale Part 2 total score	PTSD	PTSD	LOCF	0.0902240150096354	1.03070699335518
UNG8	DTS	Davidson Trauma Scale total score	PTSD	PTSD	LOCF	2.03162706958249	0.84127379382466
UNG8	TOP8	TOP8	PTSD	PTSD	LOCF	0.528015542385933	0.574236854836792
UNG9	LSAS	Liebowitz Social Anxiety Scale	social anxiety	social anxiety	LOCF	-0.528654104380476	0.132429039697646
UPD3	HAM_A	HAM-A	anxiety (general)	GAD	LOCF	-0.61730276801422	0.12501860515779

UPD3	LSAS	LSAS	social anxiety	social anxiety	LOCF	-0.523244235145171	0.225844110692154
UPD8	PARS	Pediatric Anxiety Rating Scale Severity total score	anxiety (general)(child)	GAD	LOCF	-2.4893943209734	0.514003236063282

[a] Scales names' abbreviations as standardized by review authors; [b] Scale names as reported in the primary studies; LSAS, Liebowitz Social Anxiety Scale; LOCF, last observation carried forward; SPIN , Social Phobia Inventory; BSPS, Brief Social Phobia Scale; FNE, Fear of Negative Evaluation Scale; CAS, Clinical Anxiety Scale; CAS_P, Clinical Anxiety Scale (panic attack frequency and severity item); GAD, generalized anxiety disorder; CGI-S, Clinical Global Impression – severity; PAAS_PAF_WK_N, Panic and Agoraphobia Scale - number of full panic attacks per week; PAAS_PAL_WK_N, Panic and Agoraphobia Scale - number of limited panic attacks per week; PANICSS, Panic disorder severity - DSM-III-R derived; HAM_A, Hamilton Rating Scale for Anxiety; MSPRS_A, Marks-Sheehan Phobia Scale – anxiety; MSPRS_AGO, Marks-Sheehan Phobia Scale – agoraphobia; OPS, Overall Phobia score; PAAS_AA, Panic and Agoraphobia Scale - anticipatory anxiety score; PAAS_PA_WK_N, Panic and Agoraphobia Scale - mean number of panic attacks per week; PGI, Patient Global Impression; SADS, Social Avoidance and Distress Scale; FQ, Fear Questionnaire; MSPRS_AV, Marks-Sheehan Phobia Scale – avoidance score; PA_INT, Intensity of full panic attacks; PAAS_SIPA_WK_N, Panic and Agoraphobia Scale - number of situational panic attacks; PAAS_SPA_WK_N, Panic and Agoraphobia Scale - number of spontaneous panic attacks; PAAS_AA_T_P, Panic and Agoraphobia Scale - anticipatory anxiety (percentage of time worrying); HADS_A, Hospital Anxiety and Depression Scale – anxiety subscale; PARS, Pediatric Anxiety Rating Scale; SCARED, Screen for Child Anxiety Related Emotional Disorders – child version; SCARED_P, Screen for Child Anxiety Related Emotional Disorders – parent version; PASS, Panic Attack Severity Score; FQ_F, Fear Questionnaire – fear score; FQ_AV, Fear Questionnaire – avoidance score; CAPS, Clinician Administered Post-Traumatic Stress Disorder Scale Part 2; CAPS_AF, Clinician Administered Post-Traumatic Stress Disorder Scale – associated features; PTSD, post-traumatic stress disorder; DTS, Davidson Trauma Scale; IES, Impact of Event Scale; MOCI, Maudsley Obsessive-Compulsive Inventory; OCD, obsessive-compulsive disorder; NIMH_GOCS, National Institute of Mental Health Global Obsessive-Compulsive Scale; YBOCS, Yale-Brown Obsessive-Compulsive Scale; DUKE, Duke Global Rating for Post-Traumatic Stress Disorder; SIP, Structured Interview for Post-Traumatic Stress Disorder; SVS, Vulnerability to Stress Scale; MASC, Multidimensional Anxiety Scale for Children; HADS, Hospital Anxiety and Depression Scale; STAI_STA, State-Trait Anxiety Inventory – state subscale; DESNOS, Disorders of Extreme Stress – Not Otherwise Specified Scale; MISS, Mississippi Rating Scale for Combat-Related Post-Traumatic Stress Disorder - civilian trauma Version; COIS, Child Obsessive-Compulsive Impact Scale; CYBOCS, Yale-Brown Obsessive-Compulsive Scale – child version; SPAI, Social Phobia and Anxiety Inventory; CGI, Clinical Global Impression; CPRS_OCD, Comprehensive Psychopathological Rating Scale – obsessive-compulsive subscale; GA_VAS, Global Anxiety Visual Analog Scale; ACQ, Agoraphobic Cognitions Questionnaire; BSQ, Body Sensations Questionnaire; MI-AAL, Mobility Inventory for Agoraphobia – avoidance subscale; IES_R, Impact of Event Scale – revised version; PDSS, Panic Disorder Severity Scale; PAAS_UA_WK_DN, Panic and Agoraphobia Scale - unexpected panic attack; SAS_CA, Social Anxiety Scale for Children and Adolescents; TOP8, Treatment-Outcome Post-Traumatic Stress Disorder Scale; CGI_E, Clinical Global Impression – efficacy; PSWQ, Penn State Worry Questionnaire; MSPRS_F, Marks-Sheehan Phobia Scale – fear score; SCL61, Symptom Checklist (61 items); PAAS_PAF_EB, Panic and Agoraphobia Scale - full panic attack (endpoint to baseline ratio); HADS_D, Hospital Anxiety and Depression Scale – depression subscale; ADIS_C, Anxiety Disorders Interview Schedule for Children – child version; ADIS_P, Anxiety Disorders Interview Schedule for Children - parent version; RCMAS, Revised Children's Manifest Anxiety Scale; PAAS, Panic and Agoraphobia Scale; CGI_OCD, Clinical Global Impression – Obsessive-Compulsive Disorder; LOICV, Leyton Obsessional Inventory - child version; PAGI, Parent Global Impression; CSDC, Child Stress Disorder Checklist; UCLA_PTSD, The University of California at Los Angeles Post-Traumatic Stress Disorder Reaction Index for DSM-IV; FQ_SA, Fear Questionnaire – social anxiety score; SPAI_SA, Social Phobia and Anxiety Inventory - social anxiety subscale; LSAS_AV, Liebowitz Social Anxiety Scale – avoidance subscale; SCL90, Symptom Checklist (90 items); K_GSADS_A, Kutcher Generalized Social Anxiety Disorder Scale for Adolescents; LSAS_C, Liebowitz Social Anxiety Scale – child version; SPIN_C, Social Phobia Inventory – child version

S3 Fig. A: Risk of bias summary



S3 Table E: Risk of bias in included studies

Id	Author	Randomization risk of bias	Allocation concealment risk of bias	Blinding of participants and personnel risk of bias	Blinding of outcome assessment risk of bias	Attrition risk of bias	Reporting risk of bias	Other risk of bias
JF10	Allgulander	low	high	low	low	high	unclear	unclear
JF11	Allgulander C.	low	unclear	low	low	low	low	low
JF15	Asakura S.	unclear	unclear	low	unclear	low	low	low
JF16	Asnis	unclear	unclear	low	unclear	low	low	low
JF20	Bakker	unclear	unclear	low	unclear	low	low	low
JF22	Baldwin	low	unclear	low	unclear	low	low	low
JF25	Baldwin D.	unclear	unclear	low	unclear	low	low	low
JF28	Ballenger	unclear	unclear	low	unclear	low	low	low
JF29	Bandelow	low	low	low	low	low	low	low
JF3	Alaka	low	high	low	unclear	unclear	unclear	low
JF34	Beidel D.C.	unclear	low	low	low	unclear	unclear	unclear
JF42	Birmaher	unclear	unclear	low	low	unclear	low	low
JF45	Black	unclear	unclear	low	low	unclear	low	low
JF56	Bradwejn	unclear	low	low	low	unclear	low	low
JF59	Brady	unclear	low	low	low	unclear	low	low
JF61	Brawman-Mintzer O.	low	low	low	low	unclear	low	low
JF7	Allgulander	unclear	unclear	unclear	unclear	low	low	unclear
JF72	Chouinard	unclear	unclear	low	unclear	unclear	low	low
JF78	Connor K.M.	unclear	low	low	unclear	unclear	low	low
JF80	Coric	unclear	unclear	low	unclear	unclear	low	low
JF82	Da Costa	unclear	unclear	low	unclear	unclear	low	low
JF83	Dahl	unclear	unclear	low	unclear	unclear	unclear	low
JF87	Davidson	unclear	unclear	low	unclear	unclear	unclear	low

JF88	Davidson	unclear	unclear	low	unclear	unclear	unclear	low
JF89	Davidson	unclear	unclear	low	unclear	high	low	low
JF9	Koponen	low	unclear	low	unclear	high	high	low
JF94	Asakura S.	low	high	low	unclear	low	low	low
LM10	Den Boer	unclear	unclear	unclear	unclear	low	high	unclear
LM23	Fani N.	unclear	unclear	unclear	high	low	low	low
LM24	Fani N.	unclear	unclear	unclear	high	low	low	low
LM34	Friedman M.J.	unclear	low	low	unclear	low	low	low
LM37	Gelenberg	low	low	unclear	unclear	low	high	low
LM39	Geller D.A.	unclear	unclear	unclear	unclear	low	low	low
LM4	Davidson J.	low	low	unclear	unclear	low	low	unclear
LM40	Geller D.A.	low	low	unclear	unclear	low	high	low
LM42	Gimenez M.	unclear	unclear	unclear	unclear	low	high	high
LM48	Goodman W.K.	unclear	unclear	unclear	unclear	low	high	high
LM5	Davidson J.R.T.	low	low	high	high	low	low	low
LM50	Greist	unclear	unclear	unclear	unclear	low	high	high
LM54	Hartford	unclear	unclear	unclear	unclear	low	low	low
LM57	Hertzberg	unclear	unclear	unclear	unclear	low	unclear	unclear
LM59	Hoehn-Saric	unclear	unclear	unclear	unclear	high	high	high
LM6	Davidson J.R.T.	unclear	low	unclear	unclear	low	high	unclear
LM60	Hollander	unclear	unclear	unclear	unclear	high	low	low
LM67	Jenike	unclear	unclear	unclear	unclear	low	low	low
LM69	Jenike M.A.	unclear	unclear	low	low	high	low	low
LM71	Kamijima K.	unclear	unclear	unclear	unclear	high	high	high
LM72	Kasper	low	unclear	unclear	unclear	low	low	low
LM73	Kasper	unclear	unclear	unclear	unclear	unclear	high	unclear
LM74	Kasper S.	low	low	low	low	low	low	low

LM76	Katzelnick D.J.	unclear	unclear	unclear	unclear	high	high	low
LM86	Koszycki	low	low	low	low	low	low	unclear
LM95	Li	low	low	low	low	low	low	low
MC1	Ledley	unclear	unclear	low	low	high	high	low
MC10	Lepola	unclear	unclear	low	low	high	high	low
MC12	Liebowitz	unclear	unclear	low	low	low	low	low
MC13	Liebowitz	unclear	unclear	low	low	low	low	low
MC14	Liebowitz	unclear	unclear	low	low	low	high	high
MC15	Liebowitz	unclear	unclear	low	low	low	low	high
MC16	Liebowitz	unclear	unclear	low	low	low	low	low
MC17	Liebowitz M.R.	unclear	unclear	low	low	high	high	low
MC2	Leinonen	unclear	unclear	low	low	high	high	low
MC20a	Londborg P.D.	low	unclear	low	low	low	high	high
MC20b	Londborg P.D.	low	unclear	low	low	low	high	high
MC22	Mahableshwarkar	low	unclear	low	low	high	high	high
MC25	March	low	low	low	low	low	low	low
MC26	March	low	low	low	low	high	low	low
MC28	March J.S.	low	low	low	low	high	low	low
MC3	Lenox-Smith	low	low	low	low	high	high	low
MC31	Marshall	unclear	unclear	low	low	low	low	low
MC32	Marshall	unclear	unclear	low	low	high	low	low
MC33	Martenyi	unclear	unclear	low	low	high	low	low
MC34	Martenyi	unclear	low	low	low	low	low	low
MC38	Merideth	low	unclear	low	low	high	low	low
MC39	Michelson	unclear	unclear	low	low	unclear	high	low
MC4	Lenze	low	low	low	low	high	high	low
MC40	Michelson D.	unclear	unclear	low	low	high	low	low

MC42	Montgomery	unclear	unclear	low	low	low	low	low
MC44	Montgomery	unclear	unclear	low	low	high	low	low
MC45	Montgomery	unclear	unclear	low	low	low	low	low
MC51	Nair	unclear	unclear	low	low	low	high	low
MC55	Nicolini	low	low	low	low	high	high	low
MC56	Nimatoudis I.	unclear	unclear	low	low	low	low	high
MC6	Lenze	low	low	low	low	low	low	low
MC62	Panahi	unclear	low	low	low	high	low	low
MC73	Pollack	unclear	unclear	low	low	high	low	low
MC77	Pollack	unclear	unclear	low	low	low	high	low
MC79	Pollack	unclear	unclear	low	low	high	low	low
MC81	Pollack	unclear	unclear	low	low	high	low	low
MC82	Pollack M.H.	unclear	unclear	low	low	low	low	low
MJ1	Rickels	unclear	unclear	low	unclear	high	high	unclear
MJ14	Rynn	unclear	unclear	low	unclear	high	low	low
MJ16	Rynn M.A.	unclear	unclear	low	unclear	high	low	low
MJ17	Sandmann J.	unclear	unclear	low	unclear	high	high	low
MJ2	Rickels	unclear	unclear	low	low	high	low	low
MJ22	Sharp D.M.	unclear	unclear	low	unclear	low	high	low
MJ25	Sheehan	unclear	unclear	low	unclear	high	low	low
MJ3	Rickels K.	unclear	unclear	low	unclear	low	low	low
MJ36	Stahl	unclear	unclear	low	unclear	low	low	low
MJ4	Riddle	unclear	unclear	low	low	high	high	high
MJ42	Stein	low	unclear	low	unclear	high	high	low
MJ44	Stein	low	low	low	unclear	low	low	low
MJ5	Riddle M.A.	unclear	unclear	low	unclear	high	low	low
MJ53	Stein M.B.	unclear	unclear	low	unclear	low	high	unclear

MJ54	Stein M.B.	low	low	low	unclear	high	low	low
MJ56	Strawn	unclear	low	low	unclear	low	low	low
MJ6	Robb A.S.	unclear	unclear	low	unclear	high	low	low
MJ64	Tucker	unclear	unclear	low	unclear	unclear	low	low
MJ66	Tucker P.	unclear	unclear	low	unclear	low	low	low
MJ7	Rolland P.D.	unclear	unclear	low	unclear	high	high	high
MJ70	Van Ameringen M.A.	unclear	unclear	low	unclear	high	high	low
MJ71	Van Der Kolk	low	unclear	low	unclear	high	high	unclear
MJ73	Van Vliet I.M.	unclear	unclear	low	unclear	high	high	unclear
MJ77	Wade	unclear	unclear	low	unclear	low	high	unclear
MJ78	Wagner	low	unclear	low	unclear	high	low	low
MJ79	Walkup	low	low	low	unclear	high	low	high
MJ80	Walkup	unclear	unclear	low	unclear	high	high	unclear
MJ84	Westenberg	unclear	unclear	low	unclear	high	low	low
MJ85	Westenberg	unclear	unclear	low	unclear	high	high	unclear
MJ89	Wu	unclear	unclear	low	unclear	high	low	low
MJ93	Zohar	unclear	unclear	low	unclear	low	low	low
MJ94	Zohar	unclear	unclear	low	unclear	high	low	low
MJ96	Stein D.J.	low	low	low	unclear	low	high	low
MJ97	Jenike	high	high	low	unclear	high	low	high
UNG1	unknown	unclear	unclear	low	unclear	unclear	unclear	low
UNG10	unknown	unclear	unclear	unclear	unclear	unclear	unclear	unclear
UNG11	unknown	unclear	unclear	unclear	unclear	unclear	unclear	unclear
UNG12	unknown	unclear	unclear	unclear	unclear	unclear	unclear	unclear
UNG17	unknown	unclear	unclear	unclear	unclear	unclear	unclear	unclear
UNG2	unknown	unclear	unclear	low	unclear	unclear	unclear	low
UNG3	unknown	unclear	unclear	unclear	unclear	unclear	unclear	unclear

UNG6	Hewett	unclear	unclear	unclear	unclear	unclear	unclear	unclear
UNG7	unknown	unclear	unclear	unclear	unclear	unclear	unclear	unclear
UNG8	Sonne	low	unclear	unclear	unclear	unclear	unclear	unclear
UNG9	unknown	unclear	unclear	unclear	unclear	unclear	unclear	unclear
UPD3	Liebowitz MR	unclear	unclear	low	low	low	low	unclear
UPD8	Strawn JR	low	low	low	low	low	low	low

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5 ARTICLE #2

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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 and SNRIs in the treatment of children and adults diagnosed with these disorders through a network meta-analysis. We searched MEDLINE, PsycINFO, Embase, Cochrane, websites of regulatory agencies, and international registers from inception to September 09, 2022, for randomized controlled trials assessing the efficacy of SSRIs or SNRIs. We analyzed the proportion of participants experiencing at least one adverse event and incidence rates of 17 specific adverse events. We estimated incidence rates and odds ratios through network meta-analysis with random effects and three-level models. 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. We found significant differences between medications for overall tolerability and for autonomic, gastrointestinal, and sleep related symptoms. 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 disorders (Kendrick & Pilling, 2012), leading causes of disability ("Global, Regional, and National Burden of 12 Mental Disorders in 204 Countries and Territories, 1990–2019", 2022). While antidepressants are commonly prescribed (Martin, Hales, Gu, & Ogden, 2019), most patients are non-compliant (Sundbom & Bingefors, 2013), with fear of potential adverse reactions being the second leading cause of nonadherence, after discontinuity due to remission of symptoms, the leading cause (Sundbom & Bingefors, 2013). 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 efficacy (Gosmann et al., 2021).

Previous meta-analyses assessed the tolerability of SSRIs and SNRIs in the treatment of non-depressive disorders, but three key questions remain unanswered. First, previous studies restricted their inclusion criteria to specific medications (Li et al., 2020; Li, Zhu, Su, & Fang, 2017; Li et al., 2018; Liu et al., 2018a; Zhang et al., 2020), diagnoses (Li et al., 2020, 2017, 2018; Liu et al., 2018a; Zhang et al., 2020), adverse events (Telang, Walton, Olten, & Bloch, 2018; Wang et al., 2022), or populations (Schwartz, Barican, Yung, Zheng, & Waddell, 2019). 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 power (Li et al., 2020, 2017, 2018; Liu et al., 2018b; Purgato et al., 2014). 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 in the treatment of non-depressive disorders 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 (Gosmann et al., 2021)**.** We report this study as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analysis (Supplementary Table S1) (Hutton et al., 2015). 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. Although citalopram and desvenlafaxine are not FDA-approved for the treatment of non-depressive disorders, these medications were also included in this review, given these SSRIs/SNRIs are also commonly used as off-label interventions in the treatment of anxiety, obsessive-compulsive, and stress-related disorders. 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 (Supplementary Text S1). 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 deaths by suicide. 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 defined before 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) (Altman, 1998). We estimated between-study variance through τ^2 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 symptom (Konstantopoulos, 2011). 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 evidence (Bucher, Guyatt, Griffith, & Walter, 1997).

We performed all head-to-head 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) (Hayasaka et al., 2015), 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 also

performed head-to-head comparisons of medications in RCTs designed to evaluate the efficacy of SSRIs or SNRIs in children and adolescents using the same multiple meta-regression model with clinical and methodological moderators. 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 moderators (Gosmann et al., 2021). 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' (Viechtbauer, 2010).

The risk of bias appraisal was performed using the Cochrane Collaboration's Risk of Bias Tool for RCTs (Higgins et al., 2011). 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 bias (Furukawa et al., 2016). We assessed certainty of evidence using the Confidence in Network Meta-Analysis framework (CINeMA) (Nikolakopoulou et al., 2020). We decided to evaluate certainty of evidence after registration of the study protocol in PROSPERO in order to improve results reporting.

Results

We screened 5655 titles and abstracts and evaluated 420 full text articles for inclusion (Supplementary Figure S1). 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 (Supplementary Tables S2-4).

Overall, 16 (20.00%) trials were rated as high risk of bias, 37 (46.25%) trials as moderate, and 27 (33.75%) as low (Supplementary Figure S2 and Supplementary Table S5). 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 (Supplementary Figures S3-20).

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 Tables S6-30.

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). Fig. 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 (Supplementary Figure S21) (moderate to high certainty of evidence). The network diagram of direct comparisons is presented in Supplementary Figure S22.

We performed head-to-head 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 (Fig. 2). We also found significant differences in head-to-head 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) (Supplementary Figure S23); 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) (Supplementary Figure S24); 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) (Supplementary Figure S25. There were no significant differences between medications concerning motor (low to high) and sexual adverse events (low to high) (Supplementary Figures S26-27). We did not find significant differences between medications for the aggregate measure of all specific symptoms in RCTs designed to assess children and adolescents (Supplementary Figure S28). 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 Figures S29-34). Fig. 3 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) (Supplementary Figure S35), 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) (Supplementary Figure S36). The design-by-treatment interaction models did not identify global inconsistency in the networks, we did not find clear evidence of violations of the transitivity assumption when comparing characteristics of studies across comparisons (Supplementary Figures S37-40), 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) (Supplementary Figure S41). There were a limited number of suicide attempts and deaths by suicide. While there were two suicide attempts in the placebo group, there were two suicide attempts venlafaxine and paroxetine groups (Allgulander et al., 2004; Baldwin, Bobes, Stein, Scharwächter, & Faure, 1999; Rynn, Riddle, Yeung, & Kunz, 2007). The only 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 medication (Baldwin et al., 1999).

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 (Supplementary Table S31).

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 head-to-head 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 symptoms (Arbanas, Arbanas, & Dujam, 2009; Ketter et al., 2014). 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 effects (Huhn et al., 2019; Soyka, 2017), 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 disorders (Gosmann et al., 2021), 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 treatment (Mitsikostas, Mantonakis, & Chalarakis, 2014), psychotropic medications for other mental disorders (Dodd et al., 2019; Palermo, Giovannelli, Bartoli, & Amanzio, 2019), and common interventions for clinical conditions (Luparello, Leist, Lourie, & Sweet, 1970; Mondaini et al., 2007; Silvestri et al., 2003), 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 (Sundbom & Bingefors, 2013), with fear of potential adverse reactions being the second leading cause of nonadherence (Sundbom & Bingefors, 2013), and that the interaction between patient and clinician influences the likelihood of the nocebo effect (Blasini, Peiris, Wright, & Colloca, 2018), 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 head-to-head 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 medication

(Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996). Comparisons of medications did not find significant differences of tolerability in children and adolescents for the aggregate measure of adverse events; nevertheless, future studies may explore potential distinct symptom-specific tolerability profiles of each medication in this population.

In spite of its well stablished benefit of SSRIs for improvement of depressive symptoms (Cipriani et al., 2018), concerns have been raised about the risk of suicidal behavior associated with these medications (Hayes, Lewis, & Lewis, 2019). Our findings did not indicate significant differences of SSRIs or SNRIs over placebo for suicidal ideation, suicide attempts, or deaths by suicide, 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 deaths by suicide.**

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 head-to-head 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 measures (Saad, Yekutieli, Lev-Ran, Gross, & Guyatt, 2019). 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 or 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.

Author contributions

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.

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Conflict of interest

The authors declare none.

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Zhang, B., Wang, C., Cui, L., Gao, J., Wang, C., Tan, X., & Fang, S. (2020). Short-Term Efficacy and Tolerability of Paroxetine Versus Placebo for Panic Disorder: A Meta-Analysis of Randomized Controlled Trials. *Frontiers in Pharmacology*, *11*, 275. https://doi.org/10.3389/fphar.2020.00275

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)	τ^2 (95%CI)	Heterogeneity I^2 (%) (95%CI)
Placebo	55 (7090)	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 (7541)	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 (4827)	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)[1]	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) [1]	0.044 (0.000 – 0.188)	0.002 (0.000 – 0.035)	47.8 (00.0 - 80.9)
Paroxetine	13 (1964)	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 (2714)	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 (2093)	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. [1]Non-significant differences are presented with the NNT to the left and NNH on the right

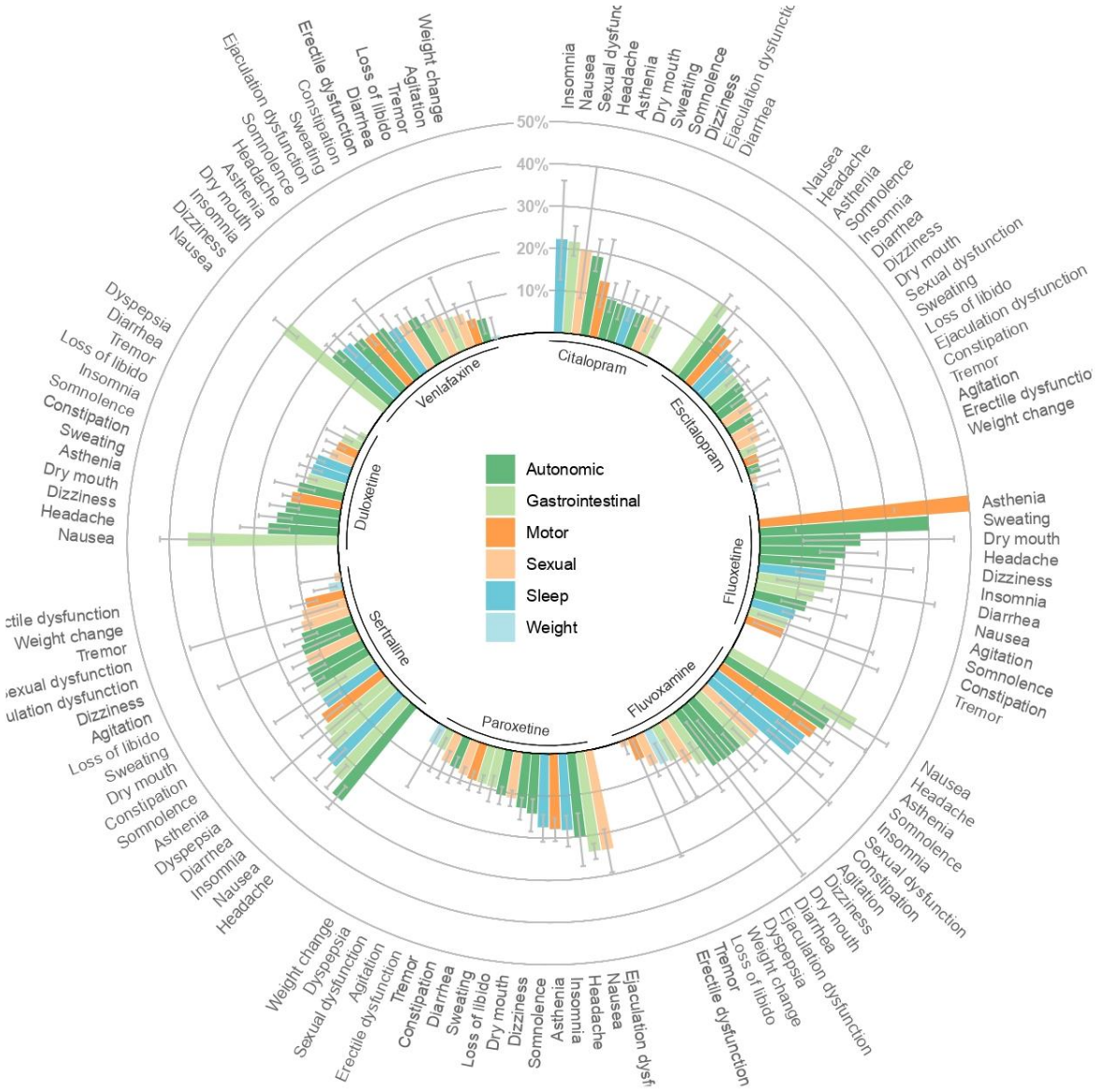
Table 2 Incidence rates of specific adverse events of placebo and medications' classes

	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 (5653)	18.91 (16.59 - 21.47)	55 (6092)	20.48 (18.01 - 23.19)	189 (NNT, 149 ∞ 58, NNH) [1]	46 (4962)	21.48 (18.84 - 24.38)	213 (NNT, 93 ∞ 50, NNH) [1]	9 (1130)	14.95 (9.36 - 23.01)	115 (NNT, 83 ∞ 34, NNH) [1]
Nausea	97 (11 249)	11.88 (10.92 - 12.90)	97 (11 583)	25.71 (23.96 - 27.54)	7 (6 - 8)	69 (7904)	23.25 (21.45 - 25.15)	9 (8 - 11)	28 (3679)	31.59 (28.46 - 34.89)	5 (4 - 6)
Insomnia	74 (8650)	10.13 (8.85 - 11.57)	74 (8881)	17.94 (15.92 - 20.16)	14 (12 - 18)	54 (6206)	19.29 (16.81 - 22.05)	15 (12 - 20)	20 (2675)	14.77 (11.75 - 18.39)	13 (10 - 19)
Dizziness	53 (5950)	8.61 (7.56 – 9.79)	53 (6179)	13.79 (12.15 – 15.60)	19 (15 – 26)	33 (3724)	11.87 (9.94 – 14.12)	25 (17 – 53)	20 (2455)	16.99 (14.70 – 19.57)	13 (11 – 17)
Asthenia	62 (7409)	7.61 (6.57 – 8.79)	62 (7627)	16.69 (15.06 – 18.47)	12 (11 – 14)	42 (5109)	18.20 (16.06 – 20.55)	11 (10 – 14)	20 (2518)	13.95 (11.86 – 16.35)	13 (11 – 17)
Diarrhea	48 (5458)	6.98 (5.65 – 8.59)	48 (5607)	11.98 (9.86 – 14.49)	24 (18 - 33)	40 (4382)	13.34 (10.93 – 16.17)	21 (16 - 28)	8 (1225)	6.87 (3.53 – 12.95)	60 (NNT, 98 ∞ 23, NNH) [1]
Somnolence	75 (9783)	6.75 (5.89 - 7.73)	75 (10 120)	14.33 (12.57 - 16.29)	13 (11 - 16)	51 (6798)	15.76 (13.58 - 18.22)	12 (10 - 15)	24 (3322)	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) [1]	8 (891)	10.43 (5.88 - 17.82)	28 (NNT, 24 ∞ 9, NNH) [1]	1 (156)	1.92 (0.62 - 5.79)	154 (NNT, 47 ∞ 29, NNH) [1]
Dry mouth	70 (8598)	5.92 (5.09 – 6.88)	70 (8686)	13.78 (12.48 – 15.19)	14 (12 – 16)	43 (5026)	12.82 (11.17 – 14.67)	17 (14 – 22)	27 (3660)	15.15 (13.18 – 17.35)	11 (9 – 13)
Agitation	19 (1947)	5.43 (3.67 - 7.96)	19 (1962)	9.17 (6.71 - 12.41)	38 (22 – 161)	15 (1549)	9.83 (6.98 - 13.68)	35 (20 – 161)	4 (413)	5.53 (1.95 - 14.70)	53 (NNT, 31 ∞ 14, NNH) [1]
Constipation	48 (5976)	4.24 (3.48 - 5.15)	48 (6160)	9.86 (8.74 - 11.11)	20 (16 - 25)	26 (2931)	9.94 (8.08 - 12.16)	23 (16 - 39)	22 (3229)	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) [1]	6 (818)	4.16 (1.96 - 8.61)	1111 (NNT, 75 ∞ 67, NNH) [1]	1 (129)	0.78 (0.11 - 5.29)	128 (NNT, 75 ∞ 35, NNH) [1]
Sweating	45 (5700)	3.39 (2.68 – 4.28)	45 (5964)	11.56 (9.99 – 13.34)	13 (11 – 15)	28 (3551)	11.29 (9.17 – 13.83)	14 (11 - 17)	17 (2413)	12.08 (9.91 – 14.65)	12 (10 - 15)
Loss of libido	35 (4945)	2.65 (2.20 - 3.18)	35 (4828)	8.96 (7.84 - 10.22)	16 (14 – 20)	24 (3129)	9.84 (8.46 - 11.43)	15 (12 – 19)	11 (1699)	7.36 (5.83 - 9.25)	20 (15 – 30)
Tremor	29 (2925)	2.24 (1.73 – 2.91)	29 (3090)	7.38 (6.15 – 8.82)	22 (18 – 30)	20 (1845)	8.29 (6.63 – 10.31)	19 (14 – 27)	9 (1245)	6.02 (4.75 – 7.61)	29 (20 – 29)
Erectile dysfunction	21 (2899)	1.87 (1.38 - 2.52)	21 (2789)	6.74 (5.07 - 8.91)	24 (17 – 47)	14 (1902)	4.96 (3.32 – 7.36)	37 (20 – 244)	7 (887)	9.72 (6.37 – 14.57)	15 (11 – 20)

Ejaculation dysfunction	46 (6292)	1.81 (1.41 - 2.31)	46 (6299)	13.80 (11.38 - 16.64)	7 (6 – 9)	36 (5039)	14.23 (11.31 - 17.74)	7 (6 – 9)	10 (1260)	12.44 (10.24 - 15.03)	9 (7 – 12)

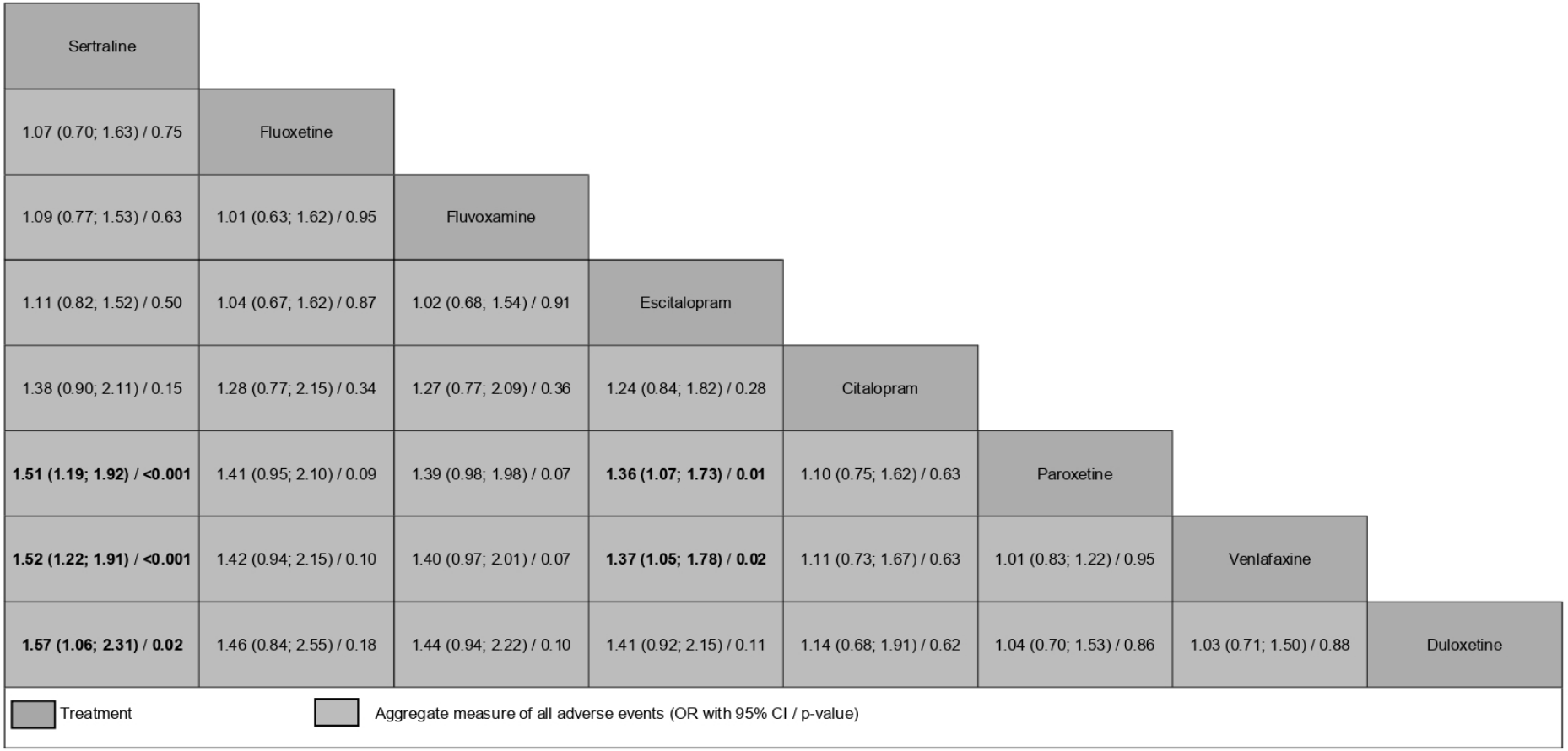
SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; k, number of studies; n, sample size; CI, confidence interval; NNH, number needed to harm; NNT, number needed to treat. NNHs were estimated using placebo group as reference. [1]Non-significant differences are presented with the NNT to the left and NNH on the right

Fig. 1 Relative frequencies of specific adverse events by medication



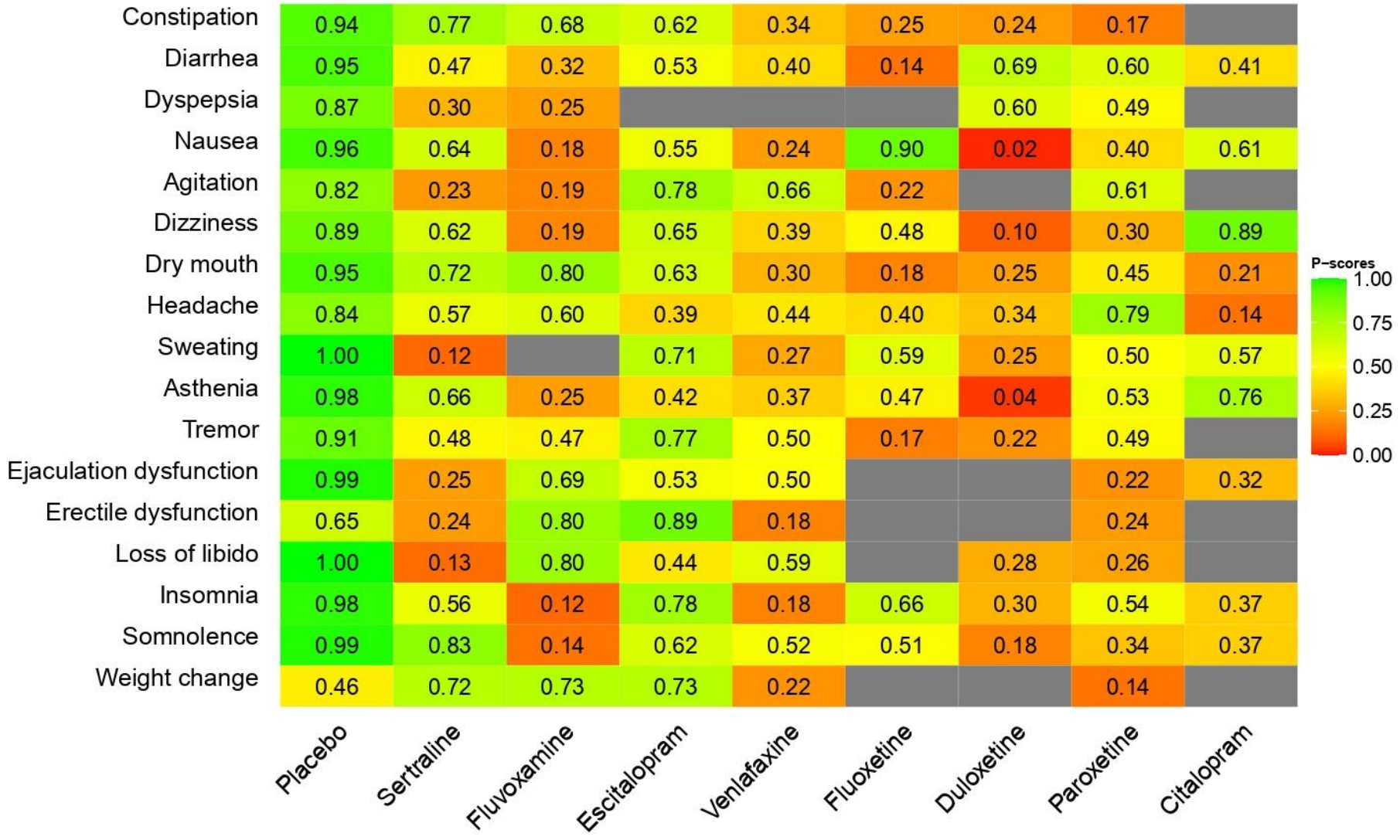
Legend: Effect sizes are presented as odds ratios, and error bars represent estimated standard errors. Specific adverse events are described outside of the circular bar plot and are colored according to the corresponding adverse event domain.

Fig. 2 Comparisons of all SSRIs and SNRIs for the aggregate measure of all adverse events in the multiple meta-regression model



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.

Fig. 3 Treatment rankings for each specific adverse event



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

Supplementary Material

Supplementary Table S1: Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses checklist

Section/Topic	Item #	Checklist Item	Section (paragraph)
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	Introduction (pg. 3; paragraphs 1-2)
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction (pg. 3; paragraph 3)
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Methods (pg. 4; paragraph 1)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	Methods (pg. 4; paragraph 2)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods (pg. 4; paragraph 3)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Methods (pg. 4; paragraph 3)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods (pg. 4; paragraph 3)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods (pg. 5; paragraph 2)

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods (pg. 5; paragraph 4)
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	Methods (pg. 6; paragraph 1)
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods (pg. 7; paragraph 2)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	Methods (pg. 6; paragraph 1)
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	Methods (pg. 6; paragraphs 1-2)
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	Methods (pg. 6; paragraph 1)
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods (pg. 6; paragraph 1)
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	Methods (pg. 6; paragraphs 2)
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Supplementary Figure S1
Presentation of network	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Supplementary Figure S21

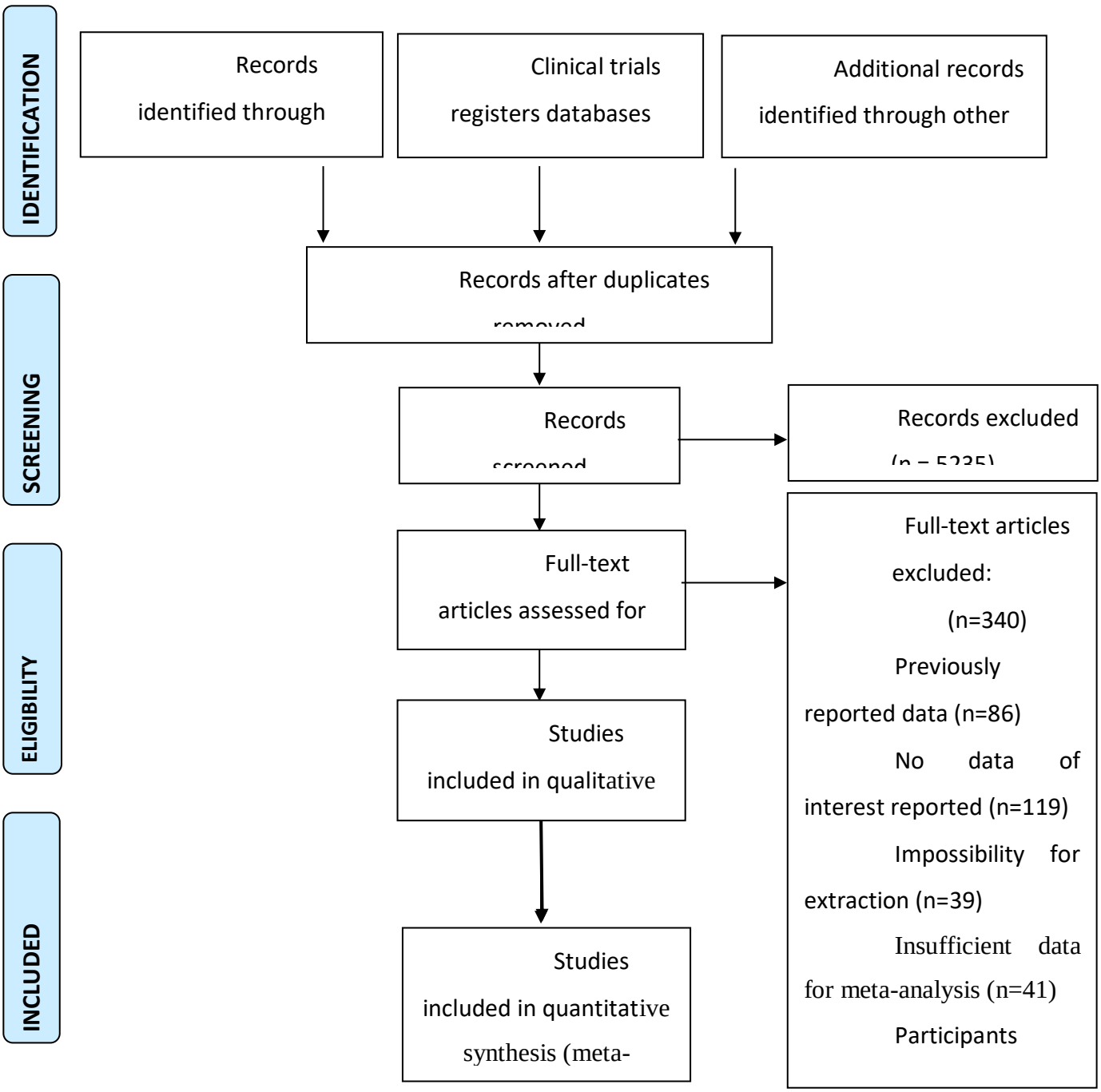
structure			
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	Results (pg. 7; paragraph 1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary Tables 2-3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Supplementary Table S5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger network*	Supplementary Table S4
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	Results (pg. 7-8)
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Results (pg. 9; paragraph 1)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Supplementary Figure S2
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	Results (pgs. 8-9)
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	Discussion (pg. 10; paragraph 1)
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	Discussion (pg. 12; paragraph 2)
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion (pg. 12; paragraph 3)
FUNDING			pg. 13; paragraph 1
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether	

	some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	

Supplementary Text S1: Search terms

(anxi* OR GAD OR phobi* OR “social anxiety” OR panic* OR obsessi* OR compulsi* OR traumatic* OR posttrauma* OR post-trauma* OR "post trauma*” OR "combat disorder*" OR "stress disorder*" OR OCD OR ptsd) AND ("selective serotonin reuptake" OR “selective serotonin re-uptake inhibitors” OR “serotonin-specific reuptake inhibitors” OR ssri OR fluoxetine OR fluvoxamine OR sertraline OR paroxetine OR citalopram OR escitalopram OR dapoxetine OR “serotonin-norepinephrine reuptake" OR SNRI* OR venlafaxine OR desvenlafaxine OR duloxetine OR milnacipran OR Levomilnacipran) AND ((randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] OR randomised[Title/Abstract]) AND controlled[Title/Abstract] AND trial[Title/Abstract]) OR (meta-analysis OR metaanalysis OR "systematic review" OR metaanalyses OR meta-analyses OR "systematic-review"))

Supplementary Figure S1: Flowchart of included and excluded studies



Supplementary Table S2: Studies publication information

id	PMID/Other ID	Publication status	Year of publication	Author	Title	Funding
MC3	2003412218	published	2003	Lenox-Smith	A double-blind, randomised, placebo controlled study of venlafaxine XL in patients with generalised anxiety disorder in primary care	Industry
MC12	2009266799	published	2009	Liebowitz	A double-blind, placebo-controlled, parallel-group, flexible-dose study of venlafaxine extended release capsules in adult outpatients with panic disorder	Industry
MC13	2002049438	published	2002	Liebowitz	A randomized, double-blind, fixed-dose comparison of paroxetine and placebo in the treatment of generalized social anxiety disorder	Industry
MC17	2005062649	published	2005	Liebowitz M.R.	Venlafaxine extended release vs placebo and paroxetine in social anxiety disorder	Industry
MC22	2013802284	published	2013	Mahableshwarkar	A randomised, double-blind, placebo-controlled, duloxetine-referenced study of the efficacy and tolerability of vortioxetine in the acute treatment of adults with generalised anxiety disorder	Industry
MC25	2007528912	published	2007	March	A Randomized Controlled Trial of Venlafaxine ER Versus Placebo in Pediatric Social Anxiety Disorder	Industry
MC33	17414240	published	2007	Martenyi	Failed efficacy of fluoxetine in the treatment of posttraumatic stress disorder: results of a fixed-dose, placebo-controlled study.	Industry
MC38	2011677266	published	2011	Merideth	Efficacy and tolerability of extended release quetiapine fumarate monotherapy in the acute treatment of generalized anxiety disorder: A randomized, placebo controlled and active-controlled study	Industry
MC40	2002013536	published	2001	Michelson D.	Efficacy of usual antidepressant dosing regimens of fluoxetine in panic disorder. Randomised, placebo-controlled trial	Industry
MC45	2001077435	published	2001	Montgomery	Citalopram 20 mg, 40 mg and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder	Industry
MC51	9160622	published	1996	Nair	Comparison of fluvoxamine, imipramine, and placebo in the treatment of outpatients with panic disorder.	Industry

MC71	9734541	published	1998	Pohl	Sertraline in the treatment of panic disorder: a double-blind multicenter trial.	doubtful
MC73	2007466592	published	2007	Pollack	A randomized controlled trial of venlafaxine ER and paroxetine in the treatment of outpatients with panic disorder	Industry
MC79	2007096532	published	2006	Pollack	A double-blind study of the efficacy of venlafaxine extended-release, paroxetine, and placebo in the treatment of panic disorder	Industry
MC82	1998374883	published	1998	Pollack M.H.	Sertraline in the treatment of panic disorder: A flexible-dose multicenter trial	Industry
MJ1	2004408566	published	2004	Rickels	A double-blind, placebo-controlled study of a flexible dose of venlafaxine ER in adult outpatients with generalized social anxiety disorder	doubtful
MJ3	2005347556	published	2003	Rickels K.	Paroxetine treatment of generalized anxiety disorder: A double-blind, placebo-controlled study	Industry
MJ5	2001046511	published	2001	Riddle M.A.	Fluvoxamine for children and adolescents with obsessive-compulsive disorder: A randomized, controlled, multicenter trial	Industry
MJ6	2011001857	published	2010	Robb A.S.	Sertraline treatment of children and adolescents with posttraumatic stress disorder: A double-blind, placebo-controlled trial	Industry
MJ14	2008171568	published	2007	Rynn	Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: A flexible-dose, progressive-titration, placebo-controlled trial	Industry
MJ17	1998292538	published	1998	Sandmann J.	Fluvoxamine or placebo in the treatment of panic disorder and relationship to blood concentrations of fluvoxamine	academic
MJ44	2007198511	published	2007	Stein	Escitalopram in obsessive-compulsive disorder: A randomized, placebo-controlled, paroxetine-referenced, fixed-dose, 24-week study	Industry
MJ56	2015802599	published	2015	Strawn	A randomized, placebo-controlled study of duloxetine for the treatment of children and adolescents with generalized anxiety disorder	Industry
MJ78	2004471921	published	2004	Wagner	A multicenter, randomized, double-blind, placebo-controlled trial of paroxetine in children and adolescents with social anxiety disorder	Industry

MJ84	2004049533	published	2004	Westenberg	A Double-Blind Placebo-Controlled Study of Controlled Release Fluvoxamine for the Treatment of Generalized Social Anxiety Disorder	Industry
MJ94	1996302206	published	1996	Zohar	Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder	Industry
JF7	2004388355	published	2004	Allgulander	Efficacy of sertraline in a 12-week trial for generalized anxiety disorder	Industry
JF15	2007092774	published	2006	Asakura S.	Fluvoxamine treatment of generalized social anxiety disorder in Japan: A randomized double-blind, placebo-controlled study	Industry
JF25	1999268351	published	1999	Baldwin D.	Paroxetine in social phobia/social anxiety disorder: Randomised, double- blind, placebo-controlled study	Industry
JF29	2010331033	published	2010	Bandelow	Extended-release quetiapine fumarate (quetiapine XR): A once-daily monotherapy effective in generalized anxiety disorder. Data from a randomized, double-blind, placebo-and active-controlled study	Industry
JF56	2005461776	published	2005	Bradwejn	Venlafaxine extended-release capsules in panic disorder: Flexible-dose, double-blind, placebo-controlled study	doubtful
LM4	2006486251	published	2006	Davidson J.	Treatment of posttraumatic stress disorder with venlafaxine extended release: A 6-month randomized controlled trial	Industry
LM34	2007265412	published	2007	Friedman M.J.	Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a department of veterans affairs setting	Industry
LM39	2001231890	published	2001	Geller D.A.	Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: A placebo-controlled clinical trial	Industry
LM48	1996126650	published	1996	Goodman W.K.	Treatment of obsessive-compulsive disorder with fluvoxamine: A multicentre, double-blind, placebo-controlled trial	Industry
LM54	2007173305	published	2007	Hartford	Duloxetine as an SNRI treatment for generalized anxiety disorder: Results from a placebo and active-controlled trial	Industry

LM60	2003250843	published	2003	Hollander	A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder	Industry
MC10	15003077	published	2004	Lepola	Controlled-release paroxetine in the treatment of patients with social anxiety disorder.	Industry
MC44	2006302530	published	2006	Montgomery	Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: A 6-week, multicenter, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine	Industry
MJ25	15669886	published	2005	Sheehan	Efficacy and tolerability of controlled-release paroxetine in the treatment of panic disorder.	Industry
MJ64	14608246	published	2003	Tucker	Can physiologic assessment and side effects tease out differences in PTSD trials? A double-blind comparison of citalopram, sertraline, and placebo.	Industry
MJ70	2001050465	published	2001	Van Ameringen M.A.	Sertraline treatment of generalized social phobia: A 20-week, double-blind, placebo-controlled study	Industry
LM69	1997265747	published	1997	Jenike M.A.	Placebo-controlled trial of fluoxetine and phenelzine for obsessive- compulsive disorder	governmental or non-profit
JF42	12649628	published	2003	Birmaher	Fluoxetine for the treatment of childhood anxiety disorders.	academic
MJ97	2192564	published	1990	Jenike	Sertraline in Obsessive-Compulsive Disorder: A double-Blind Comparison With Placebo	Industry
LM67	2143637	published	1990	Jenike	A controlled trial of fluvoxamine in obsessive-compulsive disorder: implications for a serotonergic theory.	academic
MC32	2007163092	published	2007	Marshall	A controlled trial of paroxetine for chronic PTSD, dissociation, and interpersonal problems in mostly minority adults	doubtful
JF10	2004379131	published	2004	Allgulander	Efficacy of venlafaxine ER in patients with social anxiety disorder: A double-blind, placebo-controlled, parallel-group comparison with paroxetine	Industry
MC15	2003299727	published	2003	Liebowitz	Efficacy of sertraline in severe generalized social anxiety disorder: Results of a double-blind, placebo-controlled study	Industry
MC16	12447029	published	2002	Liebowitz	Fluoxetine in children and adolescents with OCD: a placebo-controlled trial.	Industry

MC62	21349225	published	2011	Panahi	A randomized, double-blind, placebo-controlled trial on the efficacy and tolerability of sertraline in Iranian veterans with post-traumatic stress disorder.	academic
MC81	1997005505	published	1996	Pollack	Venlafaxine for panic disorder: Results from a double-blind, placebo- controlled study	doubtful
MJ2	2000222191	published	2000	Rickels	Efficacy of extended-release Venlafaxine in nondepressed outpatients with generalized anxiety disorder	Industry
MJ16	2001420736	published	2001	Rynn M.A.	Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder	governmental or non-profit
MJ36	2003496184	published	2003	Stahl	Escitalopram in the Treatment of Panic Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial	Industry
MJ54	1998297625	published	1998	Stein M.B.	Paroxetine treatment of generalized social phobia (social anxiety disorder): A randomized controlled trial	Industry
MJ66	2001431494	published	2001	Tucker P.	Paroxetine in the treatment of chronic posttraumatic stress disorder: Results of a placebo-controlled, flexible-dosage trial	doubtful
MJ93	2002132412	published	2002	Zohar	Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder	Industry
JF9	17559726	published	2007	Koponen	Efficacy of Duloxetine for the Treatment of GeneralizedAnxiety Disorder: Implications for Primary Care Physicians	Industry
JF59	2000137979	published	2000	Brady	Efficacy and safety of sertraline treatment of posttraumatic stress disorder: A randomized controlled trial	Industry
JF61	2006335133	published	2006	Brawman-Mintzer O.	Sertraline treatment for generalized anxiety disorder: A randomized, double-blind, placebo-controlled study	Industry
JF87	1999307984	published	1999	Davidson	Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder	Industry
LM3	16702890	published	2006	Davidson	Venlafaxine extended release in posttraumatic stress disorder: a sertraline- and placebo-controlled study.	Industry
LM6	2001168539	published	2001	Davidson J.R.T.	Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder	Industry

MJ72	7814344	published	1994	van der Kolk	Fluoxetine in posttraumatic stress disorder Massachussetts General Hospital Trauma Clinic	Industry
LM73	2005116331	published	2005	Kasper	Escitalopram in the treatment of social anxiety disorder: Randomised, placebo-controlled, flexible-dosage study	Industry
MC42	1994091030	published	1993	Montgomery	A double-blind, placebo-controlled study of fluoxetine in patients with DSM-III-R obsessive-compulsive disorder	doubtful
JF88	2004332730	published	2004	Davidson	Escitalopram in the treatment of generalized anxiety disorder: Double-blind, placebo controlled, flexible-dose study	Industry
JF89	15206657	published	2004	Davidson	Fluvoxamine-controlled release formulation for the treatment of generalized socialanxiety disorder.	Industry
LM72	2009168154	published	2009	Kasper	Efficacy of pregabalin and venlafaxine-XR in generalized anxiety disorder: Results of a double-blind, placebo-controlled 8-week trial	Industry
MC14	2005105216	published	2005	Liebowitz	A randomized controlled trial of venlafaxine extended release in generalized social anxiety disorder	Industry
MJ4	1429406	published	1992	Riddle	Double-blind, crossover trial of fluoxetine and placebo in children and adolescents with obsessive-compulsive disorder.	governmental or non-profit
MC77	11411817	published	2001	Pollack	Paroxetine in the treatment of generalized anxiety disorder: results of a placebo-controlled, flexible-dosage trial.	Industry
MC28	1998400055	published	1998	March J.S.	Sertraline in children and adolescents with obsessive-compulsive disorder: A multicenter randomized controlled trial	Industry
MC26	2004455374	published	2004	March	Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: The pediatric OCD treatment study (POTS) randomized controlled trial	governmental or non-profit
LM40	2004455208	published	2004	Geller D.A.	Paroxetine treatment in children and adolescents with obsessive-compulsive disorder: A randomized, multicenter, double-blind, placebo-controlled trial	Industry
MJ53	1999166603	published	1999	Stein M.B.	Fluvoxamine treatment of social phobia (social anxiety disorder): A double-blind, placebo-controlled study	Industry

JF55	2004323869	published	2004	Boyer P.	Social adjustment in generalised anxiety disorder: A long-term placebo-controlled study of venlafaxine extended release	Industry
MJ42	2005044275	published	2004	Stein	Efficacy of low and higher dose extended-release venlafaxine in generalized social anxiety disorder: A 6-month randomized controlled trial	Industry
JF28	1998025805	published	1998	Ballenger	Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder	Industry
MC55	18485261	published	2008	Nicolini	Improvement of psychic and somatic symptoms in adult patients with generalized anxiety disorder: examination from a duloxetine, venlafaxine extended-release and placebo-controlled trial.	doubtful
JF22	2006434703	published	2006	Baldwin	Escitalopram and paroxetine in the treatment of generalised anxiety disorder: Randomised, placebo-controlled, double-blind study	Industry

Supplementary Table S3: Studies general information

id	Main disorder	Population	Sampling	Comparator	Trial duration	Benzodiazepine use allowed	Placebo lead-in period
MC3	GAD	Adults/Elderly	Community	placebo	>= 16 weeks	no	no
MC12	Panic	Adults/Elderly	Outpatients	placebo	9-11 weeks	no	yes
MC13	SAD	Adults/Elderly	Outpatients	different dose	12-15 weeks	no	yes
MC17	SAD	Adults/Elderly	Outpatients	head-to-head	12-15 weeks	no	yes
MC22	GAD	Adults/Elderly	Unclear	head-to-head	5-8 weeks	unclear	not informed
MC25	SAD	Children/Adolescents	Outpatients	different dose	>= 16 weeks	no	not informed
MC33	PTSD	Adults/Elderly	Unclear	different dose	12-15 weeks	not informed	no
MC38	GAD	Adults/Elderly	Unclear	placebo	5-8 weeks	not informed	no
MC40	Panic	Adults/Elderly	Outpatients	placebo	12-15 weeks	not informed	unclear
MC45	OCD	Adults/Elderly	Unclear	different dose	12-15 weeks	no	yes
MC51	Panic	Adults/Elderly	Outpatients	placebo	5-8 weeks	yes	yes
MC71	Panic	Adults/Elderly	Outpatients	placebo	9-11 weeks	no	yes
MC73	Panic	Adults/Elderly	Outpatients	head-to-head	12-15 weeks	no	yes
MC79	Panic	Adults/Elderly	Outpatients	head-to-head	12-15 weeks	no	yes
MC82	Panic	Adults/Elderly	Outpatients	placebo	9-11 weeks	no	yes
MJ1	SAD	Adults/Elderly	Outpatients	placebo	12-15 weeks	no	yes
MJ3	GAD	Adults/Elderly	Outpatients	different dose	5-8 weeks	no	yes
MJ5	OCD	Children/Adolescents	Outpatients	placebo	9-11 weeks	no	yes
MJ6	PTSD	Children/Adolescents	Outpatients	placebo	9-11 weeks	no	no
MJ14	GAD	Adults/Elderly	Outpatients	placebo	9-11 weeks	no	yes
MJ17	Panic	Adults/Elderly	Outpatients	placebo	5-8 weeks	not informed	no
MJ44	OCD	Adults/Elderly	Outpatients	head-to-head	>= 16 weeks	no	no
MJ56	GAD	Children/Adolescents	Outpatients	placebo	9-11 weeks	no	no
MJ78	SAD	Children/Adolescents	Outpatients	placebo	>= 16 weeks	not informed	no
MJ84	SAD	Adults/Elderly	Outpatients	placebo	12-15 weeks	not informed	no
MJ94	OCD	Adults/Elderly	Outpatients	placebo	12-15 weeks	yes	yes
JF7	GAD	Adults/Elderly	Outpatients	placebo	5-8 weeks	no	yes
JF15	SAD	Adults/Elderly	Unclear	placebo	9-11 weeks	yes	not informed
JF25	SAD	Adults/Elderly	Community	placebo	12-15 weeks	no	yes
JF29	GAD	Adults/Elderly	Outpatients	placebo	5-8 weeks	no	not informed
JF56	Panic	Adults/Elderly	Outpatients	placebo	9-11 weeks	not informed	yes
LM4	PTSD	Adults/Elderly	Outpatients	placebo	>= 16 weeks	unclear	no

LM34	PTSD	Adults/Elderly	Outpatients	placebo	12-15 weeks	no	yes
LM39	OCD	Children/Adolescents	Unclear	placebo	9-11 weeks	not informed	no
LM48	OCD	Adults/Elderly	Outpatients	placebo	9-11 weeks	yes	no
LM54	GAD	Adults/Elderly	Outpatients	head-to-head	9-11 weeks	not informed	not informed
LM60	OCD	Adults/Elderly	Unclear	placebo	12-15 weeks	no	no
MC10	SAD	Adults/Elderly	Outpatients	placebo	12-15 weeks	no	unclear
MC44	GAD	Adults/Elderly	Outpatients	placebo	5-8 weeks	no	no
MJ25	Panic	Adults/Elderly	Unclear	placebo	9-11 weeks	no	yes
MJ64	PTSD	Adults/Elderly	Outpatients	head-to-head	9-11 weeks	yes	no
MJ70	SAD	Adults/Elderly	Outpatients	placebo	>= 16 weeks	no	yes
LM69	OCD	Adults/Elderly	Outpatients	placebo	9-11 weeks	no	no
JF42	More than 1 AnxDis	Children/Adolescents	Mixed	placebo	12-15 weeks	not informed	not informed
MJ97	OCD	Adults/Elderly	Outpatients	placebo	9-11 weeks	no	no
LM67	OCD	Adults/Elderly	Outpatients	placebo	9-11 weeks	no	no
MC32	PTSD	Adults/Elderly	Unclear	placebo	9-11 weeks	no	yes
JF10	SAD	Adults/Elderly	Outpatients	placebo	12-15 weeks	not informed	no
MC15	SAD	Adults/Elderly	Outpatients	placebo	12-15 weeks	no	yes
MC16	OCD	Children/Adolescents	Unclear	placebo	5-8 weeks	no	no
MC62	PTSD	Adults/Elderly	Outpatients	placebo	9-11 weeks	yes	not informed
MC81	Panic	Adults/Elderly	Outpatients	placebo	5-8 weeks	not informed	yes
MJ2	GAD	Adults/Elderly	Outpatients	different dose	5-8 weeks	no	no
MJ16	GAD	Children/Adolescents	Outpatients	placebo	9-11 weeks	not informed	no
MJ36	Panic	Adults/Elderly	Outpatients	head-to-head	9-11 weeks	no	yes
MJ54	SAD	Adults/Elderly	Outpatients	placebo	12-15 weeks	not informed	yes
MJ66	PTSD	Adults/Elderly	Outpatients	placebo	12-15 weeks	not informed	yes
MJ93	PTSD	Adults/Elderly	Outpatients	placebo	9-11 weeks	yes	yes
JF9	GAD	Adults/Elderly	Outpatients	different dose	9-11 weeks	no	yes
JF59	PTSD	Adults/Elderly	Outpatients	placebo	12-15 weeks	not informed	yes
JF61	GAD	Adults/Elderly	Outpatients	placebo	9-11 weeks	no	no
JF87	GAD	Adults/Elderly	Outpatients	placebo	5-8 weeks	no	yes
LM3	PTSD	Adults/Elderly	Outpatients	head-to-head	12-15 weeks	no	no
LM6	PTSD	Adults/Elderly	Outpatients	placebo	12-15 weeks	no	yes
MJ72	PTSD	Adults/Elderly	Outpatients	placebo	5-8 weeks	yes	no
LM73	SAD	Adults/Elderly	Outpatients	placebo	12-15 weeks	no	yes

MC42	OCD	Adults/Elderly	Unclear	different dose	5-8 weeks	yes	yes
JF88	GAD	Adults/Elderly	Outpatients	placebo	5-8 weeks	no	yes
JF89	GAD	Adults/Elderly	Mixed	placebo	12-15 weeks	not informed	yes
LM72	GAD	Adults/Elderly	Mixed	placebo	5-8 weeks	not informed	no
MC14	SAD	Adults/Elderly	Mixed	placebo	12-15 weeks	no	yes
MJ4	OCD	Children/Adolescents	Outpatients	placebo	5-8 weeks	not informed	no
MC77	GAD	Adults/Elderly	Outpatients	placebo	5-8 weeks	no	yes
MC28	OCD	Children/Adolescents	Outpatients	placebo	12-15 weeks	no	yes
MC26	OCD	Children/Adolescents	Outpatients	placebo	12-15 weeks	no	not informed
LM40	OCD	Children/Adolescents	Outpatients	placebo	9-11 weeks	not informed	no
MJ53	SAD	Adults/Elderly	Outpatients	placebo	12-15 weeks	yes	no
JF55	GAD	Adults/Elderly	Outpatients	placebo	>= 16 weeks	yes	yes
MJ42	SAD	Adults/Elderly	Outpatients	different dose	>= 16 weeks	not informed	yes
JF28	Panic	Adults/Elderly	Unclear	different dose	9-11 weeks	yes	yes
MC55	GAD	Adults/Elderly	Outpatients	head-to-head	9-11 weeks	no	no
JF22	GAD	Adults/Elderly	Outpatients	head-to-head	12-15 weeks	no	yes

GAD, generalized anxiety disorder; PTSD, post-traumatic stress disorder; OCD, obsessive-compulsive disorder

Supplementary Table S4: Outcomes assessment information

id	Adverse event	Medication	Dose equivalent	Sample size (medication)	Number of adverse events (medication)	Sample size (placebo)	Number of adverse events (placebo)	Odds ratio	Variance
MC3	any adverse event	venlafaxine	1-1.99	122	112	122	110	1.22	0.2
MC12	any adverse event	venlafaxine	2-2.99	175	154	168	133	1.93	0.09
MC13	any adverse event	paroxetine	1-1.99	97	89	31	26	2.14	0.37
MC17	any adverse event	venlafaxine	2-2.99	133	127	72	62	3.41	0.29
MC22	any adverse event	duloxetine	2-2.99	156	128	52	36	2.03	0.13
MC25	any adverse event	venlafaxine	1-1.99	137	123	148	120	2.05	0.12
MC33	any adverse event	fluoxetine	1-1.99	163	110	44	29	1.07	0.13
MC38	any adverse event	escitalopram	1-1.99	203	172	212	170	1.37	0.07
MC40	any adverse event	fluoxetine	1-1.99	90	25	90	19	1.44	0.12
MC45	any adverse event	citalopram	1-1.99	192	140	33	19	1.98	0.15
MC51	any adverse event	fluvoxamine	3-3.99	43	39	47	42	1.16	0.5
MC71	any adverse event	sertraline	2-2.99	80	74	88	83	0.74	0.39
MC73	any adverse event	venlafaxine	1-1.99	156	134	52	42	1.45	0.18
MC79	any adverse event	venlafaxine	1-1.99	158	117	52	35	1.39	0.12
MC82	any adverse event	sertraline	2-2.99	88	83	88	77	2.37	0.32
MJ1	any adverse event	venlafaxine	2-2.99	126	110	135	113	1.34	0.13
MJ3	any adverse event	paroxetine	1-1.99	189	166	90	67	2.48	0.11
MJ5	any adverse event	fluvoxamine	3-3.99	57	48	63	48	1.67	0.22
MJ6	any adverse event	sertraline	2-2.99	67	51	62	47	1.02	0.17
MJ14	any adverse event	duloxetine	3-3.99	168	140	159	116	1.85	0.07
MJ17	any adverse event	fluvoxamine	3-3.99	23	12	23	12	1	0.35
MJ44	any adverse event	escitalopram	1-1.99	116	82	38	24	1.41	0.15
MJ56	any adverse event	duloxetine	1-1.99	135	106	137	90	1.91	0.08
MJ78	any adverse event	paroxetine	1-1.99	165	146	157	126	1.89	0.1
MJ84	any adverse event	fluvoxamine	>=4	149	137	151	125	2.37	0.14
MJ94	any adverse event	paroxetine	1-1.99	201	163	99	78	1.15	0.09
JF7	any adverse event	sertraline	1-1.99	188	15	190	19	0.78	0.13
JF15	any adverse event	fluvoxamine	3-3.99	176	156	89	59	3.97	0.11
JF25	any adverse event	paroxetine	1-1.99	139	103	151	103	1.33	0.07

JF29	any adverse event	paroxetine	1-1.99	217	16	217	8	2.08	0.2
JF56	any adverse event	venlafaxine	2-2.99	181	156	180	140	1.78	0.08
JF94	any adverse event	escitalopram	1-1.99	198	127	98	55	1.4	0.06
LM4	any adverse event	venlafaxine	2-2.99	161	126	168	116	1.61	0.06
LM34	any adverse event	sertraline	2-2.99	86	74	83	60	2.36	0.16
LM39	any adverse event	fluoxetine	1-1.99	71	53	32	27	0.55	0.31
LM48	any adverse event	fluvoxamine	>=4	78	74	78	65	3.7	0.36
LM54	any adverse event	duloxetine	3-3.99	162	136	80	58	1.98	0.11
LM60	any adverse event	fluvoxamine	>=4	127	123	126	107	5.46	0.32
MC38	sexual adverse event	escitalopram	1-1.99	203	16	212	8	2.18	0.2
MJ64	sexual adverse event	citalopram	1-1.99	25	5	5	0	2.95	2.41
MJ97	sexual adverse event	sertraline	>=4	10	2	9	3	0.5	1.12
JF29	sexual adverse event	paroxetine	1-1.99	217	16	217	5	3.38	0.27
LM67	sexual adverse event	fluvoxamine	>=4	18	3	20	1	3.8	1.45
MC32	weight change	paroxetine	2-2.99	25	4	27	2	2.38	0.84
MC38	weight change	escitalopram	1-1.99	203	2	212	4	0.52	0.76
MJ5	weight change	fluvoxamine	3-3.99	57	5	63	9	0.58	0.35
JF7	weight change	sertraline	1-1.99	188	6	190	10	0.59	0.28
JF10	weight change	venlafaxine	2-2.99	129	1	66	0	1.55	2.69
JF29	weight change	paroxetine	1-1.99	217	10	217	5	2.05	0.31
MC12	dry mouth	venlafaxine	2-2.99	175	26	168	10	2.76	0.15
MC13	dry mouth	paroxetine	1-1.99	97	14	31	2	2.45	0.62
MC15	dry mouth	sertraline	3-3.99	211	30	204	11	2.91	0.13
MC16	dry mouth	fluoxetine	3-3.99	21	5	22	1	6.56	1.31
MC17	dry mouth	venlafaxine	2-2.99	133	24	72	3	5.06	0.4
MC22	dry mouth	duloxetine	2-2.99	156	25	52	3	3.12	0.4
MC38	dry mouth	escitalopram	1-1.99	203	39	212	25	1.78	0.08
MC44	dry mouth	venlafaxine	1-1.99	113	8	101	2	3.77	0.64
MC45	dry mouth	citalopram	1-1.99	192	15	33	1	2.71	1.1
MC51	dry mouth	fluvoxamine	3-3.99	43	11	47	11	1.12	0.24
MC62	dry mouth	sertraline	2-2.99	35	7	35	6	1.21	0.38
MC71	dry mouth	sertraline	2-2.99	80	15	88	7	2.67	0.24
MC79	dry mouth	venlafaxine	1-1.99	158	8	52	2	1.33	0.65
MC81	dry mouth	venlafaxine	2-2.99	13	3	12	0	8.33	2.46
MC82	dry mouth	sertraline	2-2.99	88	11	88	17	0.6	0.18

MJ1	dry mouth	venlafaxine	2-2.99	126	25	135	9	3.47	0.17
MJ2	dry mouth	venlafaxine	1-1.99	86	17	32	2	3.7	0.61
MJ3	dry mouth	paroxetine	1-1.99	189	34	90	6	3.07	0.21
MJ6	dry mouth	sertraline	2-2.99	67	5	62	0	11	2.21
MJ14	dry mouth	duloxetine	3-3.99	168	11	159	3	3.64	0.44
MJ16	dry mouth	sertraline	1-1.99	11	6	11	3	3.2	0.82
MJ25	dry mouth	paroxetine	2-2.99	444	58	445	40	1.52	0.05
MJ36	dry mouth	escitalopram	1-1.99	128	10	59	2	2.42	0.63
MJ44	dry mouth	escitalopram	1-1.99	116	5	38	1	1.67	1.24
MJ54	dry mouth	paroxetine	1-1.99	94	7	93	2	3.66	0.67
MJ66	dry mouth	paroxetine	1-1.99	151	21	156	7	3.44	0.2
MJ70	dry mouth	sertraline	2-2.99	135	18	69	4	2.5	0.33
MJ93	dry mouth	sertraline	2-2.99	23	3	19	2	1.27	0.94
MJ94	dry mouth	paroxetine	1-1.99	201	32	99	8	2.15	0.17
MJ97	dry mouth	sertraline	>=4	10	0	9	2	0.14	2.63
JF9	dry mouth	duloxetine	2-2.99	168	19	87	3	3.57	0.4
JF10	dry mouth	venlafaxine	2-2.99	129	14	66	1	7.91	1.1
JF29	dry mouth	paroxetine	1-1.99	217	21	217	13	1.68	0.13
JF56	dry mouth	venlafaxine	2-2.99	181	33	180	14	2.64	0.11
JF59	dry mouth	sertraline	2-2.99	94	11	93	4	2.95	0.36
JF61	dry mouth	sertraline	2-2.99	68	9	170	15	1.58	0.2
JF87	dry mouth	venlafaxine	1-1.99	87	13	49	2	4.13	0.61
LM3	dry mouth	venlafaxine	2-2.99	179	32	89	13	1.27	0.13
LM4	dry mouth	venlafaxine	2-2.99	161	21	168	8	3	0.19
LM6	dry mouth	sertraline	2-2.99	100	10	108	8	1.39	0.25
LM54	dry mouth	duloxetine	3-3.99	162	19	80	5	1.99	0.27
LM67	dry mouth	fluvoxamine	>=4	18	1	20	0	3.51	2.77
LM95	dry mouth	sertraline	2-2.99	36	8	36	5	1.77	0.39
MC3	sweating	venlafaxine	1-1.99	122	16	122	2	9.06	0.58
MC10	sweating	paroxetine	1-1.99	186	26	184	5	5.82	0.25
MC12	sweating	venlafaxine	2-2.99	175	12	168	2	6.11	0.6
MC13	sweating	paroxetine	1-1.99	97	8	31	0	5.98	2.16
MC15	sweating	sertraline	3-3.99	211	24	204	3	8.6	0.39
MC16	sweating	fluoxetine	3-3.99	21	4	22	2	2.35	0.86
MC17	sweating	venlafaxine	2-2.99	133	13	72	2	3.79	0.6

MC45	sweating	citalopram	1-1.99	192	9	33	1	1.57	1.15
MC79	sweating	venlafaxine	1-1.99	158	13	52	2	2.24	0.6
MC81	sweating	venlafaxine	2-2.99	13	2	12	0	5.43	2.57
MJ1	sweating	venlafaxine	2-2.99	126	15	135	3	5.95	0.42
MJ3	sweating	paroxetine	1-1.99	189	13	90	1	6.57	1.09
MJ44	sweating	escitalopram	1-1.99	116	7	38	1	2.38	1.18
MJ54	sweating	paroxetine	1-1.99	94	9	93	3	3.18	0.47
MJ64	sweating	citalopram	1-1.99	25	4	5	0	2.3	2.45
MJ70	sweating	sertraline	2-2.99	135	15	69	1	8.5	1.09
MJ72	sweating	fluoxetine	2-2.99	33	21	31	11	3.18	0.27
MJ94	sweating	paroxetine	1-1.99	201	22	99	6	1.91	0.23
JF7	sweating	sertraline	1-1.99	188	36	190	8	5.39	0.16
JF9	sweating	duloxetine	2-2.99	168	15	87	5	1.61	0.29
JF10	sweating	venlafaxine	2-2.99	129	34	66	5	4.37	0.26
JF25	sweating	paroxetine	1-1.99	139	17	151	4	5.12	0.32
JF56	sweating	venlafaxine	2-2.99	181	29	180	5	6.68	0.25
LM4	sweating	venlafaxine	2-2.99	161	21	168	6	4.05	0.23
LM73	sweating	escitalopram	1-1.99	181	11	177	4	2.8	0.35
MC3	headache	venlafaxine	1-1.99	122	19	122	14	1.42	0.14
MC16	headache	fluoxetine	3-3.99	21	11	22	8	1.92	0.39
MC22	headache	duloxetine	2-2.99	156	26	52	7	1.29	0.21
MC33	headache	fluoxetine	1-1.99	163	26	44	7	1	0.22
MC38	headache	escitalopram	1-1.99	203	52	212	34	1.8	0.06
MC40	headache	fluoxetine	1-1.99	90	3	90	4	0.74	0.61
MC42	headache	fluoxetine	1-1.99	52	7	18	4	0.54	0.49
MC44	headache	venlafaxine	1-1.99	113	10	101	13	0.66	0.2
MC45	headache	citalopram	1-1.99	192	36	33	5	1.29	0.27
MC51	headache	fluvoxamine	3-3.99	43	15	47	20	0.72	0.19
MC62	headache	sertraline	2-2.99	35	11	35	7	1.83	0.31
MC81	headache	venlafaxine	2-2.99	13	6	12	2	4.29	0.91
MC82	headache	sertraline	2-2.99	88	29	88	30	0.95	0.1
MJ5	headache	fluvoxamine	3-3.99	57	27	63	30	0.99	0.13
MJ6	headache	sertraline	2-2.99	67	17	62	12	1.42	0.18
MJ36	headache	escitalopram	1-1.99	128	20	59	9	1.03	0.19
MJ44	headache	escitalopram	1-1.99	116	19	38	7	0.87	0.24

MJ72	headache	fluoxetine	2-2.99	33	11	31	3	4.67	0.51
MJ84	headache	fluvoxamine	>=4	149	52	151	48	1.15	0.06
MJ93	headache	sertraline	2-2.99	23	6	19	3	1.88	0.62
MJ94	headache	paroxetine	1-1.99	201	50	99	19	1.39	0.09
MJ97	headache	sertraline	>=4	10	0	9	1	0.27	2.88
JF15	headache	fluvoxamine	3-3.99	176	21	89	9	1.2	0.18
JF25	headache	paroxetine	1-1.99	139	18	151	22	0.87	0.12
JF29	headache	paroxetine	1-1.99	217	37	217	39	0.94	0.06
JF59	headache	sertraline	2-2.99	94	19	93	26	0.65	0.12
JF88	headache	escitalopram	1-1.99	158	37	157	28	1.41	0.08
JF89	headache	fluvoxamine	3-3.99	139	50	140	38	1.51	0.07
JF94	headache	escitalopram	1-1.99	198	10	98	8	0.6	0.24
LM3	headache	venlafaxine	2-2.99	179	57	89	26	1.13	0.08
LM4	headache	venlafaxine	2-2.99	161	46	168	44	1.13	0.06
LM6	headache	sertraline	2-2.99	100	33	108	26	1.55	0.1
LM34	headache	sertraline	2-2.99	86	23	83	20	1.15	0.13
LM39	headache	fluoxetine	1-1.99	71	20	32	9	1	0.22
LM48	headache	fluvoxamine	>=4	78	13	78	19	0.62	0.16
LM67	headache	fluvoxamine	>=4	18	5	20	3	2.18	0.67
LM72	headache	venlafaxine	2-2.99	125	20	128	15	1.43	0.14
LM73	headache	escitalopram	1-1.99	181	45	177	44	1	0.06
LM95	headache	sertraline	2-2.99	36	11	36	6	2.2	0.33
MC3	dizziness	venlafaxine	1-1.99	122	16	122	8	2.15	0.21
MC13	dizziness	paroxetine	1-1.99	97	27	31	2	5.59	0.59
MC14	dizziness	venlafaxine	2-2.99	133	21	138	11	2.16	0.16
MC15	dizziness	sertraline	3-3.99	211	35	204	11	3.49	0.13
MC16	dizziness	fluoxetine	3-3.99	21	4	22	3	1.49	0.69
MC22	dizziness	duloxetine	2-2.99	156	17	52	2	3.06	0.59
MC38	dizziness	escitalopram	1-1.99	203	24	212	22	1.16	0.1
MC44	dizziness	venlafaxine	1-1.99	113	14	101	7	1.9	0.24
MC45	dizziness	citalopram	1-1.99	192	11	33	2	0.94	0.63
MC51	dizziness	fluvoxamine	3-3.99	43	14	47	9	2.04	0.24
MC81	dizziness	venlafaxine	2-2.99	13	1	12	0	3	2.83
MJ2	dizziness	venlafaxine	1-1.99	86	22	32	4	2.41	0.35
MJ4	dizziness	fluoxetine	1-1.99	7	1	7	0	3.46	2.95

MJ6	dizziness	sertraline	2-2.99	67	3	62	5	0.53	0.57
MJ14	dizziness	duloxetine	3-3.99	168	28	159	11	2.69	0.14
MJ16	dizziness	sertraline	1-1.99	11	2	11	7	0.13	1
MJ36	dizziness	escitalopram	1-1.99	128	8	59	6	0.59	0.32
MJ44	dizziness	escitalopram	1-1.99	116	10	38	2	1.7	0.64
MJ64	dizziness	citalopram	1-1.99	25	5	5	1	1	1.5
MJ94	dizziness	paroxetine	1-1.99	201	20	99	5	2.08	0.27
JF7	dizziness	sertraline	1-1.99	188	21	190	17	1.28	0.12
JF9	dizziness	duloxetine	2-2.99	168	20	87	7	1.54	0.21
JF10	dizziness	venlafaxine	2-2.99	129	17	66	3	3.19	0.42
JF15	dizziness	fluvoxamine	3-3.99	176	12	89	0	13.6	2.1
JF25	dizziness	paroxetine	1-1.99	139	18	151	8	2.66	0.2
JF29	dizziness	paroxetine	1-1.99	217	29	217	13	2.42	0.12
JF87	dizziness	venlafaxine	1-1.99	87	15	49	6	1.49	0.27
LM3	dizziness	venlafaxine	2-2.99	179	23	89	7	1.73	0.2
LM4	dizziness	venlafaxine	2-2.99	161	29	168	19	1.72	0.1
LM67	dizziness	fluvoxamine	>=4	18	3	20	0	9.26	2.4
LM72	dizziness	venlafaxine	2-2.99	125	12	128	8	1.59	0.23
LM73	dizziness	escitalopram	1-1.99	181	13	177	9	1.44	0.2
MC12	constipation	venlafaxine	2-2.99	175	21	168	7	3.14	0.2
MC13	constipation	paroxetine	1-1.99	97	7	31	1	2.33	1.19
MC16	constipation	fluoxetine	3-3.99	21	2	22	0	5.77	2.5
MC17	constipation	venlafaxine	2-2.99	133	15	72	3	2.92	0.42
MC22	constipation	duloxetine	2-2.99	156	8	52	2	1.35	0.65
MC38	constipation	escitalopram	1-1.99	203	14	212	9	1.67	0.19
MC44	constipation	venlafaxine	1-1.99	113	7	101	2	3.27	0.66
MC51	constipation	fluvoxamine	3-3.99	43	11	47	10	1.27	0.25
MC62	constipation	sertraline	2-2.99	35	6	35	4	1.6	0.48
MC77	constipation	paroxetine	1-1.99	161	25	163	3	9.8	0.39
MC79	constipation	venlafaxine	1-1.99	158	8	52	1	2.72	1.15
MC81	constipation	venlafaxine	2-2.99	13	1	12	0	3	2.83
MJ1	constipation	venlafaxine	2-2.99	126	13	135	5	2.99	0.29
MJ3	constipation	paroxetine	1-1.99	189	16	90	3	2.68	0.41
MJ14	constipation	duloxetine	3-3.99	168	14	159	5	2.8	0.28
MJ44	constipation	escitalopram	1-1.99	116	2	38	1	0.65	1.54

MJ54	constipation	paroxetine	1-1.99	94	7	93	2	3.66	0.67
MJ94	constipation	paroxetine	1-1.99	201	28	99	4	3.84	0.3
MJ97	constipation	sertraline	>=4	10	3	9	1	3.43	1.6
JF9	constipation	duloxetine	2-2.99	168	13	87	2	3.56	0.6
JF15	constipation	fluvoxamine	3-3.99	176	22	89	6	1.98	0.23
JF29	constipation	paroxetine	1-1.99	217	6	217	3	2.03	0.51
JF56	constipation	venlafaxine	2-2.99	181	18	180	4	4.86	0.32
LM3	constipation	venlafaxine	2-2.99	179	21	89	9	1.18	0.18
LM4	constipation	venlafaxine	2-2.99	161	20	168	5	4.62	0.26
LM48	constipation	fluvoxamine	>=4	78	13	78	10	1.36	0.21
LM54	constipation	duloxetine	3-3.99	162	23	80	3	4.25	0.4
LM67	constipation	fluvoxamine	>=4	18	3	20	2	1.8	0.96
LM72	constipation	venlafaxine	2-2.99	125	7	128	4	1.84	0.41
LM95	constipation	sertraline	2-2.99	36	7	36	4	1.93	0.46
MC13	tremor	paroxetine	1-1.99	97	4	31	0	3.03	2.26
MC16	tremor	fluoxetine	3-3.99	21	4	22	0	11.57	2.32
MC28	tremor	sertraline	3-3.99	92	6	95	0	14.35	2.18
MC32	tremor	paroxetine	2-2.99	25	2	27	1	2.26	1.58
MC40	tremor	fluoxetine	1-1.99	90	4	90	0	9.42	2.24
MC79	tremor	venlafaxine	1-1.99	158	6	52	1	2.01	1.19
MC81	tremor	venlafaxine	2-2.99	13	0	12	1	0.28	2.83
MJ14	tremor	duloxetine	3-3.99	168	9	159	1	8.94	1.12
MJ44	tremor	escitalopram	1-1.99	116	6	38	1	2.02	1.2
MJ54	tremor	paroxetine	1-1.99	94	8	93	2	4.23	0.65
MJ70	tremor	sertraline	2-2.99	135	16	69	3	2.96	0.42
MJ94	tremor	paroxetine	1-1.99	201	18	99	2	4.77	0.57
MJ97	tremor	sertraline	>=4	10	0	9	2	0.14	2.63
JF10	tremor	venlafaxine	2-2.99	129	13	66	1	7.28	1.1
LM4	tremor	venlafaxine	2-2.99	161	10	168	6	1.79	0.28
LM67	tremor	fluvoxamine	>=4	18	1	20	0	3.51	2.77
MC10	asthenia	paroxetine	1-1.99	186	33	184	13	2.84	0.12
MC13	asthenia	paroxetine	1-1.99	97	25	31	3	3.24	0.42
MC14	asthenia	venlafaxine	2-2.99	133	28	138	10	3.41	0.15
MC16	asthenia	fluoxetine	3-3.99	21	10	22	7	1.95	0.4
MC17	asthenia	venlafaxine	2-2.99	133	27	72	7	2.37	0.2

MC22	asthenia	duloxetine	2-2.99	156	15	52	1	5.43	1.09
MC44	asthenia	venlafaxine	1-1.99	113	14	101	6	2.24	0.26
MC45	asthenia	citalopram	1-1.99	192	13	33	1	2.32	1.11
MC62	asthenia	sertraline	2-2.99	35	6	35	2	3.41	0.73
MC77	asthenia	paroxetine	1-1.99	161	34	163	17	2.3	0.1
MC81	asthenia	venlafaxine	2-2.99	13	3	12	1	3.3	1.52
MJ2	asthenia	venlafaxine	1-1.99	86	9	32	3	1.13	0.49
MJ3	asthenia	paroxetine	1-1.99	189	20	90	4	2.54	0.32
MJ4	asthenia	fluoxetine	1-1.99	7	4	7	2	3.33	1.28
MJ5	asthenia	fluvoxamine	3-3.99	57	15	63	10	1.89	0.21
MJ14	asthenia	duloxetine	3-3.99	168	20	159	9	2.25	0.17
MJ25	asthenia	paroxetine	2-2.99	444	67	445	44	1.62	0.04
MJ36	asthenia	escitalopram	1-1.99	128	17	59	5	1.65	0.29
MJ44	asthenia	escitalopram	1-1.99	116	13	38	2	2.27	0.61
MJ64	asthenia	citalopram	1-1.99	25	10	5	2	1	1
MJ66	asthenia	paroxetine	1-1.99	151	20	156	9	2.49	0.18
MJ70	asthenia	sertraline	2-2.99	135	24	69	8	1.65	0.19
MJ78	asthenia	paroxetine	1-1.99	165	24	157	12	2.06	0.14
MJ84	asthenia	fluvoxamine	>=4	149	42	151	20	2.57	0.09
MJ93	asthenia	sertraline	2-2.99	23	4	19	1	3.79	1.36
MJ94	asthenia	paroxetine	1-1.99	201	52	99	18	1.57	0.09
JF7	asthenia	sertraline	1-1.99	188	19	190	10	2.02	0.16
JF9	asthenia	duloxetine	2-2.99	168	22	87	2	6.4	0.56
JF10	asthenia	venlafaxine	2-2.99	129	26	66	5	3.08	0.26
JF25	asthenia	paroxetine	1-1.99	139	28	151	26	1.21	0.09
JF29	asthenia	paroxetine	1-1.99	217	20	217	8	2.65	0.18
JF87	asthenia	venlafaxine	1-1.99	87	12	49	5	1.41	0.32
LM48	asthenia	fluvoxamine	>=4	78	22	78	9	3.01	0.19
LM54	asthenia	duloxetine	3-3.99	162	19	80	3	3.41	0.41
LM60	asthenia	fluvoxamine	>=4	127	32	126	10	3.91	0.15
LM67	asthenia	fluvoxamine	>=4	18	5	20	3	2.18	0.67
LM72	asthenia	venlafaxine	2-2.99	125	15	128	5	3.35	0.28
LM73	asthenia	escitalopram	1-1.99	181	25	177	16	1.61	0.12
LM95	asthenia	sertraline	2-2.99	36	7	36	4	1.93	0.46
MC14	agitation	venlafaxine	2-2.99	133	8	138	3	2.88	0.47

MC25	agitation	venlafaxine	1-1.99	137	1	148	3	0.36	1.35
MC26	agitation	sertraline	3-3.99	28	1	28	1	1	2.07
MC28	agitation	sertraline	3-3.99	92	12	95	2	6.98	0.61
MC81	agitation	venlafaxine	2-2.99	13	0	12	2	0.16	2.57
MJ5	agitation	fluvoxamine	3-3.99	57	7	63	2	4.27	0.68
MJ6	agitation	sertraline	2-2.99	67	4	62	2	1.9	0.78
MJ16	agitation	sertraline	1-1.99	11	6	11	3	3.2	0.82
MJ17	agitation	fluvoxamine	3-3.99	23	3	23	1	3.3	1.43
MJ25	agitation	paroxetine	2-2.99	444	36	445	31	1.18	0.06
MJ78	agitation	paroxetine	1-1.99	165	3	157	2	1.44	0.85
LM39	agitation	fluoxetine	1-1.99	71	9	32	1	4.5	1.16
LM40	agitation	paroxetine	1-1.99	98	12	105	6	2.3	0.27
LM48	agitation	fluvoxamine	>=4	78	15	78	5	3.48	0.3
MC3	insomnia	venlafaxine	1-1.99	122	16	122	9	1.9	0.19
MC10	insomnia	paroxetine	1-1.99	186	16	184	8	2.07	0.2
MC12	insomnia	venlafaxine	2-2.99	175	28	168	10	3.01	0.15
MC13	insomnia	paroxetine	1-1.99	97	28	31	5	2.11	0.29
MC14	insomnia	venlafaxine	2-2.99	133	33	138	10	4.22	0.15
MC15	insomnia	sertraline	3-3.99	211	51	204	21	2.78	0.08
MC17	insomnia	venlafaxine	2-2.99	133	37	72	6	4.24	0.22
MC28	insomnia	sertraline	3-3.99	92	34	95	12	4.05	0.14
MC38	insomnia	escitalopram	1-1.99	203	19	212	12	1.72	0.15
MC40	insomnia	fluoxetine	1-1.99	90	3	90	2	1.52	0.86
MC42	insomnia	fluoxetine	1-1.99	52	7	18	4	0.54	0.49
MC44	insomnia	venlafaxine	1-1.99	113	8	101	5	1.46	0.34
MC45	insomnia	citalopram	1-1.99	192	23	33	2	2.11	0.58
MC62	insomnia	sertraline	2-2.99	35	11	35	5	2.75	0.37
MC81	insomnia	venlafaxine	2-2.99	13	4	12	1	4.89	1.45
MC82	insomnia	sertraline	2-2.99	88	30	88	19	1.88	0.12
MJ1	insomnia	venlafaxine	2-2.99	126	26	135	11	2.93	0.15
MJ2	insomnia	venlafaxine	1-1.99	86	15	32	4	1.48	0.37
MJ4	insomnia	fluoxetine	1-1.99	7	4	7	1	8	1.75
MJ5	insomnia	fluvoxamine	3-3.99	57	17	63	6	4.04	0.27
MJ6	insomnia	sertraline	2-2.99	67	7	62	8	0.79	0.3
MJ14	insomnia	duloxetine	3-3.99	168	11	159	5	2.16	0.3

MJ17	insomnia	fluvoxamine	3-3.99	23	3	23	1	3.3	1.43
MJ25	insomnia	paroxetine	2-2.99	444	89	445	49	2.03	0.04
MJ36	insomnia	escitalopram	1-1.99	128	18	59	8	1.04	0.21
MJ44	insomnia	escitalopram	1-1.99	116	10	38	5	0.62	0.34
MJ64	insomnia	citalopram	1-1.99	25	17	5	4	0.53	1.43
MJ70	insomnia	sertraline	2-2.99	135	41	69	10	2.57	0.15
MJ78	insomnia	paroxetine	1-1.99	165	23	157	9	2.66	0.17
MJ84	insomnia	fluvoxamine	>=4	149	48	151	23	2.64	0.08
MJ94	insomnia	paroxetine	1-1.99	201	48	99	15	1.76	0.11
JF7	insomnia	sertraline	1-1.99	188	38	190	28	1.47	0.07
JF9	insomnia	duloxetine	2-2.99	168	19	87	3	3.57	0.4
JF10	insomnia	venlafaxine	2-2.99	129	22	66	5	2.51	0.27
JF15	insomnia	fluvoxamine	3-3.99	176	10	89	0	11.29	2.11
JF25	insomnia	paroxetine	1-1.99	139	27	151	25	1.22	0.09
JF29	insomnia	paroxetine	1-1.99	217	20	217	9	2.35	0.17
JF56	insomnia	venlafaxine	2-2.99	181	34	180	7	5.72	0.18
JF59	insomnia	sertraline	2-2.99	94	15	93	4	4.22	0.34
JF61	insomnia	sertraline	2-2.99	68	12	170	25	1.24	0.15
JF89	insomnia	fluvoxamine	3-3.99	139	43	140	15	3.73	0.11
LM3	insomnia	venlafaxine	2-2.99	179	23	89	8	1.49	0.19
LM4	insomnia	venlafaxine	2-2.99	161	12	168	17	0.72	0.16
LM6	insomnia	sertraline	2-2.99	100	35	108	24	1.88	0.1
LM34	insomnia	sertraline	2-2.99	86	12	83	8	1.52	0.24
LM39	insomnia	fluoxetine	1-1.99	71	9	32	3	1.4	0.5
LM48	insomnia	fluvoxamine	>=4	78	25	78	15	1.98	0.14
LM54	insomnia	duloxetine	3-3.99	162	12	80	2	3.12	0.6
LM60	insomnia	fluvoxamine	>=4	127	44	126	25	2.14	0.08
LM67	insomnia	fluvoxamine	>=4	18	7	20	1	12.09	1.29
LM72	insomnia	venlafaxine	2-2.99	125	12	128	6	2.16	0.27
LM73	insomnia	escitalopram	1-1.99	181	16	177	11	1.46	0.17
LM95	insomnia	sertraline	2-2.99	36	10	36	7	1.59	0.32
MC10	somnolence	paroxetine	1-1.99	186	17	184	7	2.54	0.21
MC12	somnolence	venlafaxine	2-2.99	175	26	168	10	2.76	0.15
MC13	somnolence	paroxetine	1-1.99	97	32	31	2	7.14	0.58
MC14	somnolence	venlafaxine	2-2.99	133	19	138	10	2.13	0.17

MC17	somnolence	venlafaxine	2-2.99	133	36	72	6	4.08	0.22
MC22	somnolence	duloxetine	2-2.99	156	19	52	2	3.47	0.58
MC33	somnolence	fluoxetine	1-1.99	163	15	44	3	1.39	0.43
MC38	somnolence	escitalopram	1-1.99	203	32	212	26	1.34	0.08
MC44	somnolence	venlafaxine	1-1.99	113	4	101	3	1.2	0.6
MC45	somnolence	citalopram	1-1.99	192	9	33	2	0.76	0.65
MC62	somnolence	sertraline	2-2.99	35	6	35	2	3.41	0.73
MC77	somnolence	paroxetine	1-1.99	161	27	163	11	2.78	0.14
MC79	somnolence	venlafaxine	1-1.99	158	5	52	1	1.67	1.23
MC81	somnolence	venlafaxine	2-2.99	13	4	12	0	11.84	2.41
MC82	somnolence	sertraline	2-2.99	88	12	88	9	1.39	0.22
MJ1	somnolence	venlafaxine	2-2.99	126	23	135	12	2.29	0.14
MJ2	somnolence	venlafaxine	1-1.99	86	14	32	4	1.36	0.37
MJ3	somnolence	paroxetine	1-1.99	189	38	90	6	3.52	0.21
MJ5	somnolence	fluvoxamine	3-3.99	57	6	63	1	7.29	1.2
MJ16	somnolence	sertraline	1-1.99	11	8	11	5	3.2	0.82
MJ17	somnolence	fluvoxamine	3-3.99	23	2	23	1	2.1	1.59
MJ25	somnolence	paroxetine	2-2.99	444	89	445	40	2.54	0.04
MJ36	somnolence	escitalopram	1-1.99	128	10	59	4	1.17	0.38
MJ44	somnolence	escitalopram	1-1.99	116	7	38	2	1.16	0.68
MJ54	somnolence	paroxetine	1-1.99	94	25	93	9	3.38	0.18
MJ66	somnolence	paroxetine	1-1.99	151	26	156	6	5.2	0.22
MJ70	somnolence	sertraline	2-2.99	135	15	69	3	2.75	0.42
MJ78	somnolence	paroxetine	1-1.99	165	21	157	13	1.62	0.14
MJ84	somnolence	fluvoxamine	>=4	149	33	151	11	3.62	0.14
MJ97	somnolence	sertraline	>=4	10	1	9	2	0.39	1.75
JF9	somnolence	duloxetine	2-2.99	168	7	87	1	3.74	1.16
JF10	somnolence	venlafaxine	2-2.99	129	17	66	3	3.19	0.42
JF15	somnolence	fluvoxamine	3-3.99	176	79	89	18	3.21	0.09
JF25	somnolence	paroxetine	1-1.99	139	16	151	9	2.05	0.19
JF29	somnolence	paroxetine	1-1.99	217	24	217	10	2.57	0.15
JF56	somnolence	venlafaxine	2-2.99	181	14	180	7	2.07	0.23
JF59	somnolence	sertraline	2-2.99	94	12	93	9	1.37	0.22
JF88	somnolence	escitalopram	1-1.99	158	19	157	9	2.25	0.18
JF89	somnolence	fluvoxamine	3-3.99	139	43	140	14	4.03	0.11

JF94	somnolence	escitalopram	1-1.99	198	36	98	9	2.2	0.16
LM3	somnolence	venlafaxine	2-2.99	179	21	89	12	0.85	0.15
LM6	somnolence	sertraline	2-2.99	100	17	108	12	1.64	0.16
LM34	somnolence	sertraline	2-2.99	86	12	83	7	1.76	0.25
LM48	somnolence	fluvoxamine	>=4	78	24	78	10	3.02	0.17
LM54	somnolence	duloxetine	3-3.99	162	19	80	3	3.41	0.41
LM60	somnolence	fluvoxamine	>=4	127	34	126	14	2.92	0.12
LM72	somnolence	venlafaxine	2-2.99	125	6	128	3	2.1	0.52
LM73	somnolence	escitalopram	1-1.99	181	18	177	9	2.06	0.18
MC3	diarrhea	venlafaxine	1-1.99	122	11	122	14	0.76	0.18
MC16	diarrhea	fluoxetine	3-3.99	21	4	22	3	1.49	0.69
MC22	diarrhea	duloxetine	2-2.99	156	6	52	3	0.65	0.53
MC26	diarrhea	sertraline	3-3.99	28	6	28	1	7.36	1.25
MC38	diarrhea	escitalopram	1-1.99	203	30	212	20	1.66	0.09
MC42	diarrhea	fluoxetine	1-1.99	52	3	18	1	1.04	1.41
MC44	diarrhea	venlafaxine	1-1.99	113	5	101	6	0.73	0.39
MC45	diarrhea	citalopram	1-1.99	192	21	33	1	3.93	1.08
MC62	diarrhea	sertraline	2-2.99	35	8	35	5	1.78	0.4
MC71	diarrhea	sertraline	2-2.99	80	19	88	10	2.43	0.18
MC79	diarrhea	venlafaxine	1-1.99	158	8	52	2	1.33	0.65
MC82	diarrhea	sertraline	2-2.99	88	24	88	9	3.29	0.18
MJ5	diarrhea	fluvoxamine	3-3.99	57	9	63	7	1.5	0.29
MJ6	diarrhea	sertraline	2-2.99	67	6	62	3	1.93	0.53
MJ17	diarrhea	fluvoxamine	3-3.99	23	1	23	3	0.3	1.43
MJ25	diarrhea	paroxetine	2-2.99	444	53	445	40	1.37	0.05
MJ44	diarrhea	escitalopram	1-1.99	116	5	38	2	0.81	0.74
MJ70	diarrhea	sertraline	2-2.99	135	28	69	11	1.38	0.15
MJ72	diarrhea	fluoxetine	2-2.99	33	27	31	18	3.25	0.34
JF7	diarrhea	sertraline	1-1.99	188	21	190	10	2.26	0.16
JF9	diarrhea	duloxetine	2-2.99	168	5	87	3	0.86	0.55
JF15	diarrhea	fluvoxamine	3-3.99	176	11	89	0	12.44	2.1
JF29	diarrhea	paroxetine	1-1.99	217	12	217	10	1.21	0.19
JF59	diarrhea	sertraline	2-2.99	94	22	93	18	1.27	0.13
JF61	diarrhea	sertraline	2-2.99	68	12	170	20	1.61	0.16
LM3	diarrhea	venlafaxine	2-2.99	179	47	89	12	2.28	0.13

LM6	diarrhea	sertraline	2-2.99	100	28	108	12	3.11	0.14
LM34	diarrhea	sertraline	2-2.99	86	27	83	15	2.07	0.14
LM39	diarrhea	fluoxetine	1-1.99	71	9	32	1	4.5	1.16
LM40	diarrhea	paroxetine	1-1.99	98	8	105	2	4.58	0.65
LM48	diarrhea	fluvoxamine	>=4	78	17	78	8	2.44	0.21
LM60	diarrhea	fluvoxamine	>=4	127	23	126	10	2.57	0.16
LM73	diarrhea	escitalopram	1-1.99	181	16	177	9	1.81	0.19
LM95	diarrhea	sertraline	2-2.99	36	5	36	2	2.74	0.76
MC3	nausea	venlafaxine	1-1.99	122	38	122	12	4.15	0.13
MC10	nausea	paroxetine	1-1.99	186	40	184	11	4.31	0.13
MC12	nausea	venlafaxine	2-2.99	175	37	168	17	2.38	0.1
MC13	nausea	paroxetine	1-1.99	97	30	31	2	6.49	0.58
MC14	nausea	venlafaxine	2-2.99	133	45	138	17	3.64	0.1
MC15	nausea	sertraline	3-3.99	211	35	204	13	2.92	0.12
MC16	nausea	fluoxetine	3-3.99	21	7	22	7	1.07	0.42
MC17	nausea	venlafaxine	2-2.99	133	43	72	8	3.82	0.17
MC22	nausea	duloxetine	2-2.99	156	58	52	9	2.83	0.16
MC25	nausea	venlafaxine	1-1.99	137	32	148	16	2.51	0.11
MC26	nausea	sertraline	3-3.99	28	7	28	1	9	1.23
MC28	nausea	sertraline	3-3.99	92	16	95	7	2.65	0.23
MC33	nausea	fluoxetine	1-1.99	163	21	44	4	1.48	0.33
MC38	nausea	escitalopram	1-1.99	203	51	212	22	2.9	0.08
MC40	nausea	fluoxetine	1-1.99	90	4	90	3	1.35	0.61
MC42	nausea	fluoxetine	1-1.99	52	6	18	4	0.46	0.51
MC44	nausea	venlafaxine	1-1.99	113	31	101	8	4.39	0.18
MC45	nausea	citalopram	1-1.99	192	45	33	3	3.06	0.4
MC51	nausea	fluvoxamine	3-3.99	43	27	47	15	3.6	0.2
MC62	nausea	sertraline	2-2.99	35	11	35	6	2.22	0.33
MC71	nausea	sertraline	2-2.99	80	26	88	15	2.34	0.14
MC77	nausea	paroxetine	1-1.99	161	41	163	10	5.23	0.14
MC81	nausea	venlafaxine	2-2.99	13	4	12	2	2.22	0.96
MC82	nausea	sertraline	2-2.99	88	29	88	20	1.67	0.12
MJ1	nausea	venlafaxine	2-2.99	126	33	135	8	5.63	0.17
MJ2	nausea	venlafaxine	1-1.99	86	37	32	4	5.29	0.33
MJ3	nausea	paroxetine	1-1.99	189	36	90	6	3.29	0.21

MJ4	nausea	fluoxetine	1-1.99	7	2	7	1	2.4	1.87
MJ5	nausea	fluvoxamine	3-3.99	57	10	63	13	0.82	0.22
MJ6	nausea	sertraline	2-2.99	67	9	62	6	1.45	0.31
MJ14	nausea	duloxetine	3-3.99	168	62	159	16	5.23	0.1
MJ16	nausea	sertraline	1-1.99	11	1	11	6	0.08	1.47
MJ17	nausea	fluvoxamine	3-3.99	23	9	23	6	1.82	0.41
MJ25	nausea	paroxetine	2-2.99	444	102	445	76	1.45	0.03
MJ36	nausea	escitalopram	1-1.99	128	17	59	8	0.98	0.21
MJ44	nausea	escitalopram	1-1.99	116	23	38	5	1.63	0.28
MJ54	nausea	paroxetine	1-1.99	94	24	93	11	2.56	0.16
MJ64	nausea	citalopram	1-1.99	25	7	5	2	0.58	1.03
MJ66	nausea	paroxetine	1-1.99	151	29	156	13	2.61	0.13
MJ70	nausea	sertraline	2-2.99	135	44	69	10	2.85	0.15
MJ84	nausea	fluvoxamine	>=4	149	70	151	23	4.93	0.08
MJ93	nausea	sertraline	2-2.99	23	8	19	4	2	0.51
MJ94	nausea	paroxetine	1-1.99	201	44	99	13	1.85	0.12
MJ97	nausea	sertraline	>=4	10	0	9	3	0.09	2.53
JF7	nausea	sertraline	1-1.99	188	53	190	25	2.59	0.07
JF9	nausea	duloxetine	2-2.99	168	72	87	7	8.57	0.18
JF10	nausea	venlafaxine	2-2.99	129	40	66	6	4.49	0.22
JF25	nausea	paroxetine	1-1.99	139	39	151	12	4.52	0.13
JF29	nausea	paroxetine	1-1.99	217	44	217	16	3.2	0.1
JF59	nausea	sertraline	2-2.99	94	15	93	11	1.42	0.18
JF61	nausea	sertraline	2-2.99	68	15	170	24	1.72	0.13
JF87	nausea	venlafaxine	1-1.99	87	29	49	6	3.58	0.24
JF88	nausea	escitalopram	1-1.99	158	30	157	14	2.39	0.12
JF89	nausea	fluvoxamine	3-3.99	139	43	140	8	7.39	0.17
JF94	nausea	escitalopram	1-1.99	198	29	98	6	2.63	0.22
LM3	nausea	venlafaxine	2-2.99	179	43	89	12	2.03	0.13
LM4	nausea	venlafaxine	2-2.99	161	35	168	19	2.18	0.1
LM6	nausea	sertraline	2-2.99	100	23	108	12	2.39	0.15
LM34	nausea	sertraline	2-2.99	86	18	83	8	2.48	0.21
LM39	nausea	fluoxetine	1-1.99	71	9	32	4	1.02	0.41
LM48	nausea	fluvoxamine	>=4	78	21	78	8	3.22	0.2
LM54	nausea	duloxetine	3-3.99	162	51	80	11	2.88	0.13

LM60	nausea	fluvoxamine	>=4	127	43	126	16	3.52	0.11
LM72	nausea	venlafaxine	2-2.99	125	32	128	11	3.66	0.14
LM73	nausea	escitalopram	1-1.99	181	40	177	21	2.11	0.09
LM95	nausea	sertraline	2-2.99	36	12	36	8	1.75	0.29
MC22	dyspepsia	duloxetine	2-2.99	156	3	52	1	1	1.36
MC26	dyspepsia	sertraline	3-3.99	28	8	28	2	5.2	0.71
MJ5	dyspepsia	fluvoxamine	3-3.99	57	8	63	4	2.41	0.41
MJ70	dyspepsia	sertraline	2-2.99	135	34	69	5	4.31	0.25
MJ78	dyspepsia	paroxetine	1-1.99	165	12	157	6	1.97	0.26
JF7	dyspepsia	sertraline	1-1.99	188	17	190	11	1.62	0.16
JF15	dyspepsia	fluvoxamine	3-3.99	176	11	89	0	12.44	2.1
MC10	loss of libido	paroxetine	1-1.99	186	15	184	2	7.98	0.58
MC13	loss of libido	paroxetine	1-1.99	97	16	31	1	5.93	1.11
MC17	loss of libido	venlafaxine	2-2.99	133	14	72	3	2.71	0.43
MC62	loss of libido	sertraline	2-2.99	35	5	35	2	2.75	0.76
MC77	loss of libido	paroxetine	1-1.99	161	19	163	4	5.32	0.32
MJ3	loss of libido	paroxetine	1-1.99	189	24	90	2	6.4	0.56
MJ14	loss of libido	duloxetine	3-3.99	168	9	159	4	2.19	0.37
MJ44	loss of libido	escitalopram	1-1.99	116	3	38	0	2.37	2.32
MJ54	loss of libido	paroxetine	1-1.99	94	6	93	0	13.73	2.18
MJ84	loss of libido	fluvoxamine	>=4	149	10	151	6	1.74	0.28
JF7	loss of libido	sertraline	1-1.99	188	25	190	6	4.7	0.22
JF9	loss of libido	duloxetine	2-2.99	168	11	87	1	6.03	1.11
JF10	loss of libido	venlafaxine	2-2.99	129	10	66	1	5.46	1.12
JF56	loss of libido	venlafaxine	2-2.99	181	16	180	4	4.27	0.32
JF61	loss of libido	sertraline	2-2.99	68	12	170	4	8.89	0.36
JF88	loss of libido	escitalopram	1-1.99	158	11	157	5	2.27	0.3
JF89	loss of libido	fluvoxamine	3-3.99	139	14	140	8	1.85	0.21
LM4	loss of libido	venlafaxine	2-2.99	161	8	168	6	1.41	0.3
LM54	loss of libido	duloxetine	3-3.99	162	11	80	0	12.22	2.11
LM60	loss of libido	fluvoxamine	>=4	127	9	126	4	2.33	0.38
LM73	loss of libido	escitalopram	1-1.99	181	11	177	2	5.66	0.6
MC12	ejaculation dysfunction	venlafaxine	2-2.99	175	10	168	3	3.33	0.45
MC13	ejaculation dysfunction	paroxetine	1-1.99	97	27	31	1	11.57	1.08
MC45	ejaculation dysfunction	citalopram	1-1.99	192	12	33	0	4.64	2.12

MC77	ejaculation dysfunction	paroxetine	1-1.99	161	56	163	6	13.96	0.2
MC82	ejaculation dysfunction	sertraline	2-2.99	88	13	88	3	4.91	0.44
MJ2	ejaculation dysfunction	venlafaxine	1-1.99	86	15	32	0	14.09	2.11
MJ3	ejaculation dysfunction	paroxetine	1-1.99	189	33	90	2	9.31	0.55
MJ25	ejaculation dysfunction	paroxetine	2-2.99	444	120	445	13	12.31	0.09
MJ44	ejaculation dysfunction	escitalopram	1-1.99	116	5	38	0	3.8	2.22
MJ53	ejaculation dysfunction	fluvoxamine	>=4	48	5	44	2	2.44	0.75
MJ66	ejaculation dysfunction	paroxetine	1-1.99	151	18	156	6	3.38	0.24
MJ84	ejaculation dysfunction	fluvoxamine	>=4	149	13	151	6	2.31	0.26
JF10	ejaculation dysfunction	venlafaxine	2-2.99	129	15	66	1	8.55	1.09
JF25	ejaculation dysfunction	paroxetine	1-1.99	139	20	151	2	12.52	0.57
JF88	ejaculation dysfunction	escitalopram	1-1.99	158	11	157	5	2.27	0.3
JF94	ejaculation dysfunction	escitalopram	1-1.99	198	11	98	0	12.08	2.1
MC12	Erectile dysfunction	venlafaxine	2-2.99	175	14	168	5	2.83	0.28
MC13	Erectile dysfunction	paroxetine	1-1.99	97	4	31	1	1.29	1.29
MC16	Erectile dysfunction	fluoxetine	3-3.99	21	0	22	0	1.05	4.09
MJ1	Erectile dysfunction	venlafaxine	2-2.99	126	10	135	1	11.55	1.12
MJ25	Erectile dysfunction	paroxetine	2-2.99	444	44	445	4	12.13	0.28
MJ44	Erectile dysfunction	escitalopram	1-1.99	116	3	38	1	0.98	1.37
MJ84	Erectile dysfunction	fluvoxamine	>=4	149	1	151	6	0.16	1.18
JF10	Erectile dysfunction	venlafaxine	2-2.99	129	8	66	1	4.3	1.15
JF61	Erectile dysfunction	sertraline	2-2.99	68	1	170	0	7.58	2.69
JF89	Erectile dysfunction	fluvoxamine	3-3.99	139	1	140	1	1.01	2.01
LM60	Erectile dysfunction	fluvoxamine	>=4	127	3	126	3	0.99	0.68
MC3	suicidal ideation	venlafaxine	1-1.99	122	0	122	0	1	4.02
MC10	suicidal ideation	paroxetine	1-1.99	186	0	184	0	0.99	4.01
MC12	suicidal ideation	venlafaxine	2-2.99	175	1	168	0	2.9	2.68
MC13	suicidal ideation	paroxetine	1-1.99	97	0	31	0	0.32	4.04
MC14	suicidal ideation	venlafaxine	2-2.99	133	0	138	0	1.04	4.01
MC15	suicidal ideation	sertraline	3-3.99	211	0	204	0	0.97	4.01
MC16	suicidal ideation	fluoxetine	3-3.99	21	0	22	0	1.05	4.09
MC17	suicidal ideation	venlafaxine	2-2.99	133	0	72	0	0.54	4.02
MC25	suicidal ideation	venlafaxine	1-1.99	137	3	148	0	7.73	2.3
MC26	suicidal ideation	sertraline	3-3.99	28	0	28	0	1	4.07
MC28	suicidal ideation	sertraline	3-3.99	92	0	95	0	1.03	4.02

MC32	suicidal ideation	paroxetine	2-2.99	25	0	27	0	1.08	4.08
MC33	suicidal ideation	fluoxetine	1-1.99	163	1	44	0	0.82	2.7
MC38	suicidal ideation	escitalopram	1-1.99	203	0	212	0	1.04	4.01
MC40	suicidal ideation	fluoxetine	1-1.99	90	0	90	0	1	4.02
MC42	suicidal ideation	fluoxetine	1-1.99	52	0	18	0	0.35	4.07
MC44	suicidal ideation	venlafaxine	1-1.99	113	0	101	0	0.89	4.02
MC45	suicidal ideation	citalopram	1-1.99	192	0	33	0	0.17	4.04
MC51	suicidal ideation	fluvoxamine	3-3.99	43	0	47	0	1.09	4.04
MC62	suicidal ideation	sertraline	2-2.99	35	0	35	0	1	4.06
MC71	suicidal ideation	sertraline	2-2.99	80	0	88	0	1.1	4.02
MC73	suicidal ideation	venlafaxine	1-1.99	156	0	52	0	0.34	4.03
MC77	suicidal ideation	paroxetine	1-1.99	161	0	163	0	1.01	4.01
MC79	suicidal ideation	venlafaxine	1-1.99	158	0	52	0	0.33	4.03
MC81	suicidal ideation	venlafaxine	2-2.99	13	0	12	0	0.93	4.15
MC82	suicidal ideation	sertraline	2-2.99	88	0	88	0	1	4.02
MJ1	suicidal ideation	venlafaxine	2-2.99	126	0	135	0	1.07	4.02
MJ2	suicidal ideation	venlafaxine	1-1.99	86	0	32	0	0.38	4.04
MJ3	suicidal ideation	paroxetine	1-1.99	189	0	90	0	0.48	4.02
MJ4	suicidal ideation	fluoxetine	1-1.99	7	1	7	0	3.46	2.95
MJ5	suicidal ideation	fluvoxamine	3-3.99	57	0	63	0	1.1	4.03
MJ6	suicidal ideation	sertraline	2-2.99	67	7	62	5	1.33	0.38
MJ14	suicidal ideation	duloxetine	3-3.99	168	0	159	0	0.95	4.01
MJ16	suicidal ideation	sertraline	1-1.99	11	0	11	0	1	4.17
MJ17	suicidal ideation	fluvoxamine	3-3.99	23	0	23	0	1	4.09
MJ25	suicidal ideation	paroxetine	2-2.99	444	0	445	0	1	4
MJ36	suicidal ideation	escitalopram	1-1.99	128	0	59	0	0.46	4.02
MJ44	suicidal ideation	escitalopram	1-1.99	116	0	38	0	0.33	4.03
MJ53	suicidal ideation	fluvoxamine	>=4	48	0	44	0	0.92	4.04
MJ54	suicidal ideation	paroxetine	1-1.99	94	0	93	0	0.99	4.02
MJ56	suicidal ideation	duloxetine	1-1.99	135	8	137	7	1.17	0.28
MJ64	suicidal ideation	citalopram	1-1.99	25	0	5	0	0.22	4.22
MJ66	suicidal ideation	paroxetine	1-1.99	151	0	156	0	1.03	4.01
MJ70	suicidal ideation	sertraline	2-2.99	135	0	69	0	0.51	4.02
MJ72	suicidal ideation	fluoxetine	2-2.99	33	0	31	0	0.94	4.06
MJ78	suicidal ideation	paroxetine	1-1.99	165	4	157	0	8.78	2.23

MJ84	suicidal ideation	fluvoxamine	>=4	149	0	151	0	1.01	4.01
MJ93	suicidal ideation	sertraline	2-2.99	23	0	19	0	0.83	4.09
MJ94	suicidal ideation	paroxetine	1-1.99	201	0	99	0	0.49	4.02
MJ97	suicidal ideation	sertraline	>=4	10	0	9	0	0.9	4.2
JF7	suicidal ideation	sertraline	1-1.99	188	0	190	0	1.01	4.01
JF9	suicidal ideation	duloxetine	2-2.99	168	0	87	0	0.52	4.02
JF10	suicidal ideation	venlafaxine	2-2.99	129	1	66	0	1.55	2.69
JF15	suicidal ideation	fluvoxamine	3-3.99	176	0	89	0	0.51	4.02
JF25	suicidal ideation	paroxetine	1-1.99	139	0	151	0	1.09	4.01
JF29	suicidal ideation	paroxetine	1-1.99	217	0	217	0	1	4.01
JF56	suicidal ideation	venlafaxine	2-2.99	181	0	180	0	0.99	4.01
JF59	suicidal ideation	sertraline	2-2.99	94	0	93	0	0.99	4.02
JF61	suicidal ideation	sertraline	2-2.99	68	0	170	0	2.49	4.02
JF87	suicidal ideation	venlafaxine	1-1.99	87	0	49	0	0.57	4.03
JF88	suicidal ideation	escitalopram	1-1.99	158	0	157	0	0.99	4.01
JF89	suicidal ideation	fluvoxamine	3-3.99	139	0	140	0	1.01	4.01
JF94	suicidal ideation	escitalopram	1-1.99	198	3	98	0	3.53	2.3
LM3	suicidal ideation	venlafaxine	2-2.99	179	0	89	0	0.5	4.02
LM4	suicidal ideation	venlafaxine	2-2.99	161	0	168	0	1.04	4.01
LM6	suicidal ideation	sertraline	2-2.99	100	0	108	0	1.08	4.02
LM34	suicidal ideation	sertraline	2-2.99	86	0	83	0	0.97	4.02
LM39	suicidal ideation	fluoxetine	1-1.99	71	0	32	0	0.45	4.04
LM40	suicidal ideation	paroxetine	1-1.99	98	1	105	0	3.25	2.69
LM48	suicidal ideation	fluvoxamine	>=4	78	0	78	0	1	4.03
LM54	suicidal ideation	duloxetine	3-3.99	162	0	80	0	0.5	4.02
LM60	suicidal ideation	fluvoxamine	>=4	127	0	126	0	0.99	4.02
LM67	suicidal ideation	fluvoxamine	>=4	18	0	20	0	1.11	4.1
LM72	suicidal ideation	venlafaxine	2-2.99	125	0	128	0	1.02	4.02
LM73	suicidal ideation	escitalopram	1-1.99	181	0	177	0	0.98	4.01
LM95	suicidal ideation	sertraline	2-2.99	36	0	36	0	1	4.05
MC3	suicide attempt	venlafaxine	1-1.99	122	0	122	0	1	4.02
MC10	suicide attempt	paroxetine	1-1.99	186	0	184	0	0.99	4.01
MC12	suicide attempt	venlafaxine	2-2.99	175	1	168	0	2.9	2.68
MC13	suicide attempt	paroxetine	1-1.99	97	0	31	0	0.32	4.04
MC14	suicide attempt	venlafaxine	2-2.99	133	0	138	0	1.04	4.01

MC15	suicide attempt	sertraline	3-3.99	211	0	204	0	0.97	4.01
MC16	suicide attempt	fluoxetine	3-3.99	21	0	22	0	1.05	4.09
MC17	suicide attempt	venlafaxine	2-2.99	133	0	72	0	0.54	4.02
MC22	suicide attempt	duloxetine	2-2.99	156	0	52	0	0.34	4.03
MC25	suicide attempt	venlafaxine	1-1.99	137	0	148	0	1.08	4.01
MC26	suicide attempt	sertraline	3-3.99	28	0	28	0	1	4.07
MC28	suicide attempt	sertraline	3-3.99	92	0	95	0	1.03	4.02
MC32	suicide attempt	paroxetine	2-2.99	25	0	27	0	1.08	4.08
MC33	suicide attempt	fluoxetine	1-1.99	163	0	44	0	0.27	4.03
MC38	suicide attempt	escitalopram	1-1.99	203	0	212	0	1.04	4.01
MC40	suicide attempt	fluoxetine	1-1.99	90	0	90	0	1	4.02
MC42	suicide attempt	fluoxetine	1-1.99	52	0	18	0	0.35	4.07
MC44	suicide attempt	venlafaxine	1-1.99	113	0	101	0	0.89	4.02
MC45	suicide attempt	citalopram	1-1.99	192	0	33	0	0.17	4.04
MC51	suicide attempt	fluvoxamine	3-3.99	43	0	47	0	1.09	4.04
MC62	suicide attempt	sertraline	2-2.99	35	0	35	0	1	4.06
MC71	suicide attempt	sertraline	2-2.99	80	0	88	0	1.1	4.02
MC73	suicide attempt	venlafaxine	1-1.99	156	0	52	0	0.34	4.03
MC77	suicide attempt	paroxetine	1-1.99	161	0	163	0	1.01	4.01
MC79	suicide attempt	venlafaxine	1-1.99	158	0	52	0	0.33	4.03
MC81	suicide attempt	venlafaxine	2-2.99	13	0	12	0	0.93	4.15
MC82	suicide attempt	sertraline	2-2.99	88	0	88	0	1	4.02
MJ1	suicide attempt	venlafaxine	2-2.99	126	0	135	0	1.07	4.02
MJ2	suicide attempt	venlafaxine	1-1.99	86	0	32	0	0.38	4.04
MJ3	suicide attempt	paroxetine	1-1.99	189	0	90	0	0.48	4.02
MJ4	suicide attempt	fluoxetine	1-1.99	7	0	7	0	1	4.27
MJ5	suicide attempt	fluvoxamine	3-3.99	57	0	63	0	1.1	4.03
MJ6	suicide attempt	sertraline	2-2.99	67	0	62	0	0.93	4.03
MJ14	suicide attempt	duloxetine	3-3.99	168	0	159	0	0.95	4.01
MJ16	suicide attempt	sertraline	1-1.99	11	0	11	0	1	4.17
MJ17	suicide attempt	fluvoxamine	3-3.99	23	0	23	0	1	4.09
MJ25	suicide attempt	paroxetine	2-2.99	444	0	445	0	1	4
MJ36	suicide attempt	escitalopram	1-1.99	128	0	59	0	0.46	4.02
MJ44	suicide attempt	escitalopram	1-1.99	116	0	38	0	0.33	4.03
MJ53	suicide attempt	fluvoxamine	>=4	48	0	44	0	0.92	4.04

MJ54	suicide attempt	paroxetine	1-1.99	94	0	93	0	0.99	4.02
MJ56	suicide attempt	duloxetine	1-1.99	135	0	137	0	1.01	4.01
MJ64	suicide attempt	citalopram	1-1.99	25	0	5	0	0.22	4.22
MJ66	suicide attempt	paroxetine	1-1.99	151	0	156	0	1.03	4.01
MJ70	suicide attempt	sertraline	2-2.99	135	0	69	0	0.51	4.02
MJ72	suicide attempt	fluoxetine	2-2.99	33	0	31	0	0.94	4.06
MJ78	suicide attempt	paroxetine	1-1.99	165	0	157	0	0.95	4.01
MJ84	suicide attempt	fluvoxamine	>=4	149	0	151	0	1.01	4.01
MJ93	suicide attempt	sertraline	2-2.99	23	0	19	0	0.83	4.09
MJ94	suicide attempt	paroxetine	1-1.99	201	0	99	0	0.49	4.02
MJ97	suicide attempt	sertraline	>=4	10	0	9	0	0.9	4.2
JF10	suicide attempt	venlafaxine	2-2.99	129	1	66	0	1.55	2.69
JF25	suicide attempt	paroxetine	1-1.99	139	0	151	0	1.09	4.01
JF94	suicide attempt	escitalopram	1-1.99	198	0	98	0	0.5	4.02
LM40	suicide attempt	paroxetine	1-1.99	98	0	105	0	1.07	4.02
MC3	death by suicide	venlafaxine	1-1.99	122	0	122	0	1	4.02
MC10	death by suicide	paroxetine	1-1.99	186	0	184	0	0.99	4.01
MC12	death by suicide	venlafaxine	2-2.99	175	0	168	0	0.96	4.01
MC13	death by suicide	paroxetine	1-1.99	97	0	31	0	0.32	4.04
MC14	death by suicide	venlafaxine	2-2.99	133	0	138	0	1.04	4.01
MC15	death by suicide	sertraline	3-3.99	211	0	204	0	0.97	4.01
MC16	death by suicide	fluoxetine	3-3.99	21	0	22	0	1.05	4.09
MC17	death by suicide	venlafaxine	2-2.99	133	0	72	0	0.54	4.02
MC22	death by suicide	duloxetine	2-2.99	156	0	52	0	0.34	4.03
MC25	death by suicide	venlafaxine	1-1.99	137	0	148	0	1.08	4.01
MC26	death by suicide	sertraline	3-3.99	28	0	28	0	1	4.07
MC28	death by suicide	sertraline	3-3.99	92	0	95	0	1.03	4.02
MC32	death by suicide	paroxetine	2-2.99	25	0	27	0	1.08	4.08
MC33	death by suicide	fluoxetine	1-1.99	163	0	44	0	0.27	4.03
MC38	death by suicide	escitalopram	1-1.99	203	0	212	0	1.04	4.01
MC40	death by suicide	fluoxetine	1-1.99	90	0	90	0	1	4.02
MC42	death by suicide	fluoxetine	1-1.99	52	0	18	0	0.35	4.07
MC44	death by suicide	venlafaxine	1-1.99	113	0	101	0	0.89	4.02
MC45	death by suicide	citalopram	1-1.99	192	0	33	0	0.17	4.04
MC51	death by suicide	fluvoxamine	3-3.99	43	0	47	0	1.09	4.04

MC62	death by suicide	sertraline	2-2.99	35	0	35	0	1	4.06
MC71	death by suicide	sertraline	2-2.99	80	0	88	0	1.1	4.02
MC73	death by suicide	venlafaxine	1-1.99	156	0	52	0	0.34	4.03
MC77	death by suicide	paroxetine	1-1.99	161	0	163	0	1.01	4.01
MC79	death by suicide	venlafaxine	1-1.99	158	0	52	0	0.33	4.03
MC81	death by suicide	venlafaxine	2-2.99	13	0	12	0	0.93	4.15
MC82	death by suicide	sertraline	2-2.99	88	0	88	0	1	4.02
MJ1	death by suicide	venlafaxine	2-2.99	126	0	135	0	1.07	4.02
MJ2	death by suicide	venlafaxine	1-1.99	86	0	32	0	0.38	4.04
MJ3	death by suicide	paroxetine	1-1.99	189	0	90	0	0.48	4.02
MJ4	death by suicide	fluoxetine	1-1.99	7	0	7	0	1	4.27
MJ5	death by suicide	fluvoxamine	3-3.99	57	0	63	0	1.1	4.03
MJ6	death by suicide	sertraline	2-2.99	67	0	62	0	0.93	4.03
MJ16	death by suicide	sertraline	1-1.99	11	0	11	0	1	4.17
MJ17	death by suicide	fluvoxamine	3-3.99	23	0	23	0	1	4.09
MJ25	death by suicide	paroxetine	2-2.99	444	0	445	0	1	4
MJ36	death by suicide	escitalopram	1-1.99	128	0	59	0	0.46	4.02
MJ44	death by suicide	escitalopram	1-1.99	116	0	38	0	0.33	4.03
MJ53	death by suicide	fluvoxamine	>=4	48	0	44	0	0.92	4.04
MJ54	death by suicide	paroxetine	1-1.99	94	0	93	0	0.99	4.02
MJ56	death by suicide	duloxetine	1-1.99	135	0	137	0	1.01	4.01
MJ64	death by suicide	citalopram	1-1.99	25	0	5	0	0.22	4.22
MJ66	death by suicide	paroxetine	1-1.99	151	0	156	0	1.03	4.01
MJ70	death by suicide	sertraline	2-2.99	135	0	69	0	0.51	4.02
MJ72	death by suicide	fluoxetine	2-2.99	33	0	31	0	0.94	4.06
MJ78	death by suicide	paroxetine	1-1.99	165	0	157	0	0.95	4.01
MJ84	death by suicide	fluvoxamine	>=4	149	0	151	0	1.01	4.01
MJ93	death by suicide	sertraline	2-2.99	23	0	19	0	0.83	4.09
MJ94	death by suicide	paroxetine	1-1.99	201	0	99	0	0.49	4.02
MJ97	death by suicide	sertraline	>=4	10	0	9	0	0.9	4.2
JF7	death by suicide	sertraline	1-1.99	188	0	190	0	1.01	4.01
JF9	death by suicide	duloxetine	2-2.99	168	0	87	0	0.52	4.02
JF10	death by suicide	venlafaxine	2-2.99	129	0	66	0	0.51	4.02
JF15	death by suicide	fluvoxamine	3-3.99	176	0	89	0	0.51	4.02
JF25	death by suicide	paroxetine	1-1.99	139	1	151	0	3.28	2.68

JF29	death by suicide	paroxetine	1-1.99	217	0	217	0	1	4.01
JF56	death by suicide	venlafaxine	2-2.99	181	0	180	0	0.99	4.01
JF59	death by suicide	sertraline	2-2.99	94	0	93	0	0.99	4.02
JF61	death by suicide	sertraline	2-2.99	68	0	170	0	2.49	4.02
JF87	death by suicide	venlafaxine	1-1.99	87	0	49	0	0.57	4.03
JF88	death by suicide	escitalopram	1-1.99	158	0	157	0	0.99	4.01
JF89	death by suicide	fluvoxamine	3-3.99	139	0	140	0	1.01	4.01
JF94	death by suicide	escitalopram	1-1.99	198	0	98	0	0.5	4.02
LM3	death by suicide	venlafaxine	2-2.99	179	0	89	0	0.5	4.02
LM4	death by suicide	venlafaxine	2-2.99	161	0	168	0	1.04	4.01
LM6	death by suicide	sertraline	2-2.99	100	0	108	0	1.08	4.02
LM34	death by suicide	sertraline	2-2.99	86	0	83	0	0.97	4.02
LM39	death by suicide	fluoxetine	1-1.99	71	0	32	0	0.45	4.04
LM40	death by suicide	paroxetine	1-1.99	98	0	105	0	1.07	4.02
LM48	death by suicide	fluvoxamine	>=4	78	0	78	0	1	4.03
LM54	death by suicide	duloxetine	3-3.99	162	0	80	0	0.5	4.02
LM60	death by suicide	fluvoxamine	>=4	127	0	126	0	0.99	4.02
LM67	death by suicide	fluvoxamine	>=4	18	0	20	0	1.11	4.1
LM72	death by suicide	venlafaxine	2-2.99	125	0	128	0	1.02	4.02
LM73	death by suicide	escitalopram	1-1.99	181	0	177	0	0.98	4.01
LM95	death by suicide	sertraline	2-2.99	36	0	36	0	1	4.05
MC13	any adverse event	paroxetine	2-2.99	95	86	32	27	1.77	0.36
MC17	any adverse event	paroxetine	2-2.99	136	124	72	62	1.67	0.21
MC33	any adverse event	fluoxetine	2-2.99	160	124	44	29	1.78	0.14
MC45	any adverse event	citalopram	2-2.99	98	67	34	20	1.51	0.17
MC73	any adverse event	venlafaxine	3-3.99	160	141	53	42	1.94	0.17
MC79	any adverse event	venlafaxine	2-2.99	159	113	52	35	1.19	0.12
MJ3	any adverse event	paroxetine	2-2.99	197	169	90	67	2.07	0.1
MJ44	any adverse event	escitalopram	2-2.99	116	87	39	25	1.68	0.16
JF55	any adverse event	venlafaxine	1-1.99	130	90	44	25	1.71	0.13
JF94	any adverse event	escitalopram	2-2.99	194	127	98	55	1.48	0.06
LM54	any adverse event	venlafaxine	2-2.99	164	140	81	59	2.18	0.11
MJ64	sexual adverse event	sertraline	2-2.99	23	1	5	0	0.73	2.89
JF10	weight change	paroxetine	2-2.99	128	1	66	0	1.56	2.69
MC13	dry mouth	paroxetine	2-2.99	95	10	32	2	1.76	0.65

MC17	dry mouth	paroxetine	2-2.99	136	22	72	3	4.44	0.4
MC45	dry mouth	citalopram	2-2.99	98	10	34	1	3.75	1.14
MC55	dry mouth	duloxetine	3-3.99	158	21	57	2	4.22	0.57
MC79	dry mouth	venlafaxine	2-2.99	159	16	52	2	2.8	0.59
MJ2	dry mouth	venlafaxine	2-2.99	81	20	32	2	4.92	0.6
MJ3	dry mouth	paroxetine	2-2.99	197	26	90	6	2.13	0.22
MJ36	dry mouth	citalopram	1-1.99	119	17	60	2	4.83	0.59
MJ42	dry mouth	venlafaxine	2-2.99	130	25	67	4	3.75	0.32
MJ44	dry mouth	escitalopram	2-2.99	116	6	39	1	2.07	1.2
JF9	dry mouth	duloxetine	>=4	170	33	88	4	5.06	0.3
JF22	dry mouth	escitalopram	2-2.99	133	9	47	1	3.34	1.14
JF28	dry mouth	paroxetine	1-1.99	70	8	23	3	0.86	0.52
JF55	dry mouth	venlafaxine	1-1.99	130	17	44	2	3.16	0.59
JF87	dry mouth	venlafaxine	2-2.99	87	22	49	2	7.95	0.58
LM3	dry mouth	sertraline	3-3.99	173	26	90	14	0.96	0.13
LM54	dry mouth	venlafaxine	2-2.99	164	29	81	5	3.27	0.26
MC13	sweating	paroxetine	2-2.99	95	12	32	0	9.73	2.12
MC17	sweating	paroxetine	2-2.99	136	10	72	2	2.78	0.62
MC45	sweating	citalopram	2-2.99	98	12	34	1	4.6	1.13
MC55	sweating	duloxetine	3-3.99	158	13	57	1	5.02	1.1
MC79	sweating	venlafaxine	2-2.99	159	21	52	2	3.8	0.57
MJ3	sweating	paroxetine	2-2.99	197	12	90	1	5.77	1.1
MJ42	sweating	venlafaxine	2-2.99	130	16	67	1	9.26	1.09
MJ44	sweating	escitalopram	2-2.99	116	6	39	1	2.07	1.2
MJ64	sweating	sertraline	2-2.99	23	5	5	0	3.27	2.42
JF9	sweating	duloxetine	>=4	170	27	88	5	3.13	0.26
JF10	sweating	paroxetine	2-2.99	128	28	66	5	3.42	0.26
JF22	sweating	escitalopram	2-2.99	133	12	47	1	4.56	1.11
JF55	sweating	venlafaxine	1-1.99	130	14	44	2	2.53	0.6
MC33	headache	fluoxetine	2-2.99	160	30	44	7	1.22	0.21
MC42	headache	fluoxetine	2-2.99	52	9	19	4	0.78	0.45
MC45	headache	citalopram	2-2.99	98	15	34	5	1.05	0.31
MJ36	headache	citalopram	1-1.99	119	29	60	9	1.83	0.18
MJ44	headache	escitalopram	2-2.99	116	25	39	7	1.26	0.23
JF22	headache	escitalopram	2-2.99	133	21	47	8	0.91	0.21

JF28	headache	paroxetine	1-1.99	70	27	23	10	0.82	0.24
JF55	headache	venlafaxine	1-1.99	130	3	44	1	1.02	1.36
JF94	headache	escitalopram	2-2.99	194	9	98	8	0.55	0.25
LM3	headache	sertraline	3-3.99	173	50	90	26	1	0.08
MC13	dizziness	paroxetine	2-2.99	95	23	32	2	4.79	0.59
MC45	dizziness	citalopram	2-2.99	98	11	34	2	2.02	0.63
MJ2	dizziness	venlafaxine	2-2.99	81	18	32	4	2	0.36
MJ36	dizziness	citalopram	1-1.99	119	6	60	6	0.48	0.36
MJ42	dizziness	venlafaxine	2-2.99	130	25	67	8	1.76	0.19
MJ44	dizziness	escitalopram	2-2.99	116	9	39	2	1.56	0.65
MJ64	dizziness	sertraline	2-2.99	23	5	5	1	1.11	1.51
JF9	dizziness	duloxetine	>=4	170	33	88	7	2.79	0.19
JF10	dizziness	paroxetine	2-2.99	128	17	66	3	3.22	0.42
JF22	dizziness	escitalopram	2-2.99	133	12	47	3	1.45	0.45
JF28	dizziness	paroxetine	1-1.99	70	9	23	4	0.7	0.43
JF55	dizziness	venlafaxine	1-1.99	130	29	44	6	1.82	0.24
JF87	dizziness	venlafaxine	2-2.99	87	18	49	6	1.87	0.26
LM3	dizziness	sertraline	3-3.99	173	17	90	7	1.29	0.22
MC13	constipation	paroxetine	2-2.99	95	8	32	1	2.85	1.17
MC17	constipation	paroxetine	2-2.99	136	10	72	3	1.83	0.46
MC55	constipation	duloxetine	3-3.99	158	17	57	2	3.32	0.58
MC79	constipation	venlafaxine	2-2.99	159	10	52	1	3.42	1.13
MJ3	constipation	paroxetine	2-2.99	197	28	90	3	4.8	0.39
MJ42	constipation	venlafaxine	2-2.99	130	12	67	1	6.71	1.11
MJ44	constipation	escitalopram	2-2.99	116	4	39	1	1.36	1.29
JF9	constipation	duloxetine	>=4	170	15	88	2	4.16	0.58
JF28	constipation	paroxetine	1-1.99	70	3	23	2	0.47	0.9
JF55	constipation	venlafaxine	1-1.99	130	17	44	2	3.16	0.59
LM3	constipation	sertraline	3-3.99	173	12	90	9	0.67	0.21
LM54	constipation	venlafaxine	2-2.99	164	22	81	3	4.03	0.4
MC13	tremor	paroxetine	2-2.99	95	13	32	0	10.64	2.12
MC55	tremor	duloxetine	3-3.99	158	8	57	1	2.99	1.15
MC79	tremor	venlafaxine	2-2.99	159	11	52	1	3.79	1.12
MJ42	tremor	venlafaxine	2-2.99	130	9	67	1	4.91	1.13
MJ44	tremor	escitalopram	2-2.99	116	2	39	1	0.67	1.54

JF10	tremor	paroxetine	2-2.99	128	10	66	1	5.51	1.12
JF28	tremor	paroxetine	1-1.99	70	6	23	1	2.06	1.23
MC13	asthenia	paroxetine	2-2.99	95	31	32	3	4.68	0.42
MC17	asthenia	paroxetine	2-2.99	136	33	72	7	2.98	0.2
MC45	asthenia	citalopram	2-2.99	98	17	34	1	6.93	1.1
MC55	asthenia	duloxetine	3-3.99	158	14	57	1	5.44	1.1
MJ2	asthenia	venlafaxine	2-2.99	81	11	32	3	1.52	0.47
MJ3	asthenia	paroxetine	2-2.99	197	38	90	4	5.14	0.29
MJ36	asthenia	citalopram	1-1.99	119	10	60	5	1.01	0.33
MJ42	asthenia	venlafaxine	2-2.99	130	25	67	7	2.04	0.21
MJ44	asthenia	escitalopram	2-2.99	116	20	39	2	3.85	0.59
MJ64	asthenia	sertraline	2-2.99	23	8	5	2	0.8	1.02
JF9	asthenia	duloxetine	>=4	170	26	88	2	7.76	0.56
JF10	asthenia	paroxetine	2-2.99	128	24	66	5	2.82	0.27
JF22	asthenia	escitalopram	2-2.99	133	22	47	1	9.12	1.08
JF28	asthenia	paroxetine	1-1.99	70	9	23	1	3.25	1.17
JF87	asthenia	venlafaxine	2-2.99	87	19	49	5	2.46	0.29
LM54	asthenia	venlafaxine	2-2.99	164	12	81	3	2.05	0.44
MJ42	agitation	venlafaxine	2-2.99	130	18	67	4	2.53	0.33
JF22	agitation	escitalopram	2-2.99	133	4	47	1	1.43	1.28
JF28	agitation	paroxetine	1-1.99	70	8	23	4	0.61	0.44
MC13	insomnia	paroxetine	2-2.99	95	22	32	5	1.63	0.3
MC17	insomnia	paroxetine	2-2.99	136	25	72	6	2.48	0.23
MC42	insomnia	fluoxetine	2-2.99	52	9	19	4	0.78	0.45
MC45	insomnia	citalopram	2-2.99	98	16	34	2	3.12	0.61
MJ2	insomnia	venlafaxine	2-2.99	81	24	32	4	2.95	0.34
MJ36	insomnia	citalopram	1-1.99	119	20	60	8	1.31	0.2
MJ44	insomnia	escitalopram	2-2.99	116	12	39	5	0.78	0.32
MJ64	insomnia	sertraline	2-2.99	23	8	5	4	0.13	1.44
JF9	insomnia	duloxetine	>=4	170	14	88	3	2.54	0.42
JF10	insomnia	paroxetine	2-2.99	128	17	66	5	1.87	0.28
JF22	insomnia	escitalopram	2-2.99	133	14	47	1	5.41	1.1
JF28	insomnia	paroxetine	1-1.99	70	13	23	5	0.82	0.35
LM3	insomnia	sertraline	3-3.99	173	17	90	8	1.12	0.2
LM54	insomnia	venlafaxine	2-2.99	164	15	81	2	3.98	0.59

MC13	somnolence	paroxetine	2-2.99	95	24	32	2	5.07	0.59
MC17	somnolence	paroxetine	2-2.99	136	36	72	6	3.96	0.22
MC33	somnolence	fluoxetine	2-2.99	160	19	44	3	1.84	0.42
MC45	somnolence	citalopram	2-2.99	98	10	34	2	1.82	0.64
MC55	somnolence	duloxetine	3-3.99	158	12	57	1	4.6	1.11
MC79	somnolence	venlafaxine	2-2.99	159	6	52	1	2	1.19
MJ2	somnolence	venlafaxine	2-2.99	81	21	32	4	2.45	0.35
MJ3	somnolence	paroxetine	2-2.99	197	35	90	6	3.02	0.21
MJ36	somnolence	citalopram	1-1.99	119	15	60	4	2.02	0.34
MJ42	somnolence	venlafaxine	2-2.99	130	38	67	9	2.66	0.17
MJ44	somnolence	escitalopram	2-2.99	116	14	39	2	2.54	0.61
JF9	somnolence	duloxetine	>=4	170	10	88	1	5.44	1.12
JF10	somnolence	paroxetine	2-2.99	128	9	66	3	1.59	0.47
JF22	somnolence	escitalopram	2-2.99	133	10	47	1	3.74	1.13
JF28	somnolence	paroxetine	1-1.99	70	14	23	4	1.19	0.39
JF94	somnolence	escitalopram	2-2.99	194	43	98	9	2.82	0.15
LM3	somnolence	sertraline	3-3.99	173	17	90	12	0.71	0.16
LM54	somnolence	venlafaxine	2-2.99	164	22	81	3	4.03	0.4
MC42	diarrhea	fluoxetine	2-2.99	52	1	19	1	0.35	2.08
MC45	diarrhea	citalopram	2-2.99	98	5	34	1	1.77	1.24
MC79	diarrhea	venlafaxine	2-2.99	159	10	52	2	1.68	0.63
MJ44	diarrhea	escitalopram	2-2.99	116	8	39	2	1.37	0.66
JF9	diarrhea	duloxetine	>=4	170	14	88	3	2.54	0.42
JF22	diarrhea	escitalopram	2-2.99	133	13	47	1	4.98	1.11
JF28	diarrhea	paroxetine	1-1.99	70	7	23	1	2.44	1.2
LM3	diarrhea	sertraline	3-3.99	173	21	90	12	0.9	0.15
MC13	nausea	paroxetine	2-2.99	95	26	32	2	5.65	0.59
MC17	nausea	paroxetine	2-2.99	136	35	72	8	2.77	0.18
MC33	nausea	fluoxetine	2-2.99	160	22	44	4	1.59	0.33
MC42	nausea	fluoxetine	2-2.99	52	7	19	4	0.58	0.48
MC45	nausea	citalopram	2-2.99	98	17	34	3	2.17	0.44
MC55	nausea	duloxetine	3-3.99	158	35	57	6	2.42	0.22
MJ2	nausea	venlafaxine	2-2.99	81	41	32	4	7.18	0.34
MJ3	nausea	paroxetine	2-2.99	197	33	90	6	2.82	0.21
MJ36	nausea	citalopram	1-1.99	119	21	60	8	1.39	0.2

MJ42	nausea	venlafaxine	2-2.99	130	44	67	7	4.39	0.19
MJ44	nausea	escitalopram	2-2.99	116	32	39	5	2.59	0.27
MJ64	nausea	sertraline	2-2.99	23	10	5	2	1.15	1.01
JF9	nausea	duloxetine	>=4	170	75	88	7	9.14	0.18
JF10	nausea	paroxetine	2-2.99	128	40	66	6	4.55	0.22
JF22	nausea	escitalopram	2-2.99	133	28	47	6	1.82	0.24
JF28	nausea	paroxetine	1-1.99	70	17	23	6	0.91	0.3
JF55	nausea	venlafaxine	1-1.99	130	44	44	5	3.99	0.26
JF87	nausea	venlafaxine	2-2.99	87	38	49	6	5.56	0.24
JF94	nausea	escitalopram	2-2.99	194	31	98	6	2.92	0.22
LM3	nausea	sertraline	3-3.99	173	40	90	13	1.78	0.12
LM54	nausea	venlafaxine	2-2.99	164	38	81	11	1.92	0.14
JF28	dyspepsia	paroxetine	1-1.99	70	3	23	3	0.3	0.73
MC13	loss of libido	paroxetine	2-2.99	95	17	32	1	6.76	1.1
MC17	loss of libido	paroxetine	2-2.99	136	17	72	3	3.29	0.42
MJ3	loss of libido	paroxetine	2-2.99	197	21	90	2	5.25	0.56
MJ42	loss of libido	venlafaxine	2-2.99	130	13	67	1	7.33	1.1
MJ44	loss of libido	escitalopram	2-2.99	116	8	39	0	6.19	2.15
JF9	loss of libido	duloxetine	>=4	170	8	88	1	4.3	1.14
JF10	loss of libido	paroxetine	2-2.99	128	12	66	1	6.72	1.11
JF22	loss of libido	escitalopram	2-2.99	133	8	47	1	2.94	1.15
LM54	loss of libido	venlafaxine	2-2.99	164	5	81	0	5.62	2.2
MC45	ejaculation dysfunction	citalopram	2-2.99	98	13	34	0	10.89	2.11
MJ2	ejaculation dysfunction	venlafaxine	2-2.99	81	12	32	0	11.69	2.13
MJ42	ejaculation dysfunction	venlafaxine	2-2.99	130	23	67	1	14.19	1.07
MJ44	ejaculation dysfunction	escitalopram	2-2.99	116	12	39	0	9.45	2.11
JF10	ejaculation dysfunction	paroxetine	2-2.99	128	24	66	1	15	1.07
JF28	ejaculation dysfunction	paroxetine	1-1.99	70	12	23	0	10.04	2.14
JF94	ejaculation dysfunction	escitalopram	2-2.99	194	4	98	0	4.65	2.24
MC13	Erectile dysfunction	paroxetine	2-2.99	95	11	32	1	4.06	1.14
MJ42	Erectile dysfunction	venlafaxine	2-2.99	130	10	67	0	11.76	2.12
MJ44	Erectile dysfunction	escitalopram	2-2.99	116	0	39	1	0.11	2.7
JF10	Erectile dysfunction	paroxetine	2-2.99	128	5	66	1	2.64	1.22
MC13	suicidal ideation	paroxetine	2-2.99	95	0	32	0	0.34	4.04
MC17	suicidal ideation	paroxetine	2-2.99	136	0	72	0	0.53	4.02

MC33	suicidal ideation	fluoxetine	2-2.99	160	3	44	0	1.98	2.31
MC42	suicidal ideation	fluoxetine	2-2.99	52	0	19	0	0.37	4.07
MC45	suicidal ideation	citalopram	2-2.99	98	0	34	0	0.35	4.04
MC73	suicidal ideation	venlafaxine	3-3.99	160	0	53	0	0.33	4.02
MC79	suicidal ideation	venlafaxine	2-2.99	159	0	52	0	0.33	4.03
MJ2	suicidal ideation	venlafaxine	2-2.99	81	0	32	0	0.4	4.04
MJ3	suicidal ideation	paroxetine	2-2.99	197	0	90	0	0.46	4.02
MJ36	suicidal ideation	citalopram	1-1.99	119	0	60	0	0.51	4.02
MJ42	suicidal ideation	venlafaxine	2-2.99	130	0	67	0	0.52	4.02
MJ44	suicidal ideation	escitalopram	2-2.99	116	0	39	0	0.34	4.03
MJ64	suicidal ideation	sertraline	2-2.99	23	0	5	0	0.23	4.22
JF9	suicidal ideation	duloxetine	>=4	170	0	88	0	0.52	4.02
JF10	suicidal ideation	paroxetine	2-2.99	128	0	66	0	0.52	4.02
JF22	suicidal ideation	escitalopram	2-2.99	133	0	47	0	0.36	4.03
JF28	suicidal ideation	paroxetine	1-1.99	70	0	23	0	0.33	4.06
JF55	suicidal ideation	venlafaxine	1-1.99	130	0	44	0	0.34	4.03
JF87	suicidal ideation	venlafaxine	2-2.99	87	0	49	0	0.57	4.03
JF94	suicidal ideation	escitalopram	2-2.99	194	0	98	0	0.51	4.02
LM3	suicidal ideation	sertraline	3-3.99	173	0	90	0	0.52	4.02
LM54	suicidal ideation	venlafaxine	2-2.99	164	0	81	0	0.5	4.02
MC13	suicide attempt	paroxetine	2-2.99	95	0	32	0	0.34	4.04
MC17	suicide attempt	paroxetine	2-2.99	136	0	72	0	0.53	4.02
MC33	suicide attempt	fluoxetine	2-2.99	160	0	44	0	0.28	4.03
MC42	suicide attempt	fluoxetine	2-2.99	52	0	19	0	0.37	4.07
MC45	suicide attempt	citalopram	2-2.99	98	0	34	0	0.35	4.04
MC73	suicide attempt	venlafaxine	3-3.99	160	0	53	0	0.33	4.02
MC79	suicide attempt	venlafaxine	2-2.99	159	0	52	0	0.33	4.03
MJ2	suicide attempt	venlafaxine	2-2.99	81	0	32	0	0.4	4.04
MJ3	suicide attempt	paroxetine	2-2.99	197	0	90	0	0.46	4.02
MJ36	suicide attempt	citalopram	1-1.99	119	0	60	0	0.51	4.02
MJ42	suicide attempt	venlafaxine	2-2.99	130	0	67	0	0.52	4.02
MJ44	suicide attempt	escitalopram	2-2.99	116	0	39	0	0.34	4.03
MJ64	suicide attempt	sertraline	2-2.99	23	0	5	0	0.23	4.22
JF10	suicide attempt	paroxetine	2-2.99	128	0	66	0	0.52	4.02
JF94	suicide attempt	escitalopram	2-2.99	194	0	98	0	0.51	4.02

MC13	death by suicide	paroxetine	2-2.99	95	0	32	0	0.34	4.04
MC17	death by suicide	paroxetine	2-2.99	136	0	72	0	0.53	4.02
MC33	death by suicide	fluoxetine	2-2.99	160	0	44	0	0.28	4.03
MC42	death by suicide	fluoxetine	2-2.99	52	0	19	0	0.37	4.07
MC45	death by suicide	citalopram	2-2.99	98	0	34	0	0.35	4.04
MC73	death by suicide	venlafaxine	3-3.99	160	0	53	0	0.33	4.02
MC79	death by suicide	venlafaxine	2-2.99	159	0	52	0	0.33	4.03
MJ2	death by suicide	venlafaxine	2-2.99	81	0	32	0	0.4	4.04
MJ3	death by suicide	paroxetine	2-2.99	197	0	90	0	0.46	4.02
MJ36	death by suicide	citalopram	1-1.99	119	0	60	0	0.51	4.02
MJ42	death by suicide	venlafaxine	2-2.99	130	0	67	0	0.52	4.02
MJ44	death by suicide	escitalopram	2-2.99	116	0	39	0	0.34	4.03
MJ64	death by suicide	sertraline	2-2.99	23	0	5	0	0.23	4.22
JF9	death by suicide	duloxetine	>=4	170	0	88	0	0.52	4.02
JF10	death by suicide	paroxetine	2-2.99	128	0	66	0	0.52	4.02
JF22	death by suicide	escitalopram	2-2.99	133	0	47	0	0.36	4.03
JF28	death by suicide	paroxetine	1-1.99	70	0	23	0	0.33	4.06
JF55	death by suicide	venlafaxine	1-1.99	130	0	44	0	0.34	4.03
JF87	death by suicide	venlafaxine	2-2.99	87	0	49	0	0.57	4.03
JF94	death by suicide	escitalopram	2-2.99	194	0	98	0	0.51	4.02
LM3	death by suicide	sertraline	3-3.99	173	0	90	0	0.52	4.02
LM54	death by suicide	venlafaxine	2-2.99	164	0	81	0	0.5	4.02
MC13	any adverse event	paroxetine	3-3.99	97	85	31	26	1.36	0.33
MC45	any adverse event	citalopram	3-3.99	100	72	33	19	1.89	0.17
MC73	any adverse event	paroxetine	2-2.99	151	121	52	42	0.96	0.17
MC79	any adverse event	paroxetine	2-2.99	161	121	52	35	1.47	0.12
MJ44	any adverse event	paroxetine	2-2.99	119	95	38	24	2.31	0.17
JF55	any adverse event	venlafaxine	2-2.99	131	85	43	24	1.46	0.13
MC13	dry mouth	paroxetine	3-3.99	97	10	31	2	1.67	0.65
MC45	dry mouth	citalopram	3-3.99	100	6	33	1	2.04	1.21
MC55	dry mouth	venlafaxine	2-2.99	169	16	56	2	2.82	0.59
MC79	dry mouth	paroxetine	2-2.99	161	11	52	2	1.83	0.62
MJ2	dry mouth	venlafaxine	3-3.99	86	26	32	2	6.5	0.59
MJ44	dry mouth	paroxetine	2-2.99	119	11	38	1	3.77	1.13
JF22	dry mouth	paroxetine	1-1.99	140	7	46	1	2.37	1.17

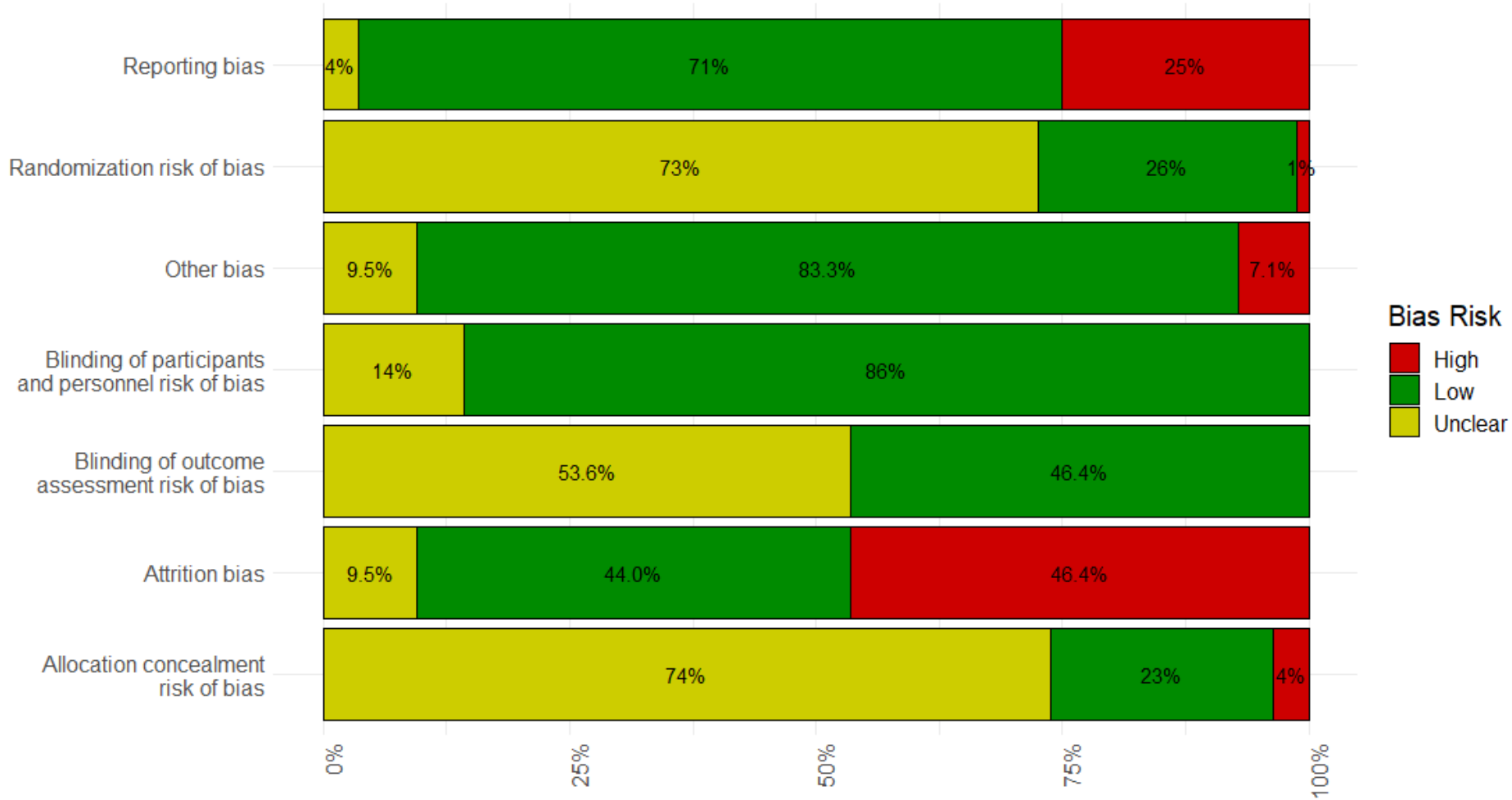
JF28	dry mouth	paroxetine	2-2.99	72	25	23	3	3.55	0.44
JF55	dry mouth	venlafaxine	2-2.99	131	22	43	2	4.14	0.58
MC13	sweating	paroxetine	3-3.99	97	11	31	0	8.38	2.13
MC45	sweating	citalopram	3-3.99	100	9	33	1	3.16	1.15
MC55	sweating	venlafaxine	2-2.99	169	9	56	1	3.09	1.14
MC79	sweating	paroxetine	2-2.99	161	16	52	2	2.76	0.59
MJ44	sweating	paroxetine	2-2.99	119	16	38	1	5.75	1.1
JF22	sweating	paroxetine	1-1.99	140	12	46	1	4.22	1.11
JF55	sweating	venlafaxine	2-2.99	131	24	43	2	4.6	0.58
MC42	headache	fluoxetine	3-3.99	54	11	18	4	0.9	0.44
MC45	headache	citalopram	3-3.99	100	16	33	5	1.07	0.31
MJ44	headache	paroxetine	2-2.99	119	23	38	7	1.06	0.23
JF22	headache	paroxetine	1-1.99	140	13	46	8	0.49	0.24
JF28	headache	paroxetine	2-2.99	72	19	23	10	0.47	0.25
JF55	headache	venlafaxine	2-2.99	131	3	43	1	0.98	1.36
MC13	dizziness	paroxetine	3-3.99	97	22	31	2	4.25	0.59
MC45	dizziness	citalopram	3-3.99	100	8	33	2	1.35	0.67
MJ2	dizziness	venlafaxine	3-3.99	86	16	32	4	1.6	0.36
MJ44	dizziness	paroxetine	2-2.99	119	11	38	2	1.83	0.63
JF22	dizziness	paroxetine	1-1.99	140	8	46	3	0.87	0.49
JF28	dizziness	paroxetine	2-2.99	72	9	23	4	0.68	0.43
JF55	dizziness	venlafaxine	2-2.99	131	41	43	6	2.81	0.23
MC13	constipation	paroxetine	3-3.99	97	11	31	1	3.84	1.14
MC55	constipation	venlafaxine	2-2.99	169	12	56	2	2.06	0.61
MC79	constipation	paroxetine	2-2.99	161	13	52	1	4.48	1.1
MJ44	constipation	paroxetine	2-2.99	119	7	38	1	2.31	1.18
JF28	constipation	paroxetine	2-2.99	72	9	23	2	1.5	0.67
JF55	constipation	venlafaxine	2-2.99	131	20	43	2	3.69	0.58
MC13	tremor	paroxetine	3-3.99	97	13	31	0	10.07	2.12
MC55	tremor	venlafaxine	2-2.99	169	5	56	1	1.68	1.22
MC79	tremor	paroxetine	2-2.99	161	10	52	1	3.38	1.13
MJ44	tremor	paroxetine	2-2.99	119	4	38	1	1.29	1.29
JF28	tremor	paroxetine	2-2.99	72	12	23	1	4.4	1.15
MC13	asthenia	paroxetine	3-3.99	97	21	31	3	2.58	0.43
MC45	asthenia	citalopram	3-3.99	100	10	33	1	3.56	1.14

MC55	asthenia	venlafaxine	2-2.99	169	10	56	1	3.46	1.12
MJ2	asthenia	venlafaxine	3-3.99	86	18	32	3	2.56	0.44
MJ44	asthenia	paroxetine	2-2.99	119	22	38	2	4.08	0.58
JF22	asthenia	paroxetine	1-1.99	140	12	46	1	4.22	1.11
JF28	asthenia	paroxetine	2-2.99	72	13	23	1	4.85	1.14
JF22	agitation	paroxetine	1-1.99	140	6	46	1	2.01	1.2
JF28	agitation	paroxetine	2-2.99	72	8	23	4	0.59	0.44
MC13	insomnia	paroxetine	3-3.99	97	34	31	5	2.81	0.28
MC42	insomnia	fluoxetine	3-3.99	54	13	18	4	1.11	0.42
MC45	insomnia	citalopram	3-3.99	100	19	33	2	3.64	0.6
MJ2	insomnia	venlafaxine	3-3.99	86	27	32	4	3.2	0.34
MJ44	insomnia	paroxetine	2-2.99	119	17	38	5	1.1	0.3
JF22	insomnia	paroxetine	1-1.99	140	15	46	1	5.4	1.1
JF28	insomnia	paroxetine	2-2.99	72	21	23	5	1.48	0.32
MC13	somnolence	paroxetine	3-3.99	97	30	31	2	6.49	0.58
MC45	somnolence	citalopram	3-3.99	100	10	33	2	1.72	0.64
MC55	somnolence	venlafaxine	2-2.99	169	8	56	1	2.73	1.15
MC79	somnolence	paroxetine	2-2.99	161	21	52	1	7.65	1.07
MJ2	somnolence	venlafaxine	3-3.99	86	24	32	4	2.71	0.34
MJ44	somnolence	paroxetine	2-2.99	119	13	38	2	2.21	0.61
JF22	somnolence	paroxetine	1-1.99	140	10	46	1	3.46	1.13
JF28	somnolence	paroxetine	2-2.99	72	23	23	4	2.23	0.37
MC42	diarrhea	fluoxetine	3-3.99	54	7	18	1	2.53	1.22
MC45	diarrhea	citalopram	3-3.99	100	6	33	1	2.04	1.21
MC79	diarrhea	paroxetine	2-2.99	161	8	52	2	1.31	0.65
MJ44	diarrhea	paroxetine	2-2.99	119	11	38	2	1.83	0.63
JF22	diarrhea	paroxetine	1-1.99	140	11	46	1	3.84	1.12
JF28	diarrhea	paroxetine	2-2.99	72	16	23	1	6.29	1.13
MC13	nausea	paroxetine	3-3.99	97	23	31	2	4.51	0.59
MC42	nausea	fluoxetine	3-3.99	54	9	18	4	0.7	0.45
MC45	nausea	citalopram	3-3.99	100	25	33	3	3.33	0.42
MC55	nausea	venlafaxine	2-2.99	169	29	56	6	1.73	0.23
MJ2	nausea	venlafaxine	3-3.99	86	40	32	4	6.09	0.33
MJ44	nausea	paroxetine	2-2.99	119	32	38	5	2.43	0.27
JF22	nausea	paroxetine	1-1.99	140	30	46	6	1.82	0.23

JF28	nausea	paroxetine	2-2.99	72	23	23	6	1.33	0.29
JF55	nausea	venlafaxine	2-2.99	131	42	43	5	3.59	0.26
JF28	dyspepsia	paroxetine	2-2.99	72	0	23	3	0.04	2.35
MC13	loss of libido	paroxetine	3-3.99	97	11	31	1	3.84	1.14
MJ44	loss of libido	paroxetine	2-2.99	119	10	38	0	7.38	2.13
JF22	loss of libido	paroxetine	1-1.99	140	9	46	1	3.09	1.14
MC45	ejaculation dysfunction	citalopram	3-3.99	100	7	33	0	5.37	2.17
MJ2	ejaculation dysfunction	venlafaxine	3-3.99	86	9	32	0	7.97	2.15
MJ44	ejaculation dysfunction	paroxetine	2-2.99	119	11	38	0	8.16	2.12
MC13	Erectile dysfunction	paroxetine	3-3.99	97	7	31	1	2.33	1.19
MJ44	Erectile dysfunction	paroxetine	2-2.99	119	11	38	1	3.77	1.13
MC13	suicidal ideation	paroxetine	3-3.99	97	0	31	0	0.32	4.04
MC42	suicidal ideation	fluoxetine	3-3.99	54	0	18	0	0.34	4.07
MC45	suicidal ideation	citalopram	3-3.99	100	0	33	0	0.33	4.04
MC73	suicidal ideation	paroxetine	2-2.99	151	0	52	0	0.35	4.03
MC79	suicidal ideation	paroxetine	2-2.99	161	0	52	0	0.33	4.03
MJ2	suicidal ideation	venlafaxine	3-3.99	86	0	32	0	0.38	4.04
MJ44	suicidal ideation	paroxetine	2-2.99	119	0	38	0	0.32	4.03
JF22	suicidal ideation	paroxetine	1-1.99	140	0	46	0	0.33	4.03
JF28	suicidal ideation	paroxetine	2-2.99	72	0	23	0	0.32	4.06
JF55	suicidal ideation	venlafaxine	2-2.99	131	0	43	0	0.33	4.03
MC13	suicide attempt	paroxetine	3-3.99	97	0	31	0	0.32	4.04
MC42	suicide attempt	fluoxetine	3-3.99	54	0	18	0	0.34	4.07
MC45	suicide attempt	citalopram	3-3.99	100	0	33	0	0.33	4.04
MC73	suicide attempt	paroxetine	2-2.99	151	0	52	0	0.35	4.03
MC79	suicide attempt	paroxetine	2-2.99	161	0	52	0	0.33	4.03
MJ2	suicide attempt	venlafaxine	3-3.99	86	0	32	0	0.38	4.04
MJ44	suicide attempt	paroxetine	2-2.99	119	0	38	0	0.32	4.03
MC13	death by suicide	paroxetine	3-3.99	97	0	31	0	0.32	4.04
MC42	death by suicide	fluoxetine	3-3.99	54	0	18	0	0.34	4.07
MC45	death by suicide	citalopram	3-3.99	100	0	33	0	0.33	4.04
MC73	death by suicide	paroxetine	2-2.99	151	0	52	0	0.35	4.03
MC79	death by suicide	paroxetine	2-2.99	161	0	52	0	0.33	4.03
MJ2	death by suicide	venlafaxine	3-3.99	86	0	32	0	0.38	4.04
MJ44	death by suicide	paroxetine	2-2.99	119	0	38	0	0.32	4.03

JF22	death by suicide	paroxetine	1-1.99	140	0	46	0	0.33	4.03
JF28	death by suicide	paroxetine	2-2.99	72	0	23	0	0.32	4.06
JF55	death by suicide	venlafaxine	2-2.99	131	0	43	0	0.33	4.03

Supplementary Figure S2: Risk of bias summary



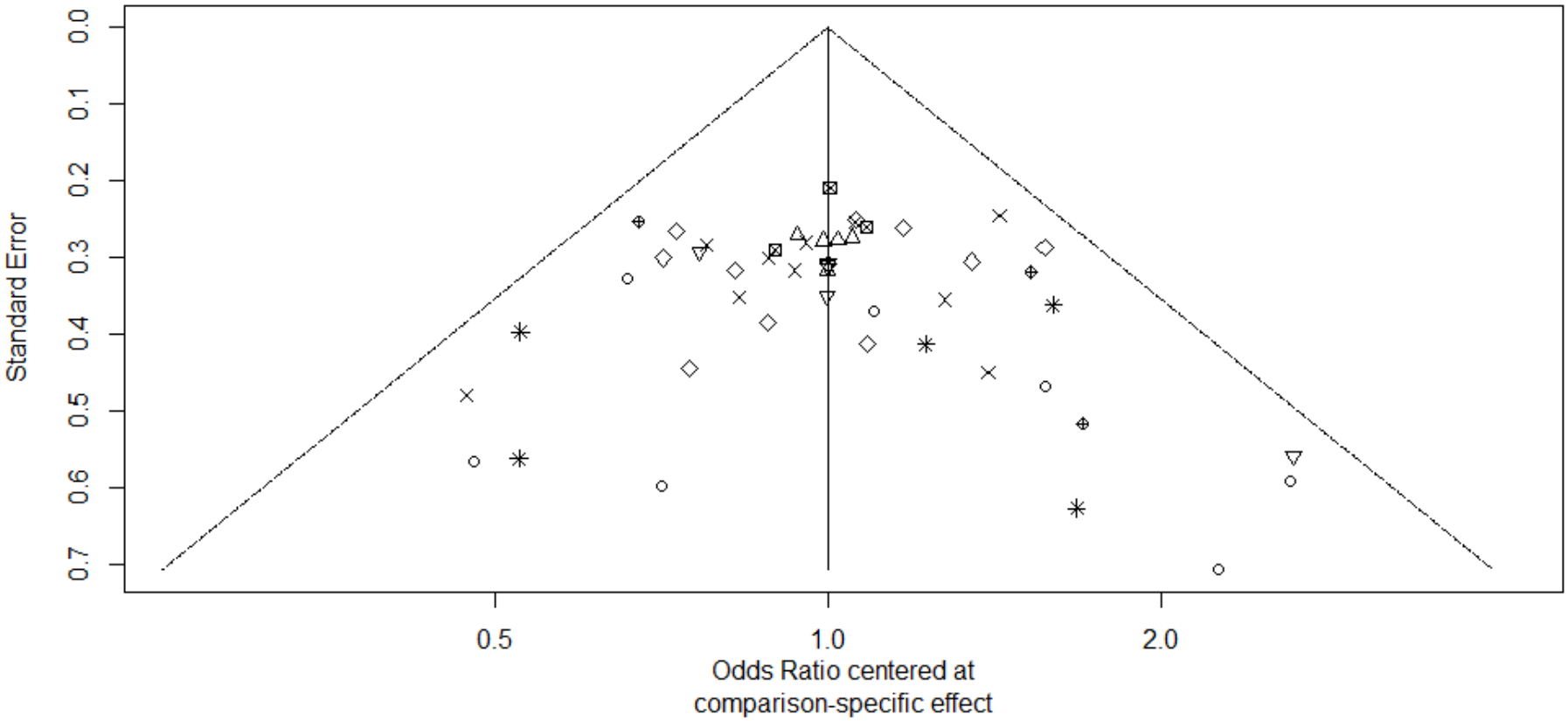
Supplementary Table S5: Risk of bias in included studies

id	Randomization risk of bias	Allocation concealment risk of bias	Blinding of participants and personnel risk of bias	Blinding of outcome assessment risk of bias	Attrition risk of bias	Reporting risk of bias	Other risk of bias
MC3	low	low	low	low	high	high	low
MC12	unclear	unclear	low	low	low	low	low
MC13	unclear	unclear	low	low	low	low	low
MC17	unclear	unclear	low	low	high	high	low
MC22	low	unclear	low	low	high	high	high
MC25	low	low	low	low	low	low	low
MC33	unclear	unclear	low	low	high	low	low
MC38	low	unclear	low	low	high	low	low
MC40	unclear	unclear	low	low	high	low	low
MC45	unclear	unclear	low	low	low	low	low
MC51	unclear	unclear	low	low	low	high	low
MC71	unclear	unclear	low	low	high	high	low
MC73	unclear	unclear	low	low	high	low	low
MC79	unclear	unclear	low	low	high	low	low
MC82	unclear	unclear	low	low	low	low	low
MJ1	unclear	unclear	low	unclear	high	high	unclear
MJ3	unclear	unclear	low	unclear	low	low	low
MJ5	unclear	unclear	low	unclear	high	low	low
MJ6	unclear	unclear	low	unclear	high	low	low
MJ14	unclear	unclear	low	unclear	high	low	low
MJ17	unclear	unclear	low	unclear	high	high	low
MJ44	low	low	low	unclear	low	low	low
MJ56	unclear	low	low	unclear	low	low	low
MJ78	low	unclear	low	unclear	high	low	low
MJ84	unclear	unclear	low	unclear	high	low	low
MJ94	unclear	unclear	low	unclear	high	low	low
JF7	unclear	unclear	unclear	unclear	low	low	unclear
JF15	unclear	unclear	low	unclear	low	low	low
JF25	unclear	unclear	low	unclear	low	low	low
JF29	low	low	low	low	low	low	low

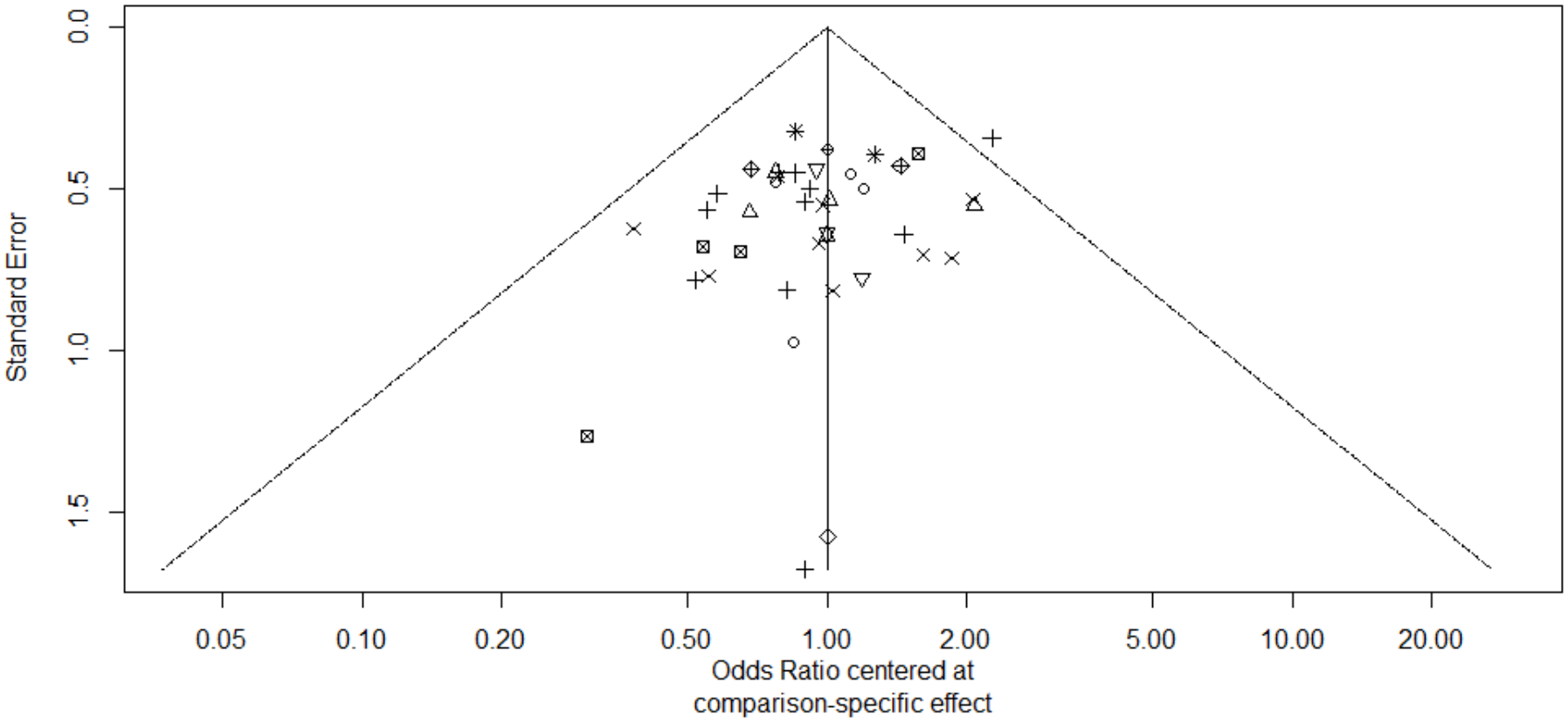
JF56	unclear	low	low	low	unclear	low	low
JF94	low	high	low	unclear	low	low	low
LM4	low	low	unclear	unclear	low	low	unclear
LM34	unclear	low	low	unclear	low	low	low
LM39	unclear	unclear	unclear	unclear	low	low	low
LM48	unclear	unclear	unclear	unclear	low	high	high
LM54	unclear	unclear	unclear	unclear	low	low	low
LM60	unclear	unclear	unclear	unclear	high	low	low
MC10	unclear	unclear	low	low	high	high	low
MC44	unclear	unclear	low	low	high	low	low
MJ25	unclear	unclear	low	unclear	high	low	low
MJ64	unclear	unclear	low	unclear	unclear	low	low
MJ70	unclear	unclear	low	unclear	high	high	low
LM69	unclear	unclear	low	low	high	low	low
JF42	unclear	unclear	low	low	unclear	low	low
MJ97	high	high	low	unclear	high	low	high
LM67	unclear	unclear	unclear	unclear	low	low	low
MC32	unclear	unclear	low	low	high	low	low
JF10	low	high	low	low	high	unclear	unclear
MC15	unclear	unclear	low	low	low	low	high
MC16	unclear	unclear	low	low	low	low	low
MC62	unclear	low	low	low	high	low	low
MC81	unclear	unclear	low	low	high	low	low
MJ2	unclear	unclear	low	low	high	low	low
MJ16	unclear	unclear	low	unclear	high	low	low
MJ36	unclear	unclear	low	unclear	low	low	low
MJ54	low	low	low	unclear	high	low	low
MJ66	unclear	unclear	low	unclear	low	low	low
MJ93	unclear	unclear	low	unclear	low	low	low
JF9	low	unclear	low	unclear	high	high	low
JF59	unclear	low	low	low	unclear	low	low
JF61	low	low	low	low	unclear	low	low
JF87	unclear	unclear	low	unclear	unclear	unclear	low
LM3	unclear	unclear	unclear	unclear	low	low	low
LM6	unclear	low	unclear	unclear	low	high	unclear

LM95	low	low	low	low	low	low	low
MJ72	unclear	unclear	low	unclear	high	high	unclear
LM73	unclear	unclear	unclear	unclear	unclear	high	unclear
MC42	unclear	unclear	low	low	low	low	low
JF88	unclear	unclear	low	unclear	unclear	unclear	low
JF89	unclear	unclear	low	unclear	high	low	low
LM72	low	unclear	unclear	unclear	low	low	low
MC14	unclear	unclear	low	low	low	high	high
MJ4	unclear	unclear	low	low	high	high	high
MC77	unclear	unclear	low	low	low	high	low
MC28	low	low	low	low	high	low	low
MC26	low	low	low	low	high	low	low
LM40	low	low	unclear	unclear	low	high	low
MJ53	unclear	unclear	low	unclear	low	high	unclear
JF55	low	low	low	low	low	low	low
MJ42	low	unclear	low	unclear	high	high	low
JF28	unclear	unclear	low	unclear	low	low	low
MC55	low	low	low	low	high	high	low
JF22	low	unclear	low	unclear	low	low	low

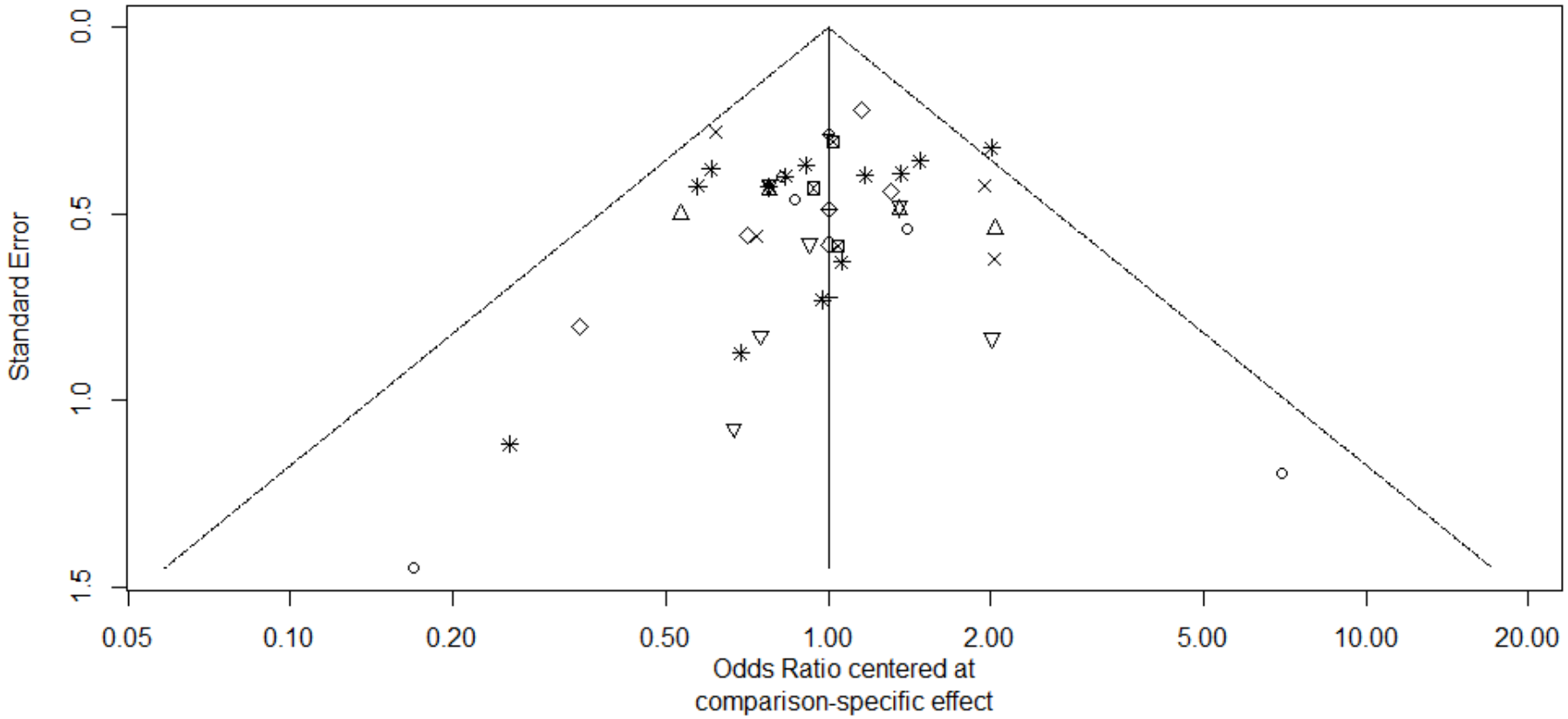
Supplementary Figure S3: Comparison-adjusted funnel plot for overall tolerability



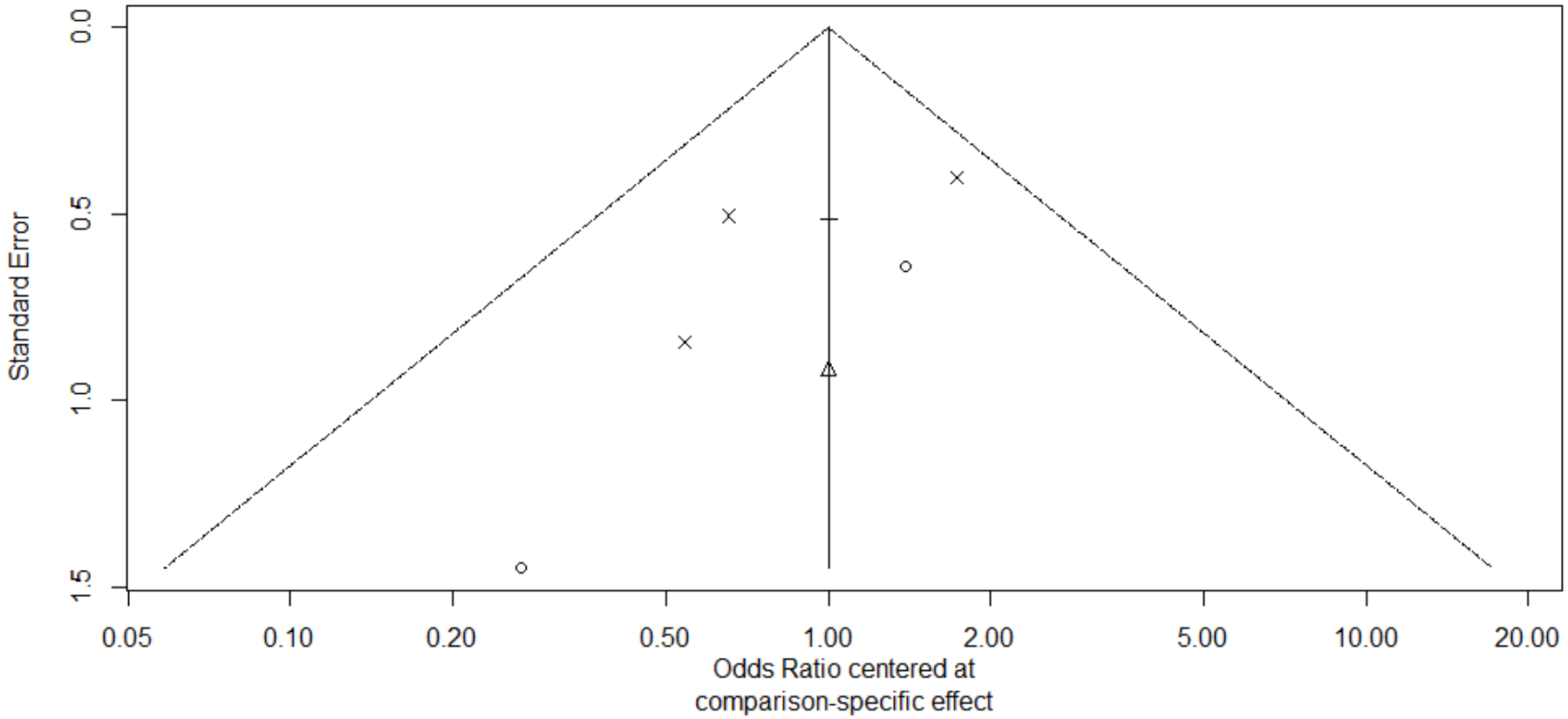
Supplementary Figure S4: Comparison-adjusted funnel plot for constipation



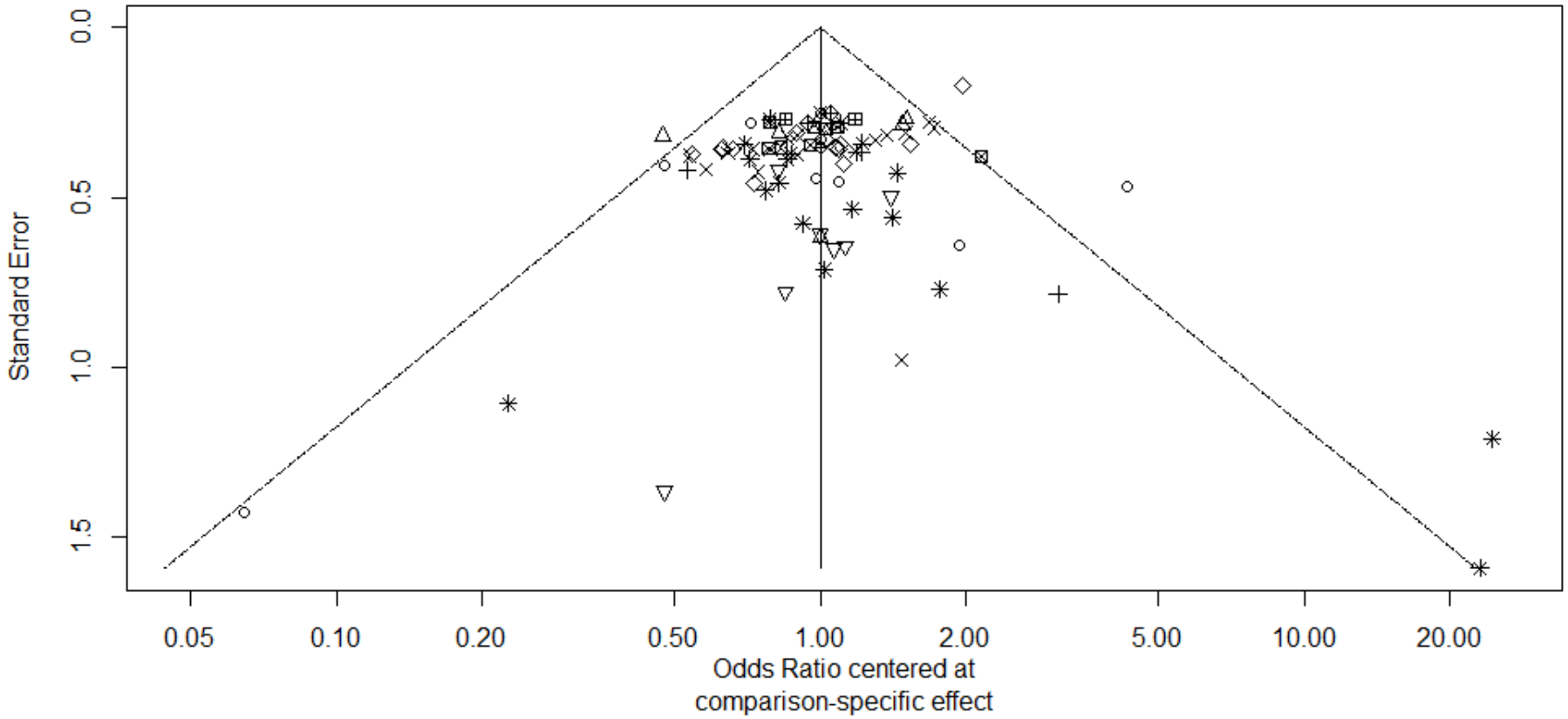
Supplementary Figure S5: Comparison-adjusted funnel plot for diarrhea



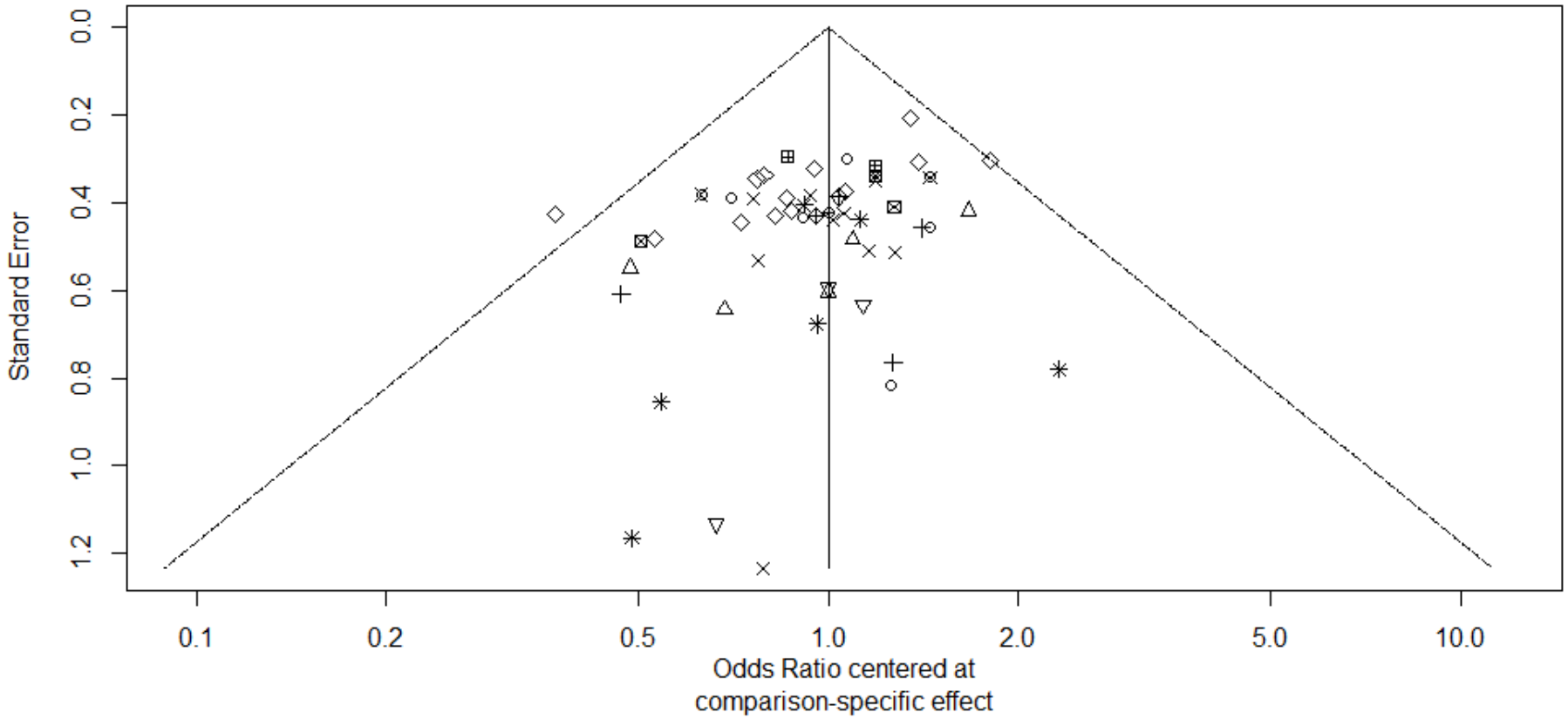
Supplementary Figure S6: Comparison-adjusted funnel plot for dyspepsia



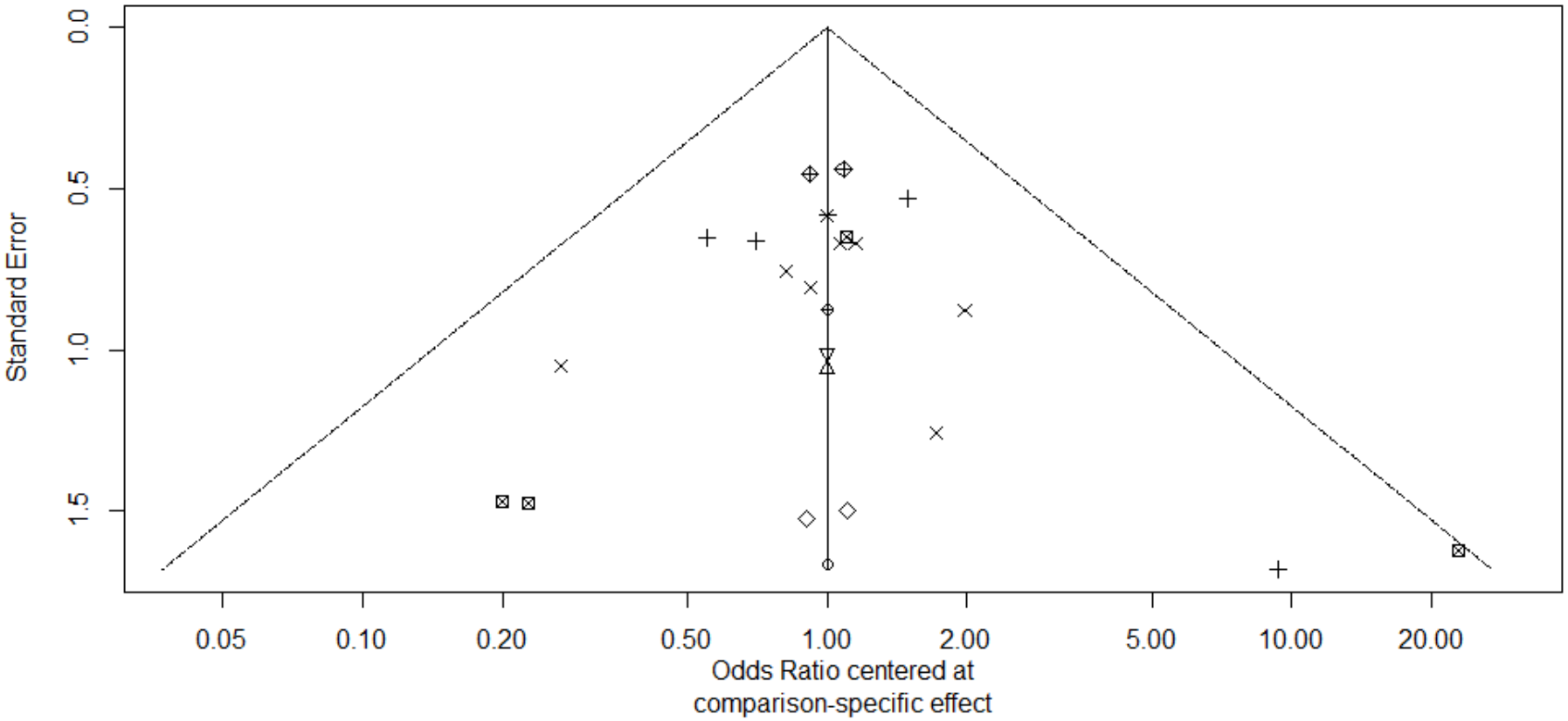
Supplementary Figure S7: Comparison-adjusted funnel plot for nausea



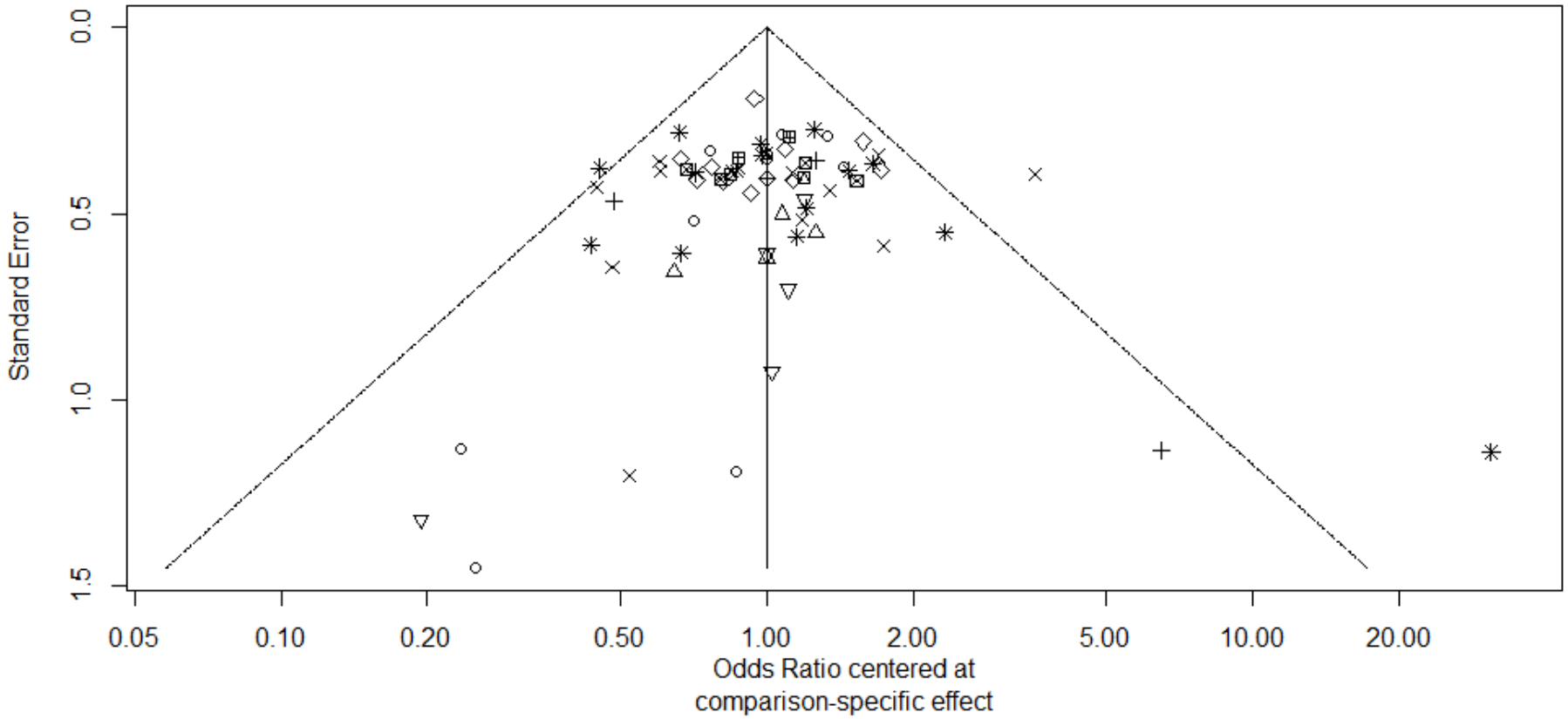
Supplementary Figure S8: Comparison-adjusted funnel plot for asthenia



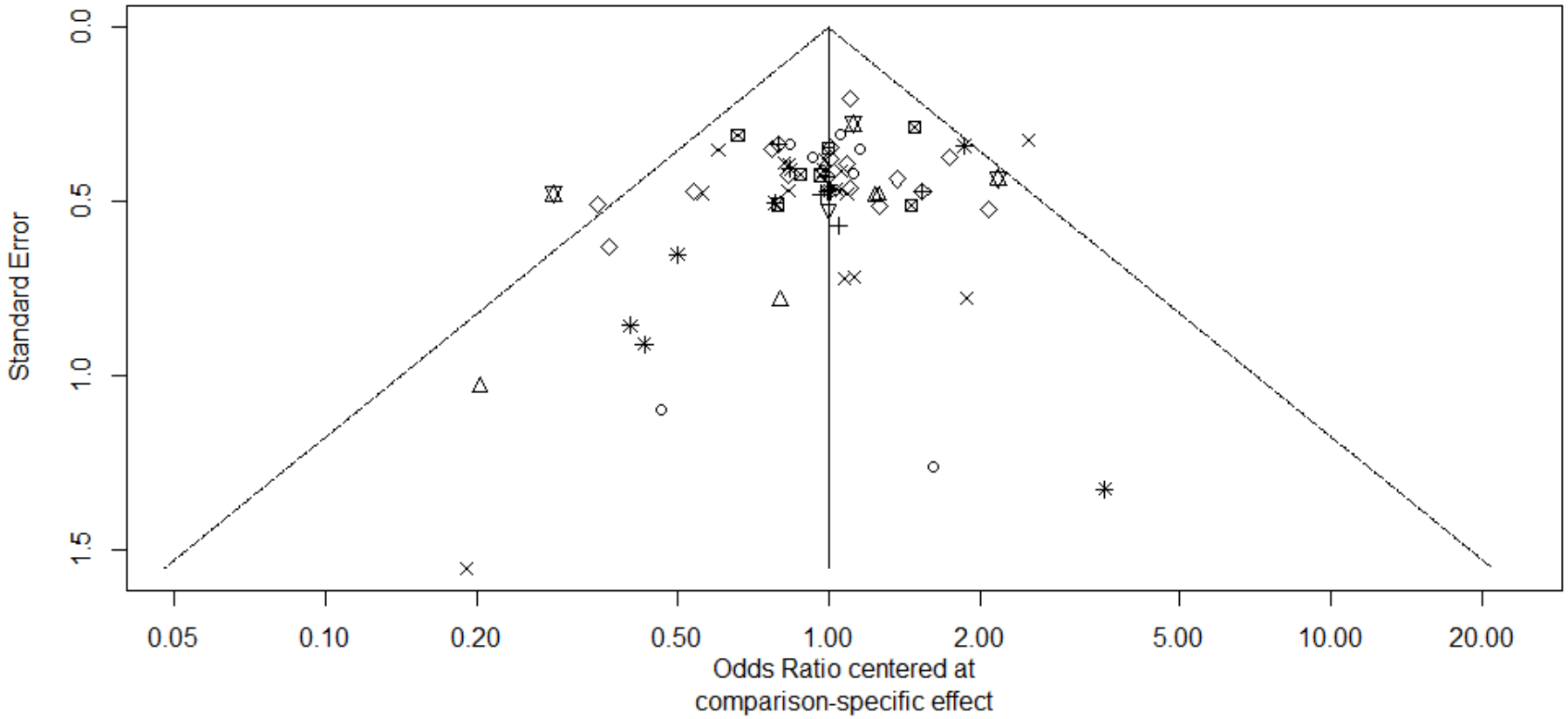
Supplementary Figure S9: Comparison-adjusted funnel plot for tremor



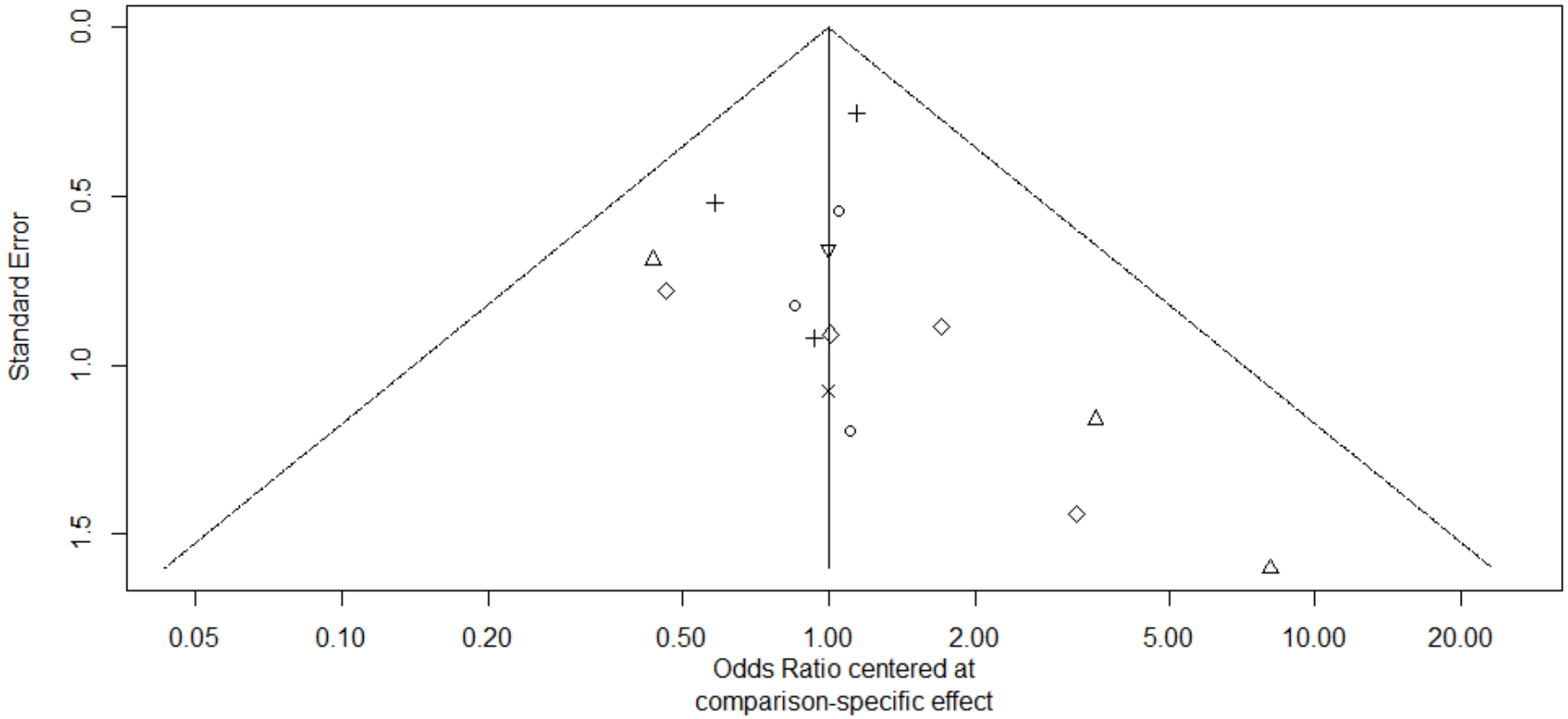
Supplementary Figure S10: Comparison-adjusted funnel plot for insomnia



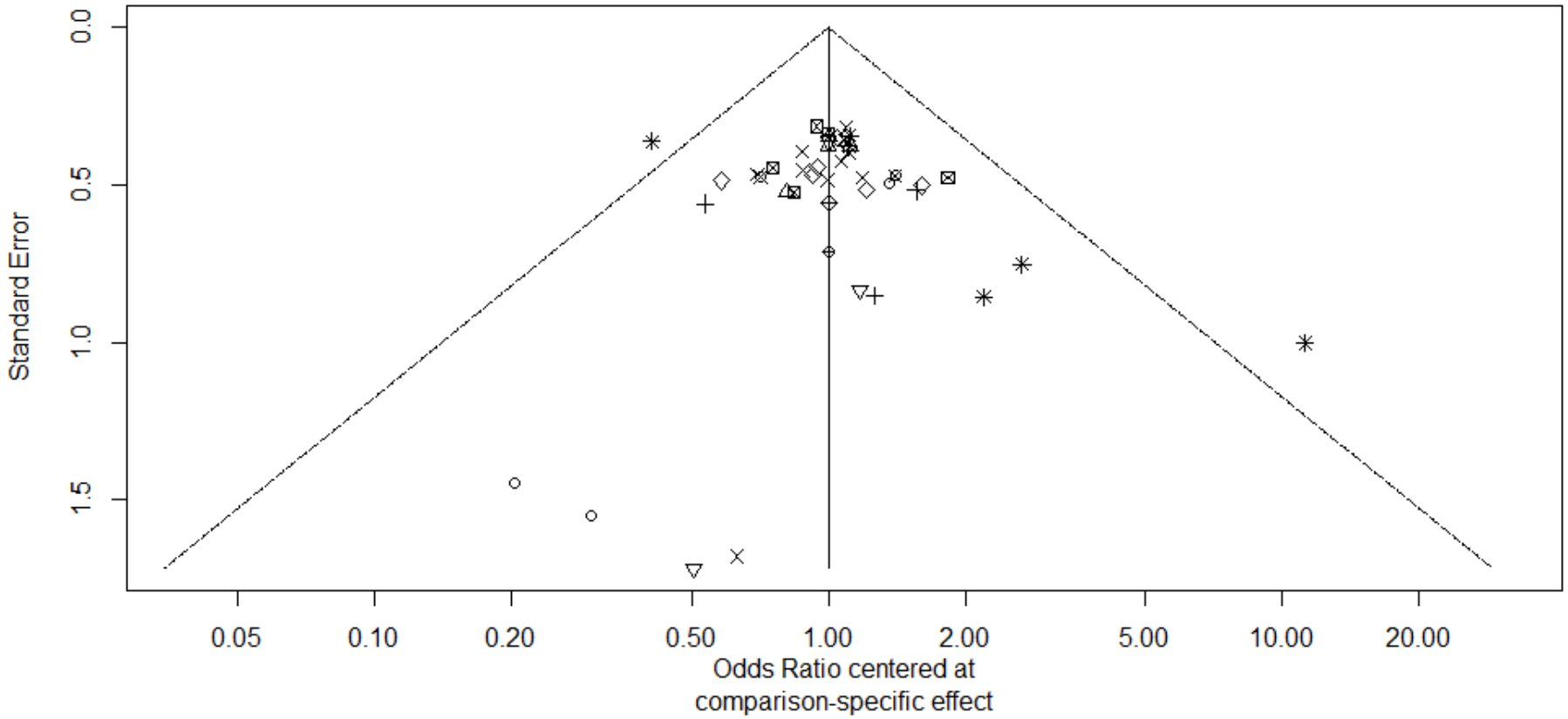
Supplementary Figure S11: Comparison-adjusted funnel plot for somnolence



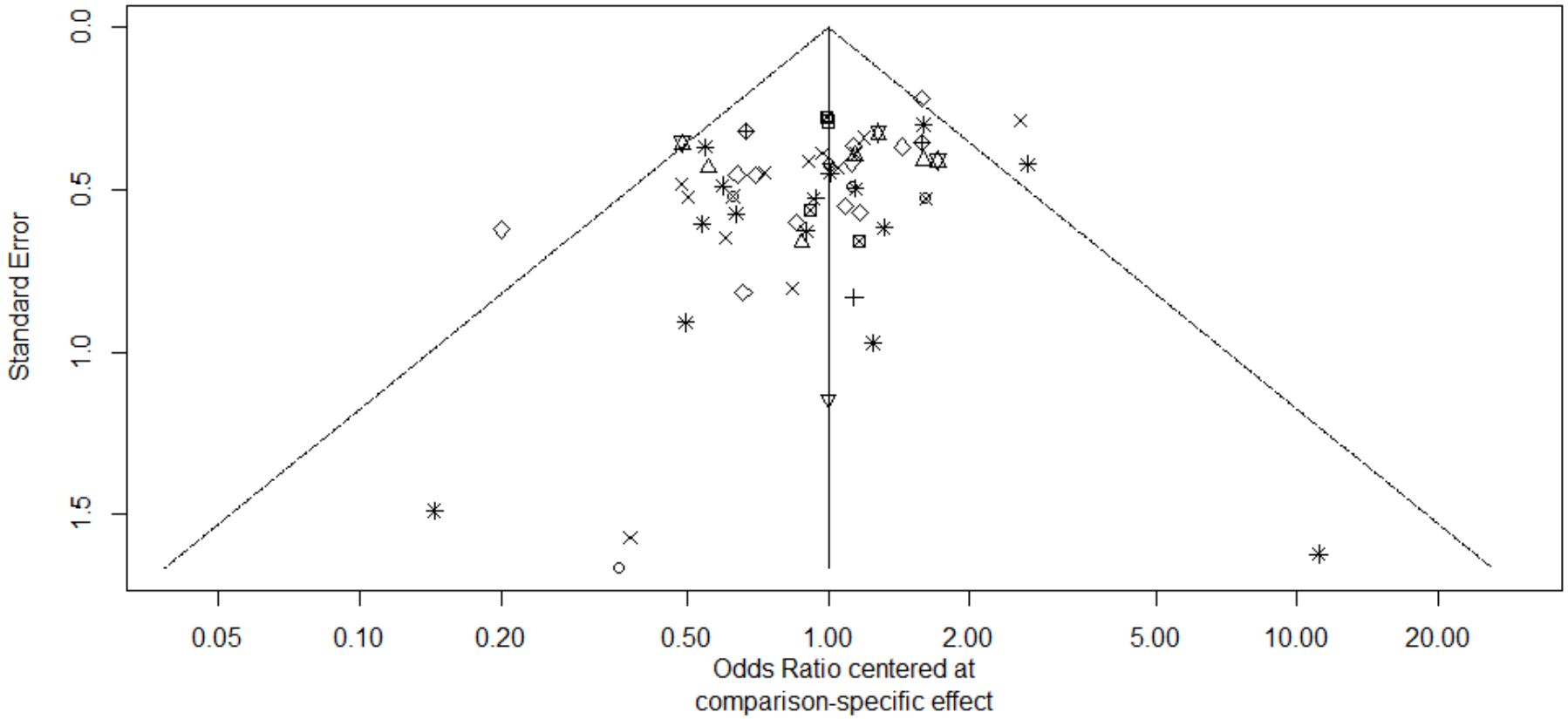
Supplementary Figure S12: Comparison-adjusted funnel plot for agitation



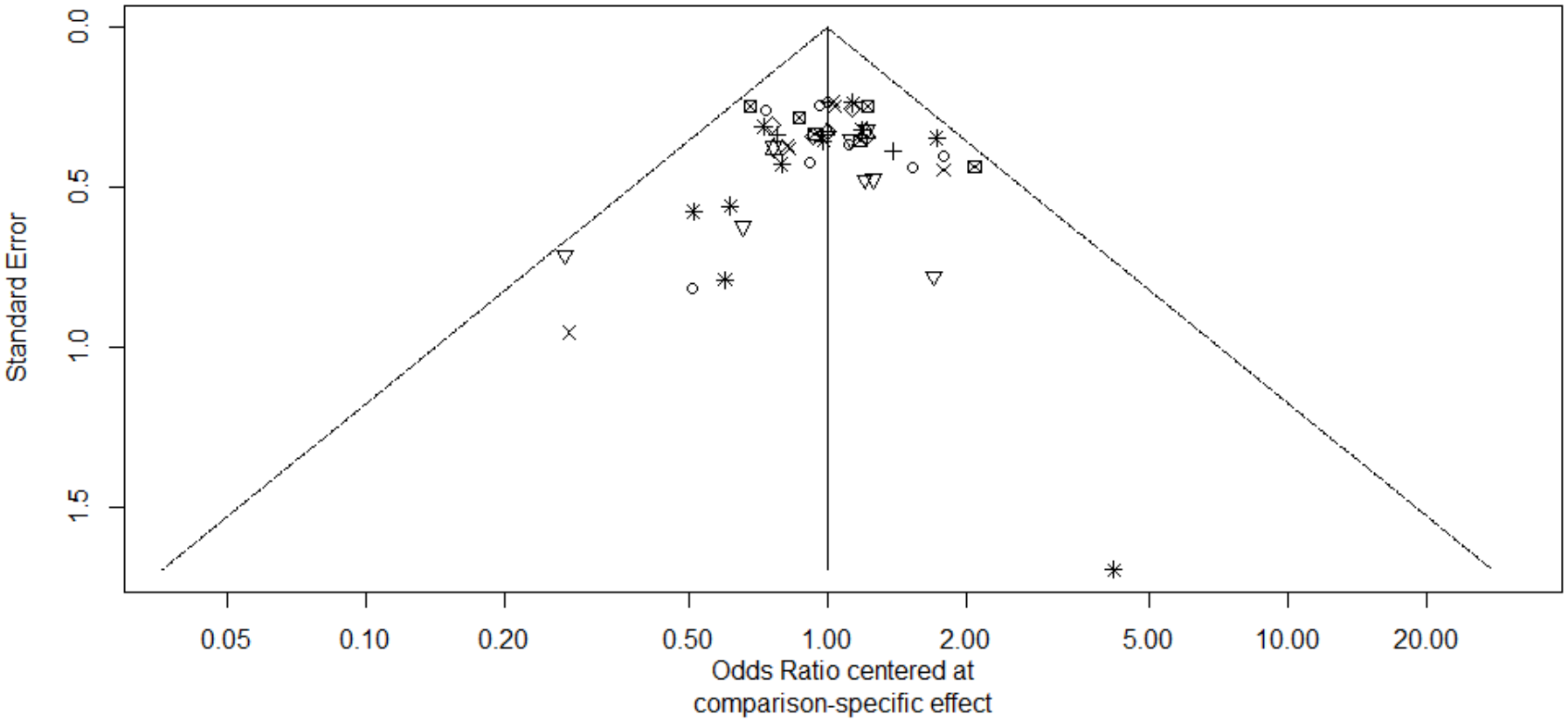
Supplementary Figure S13: Comparison-adjusted funnel plot for dizziness



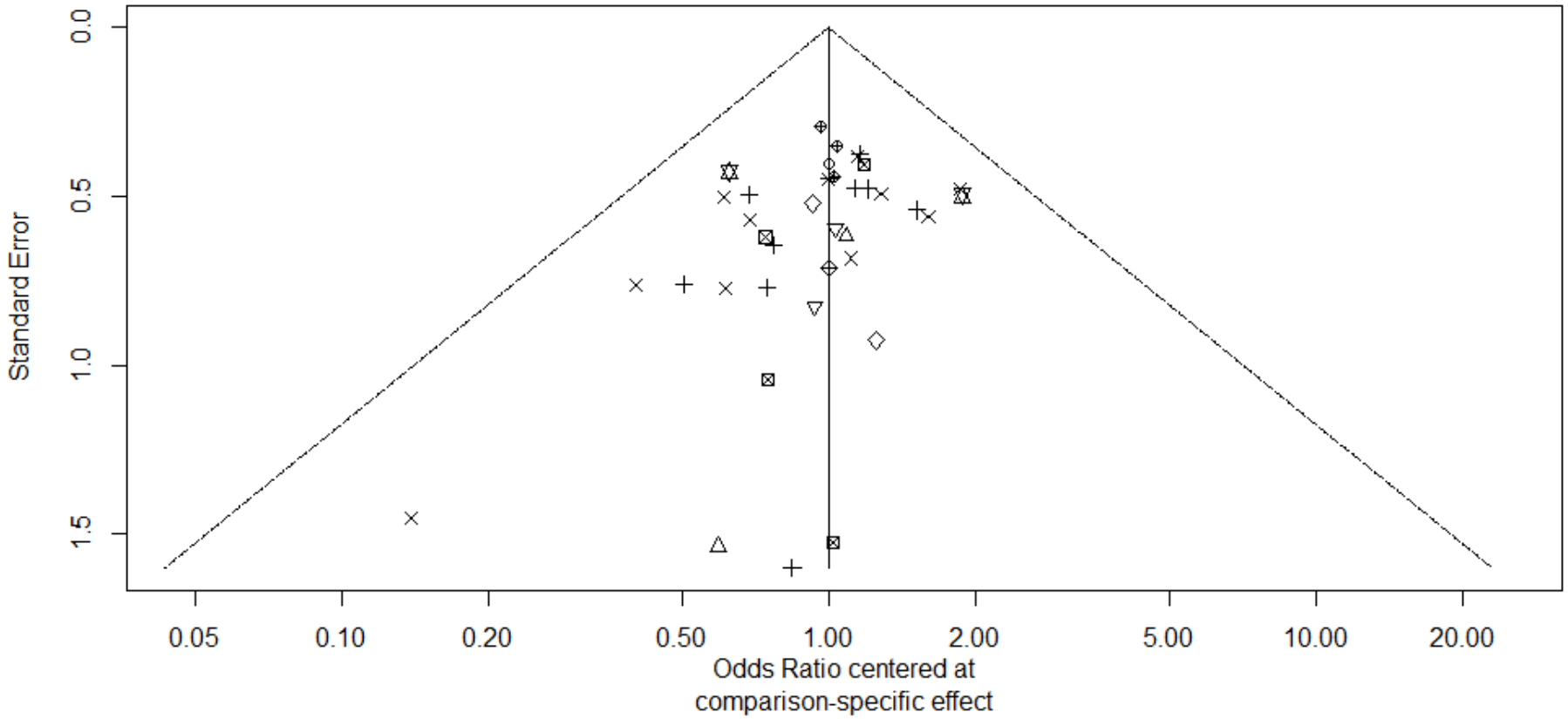
Supplementary Figure S14: Comparison-adjusted funnel plot for dry mouth



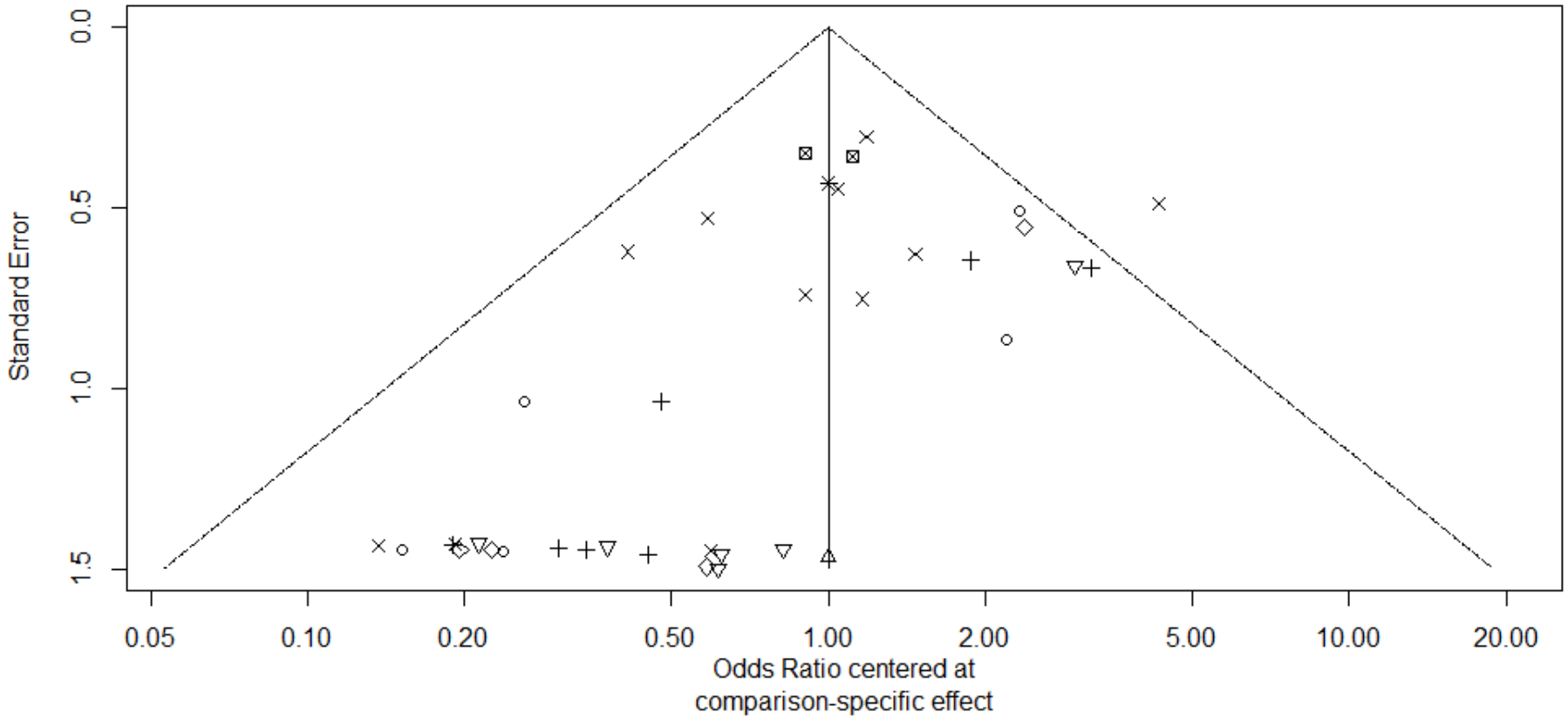
Supplementary Figure S15: Comparison-adjusted funnel plot for headache



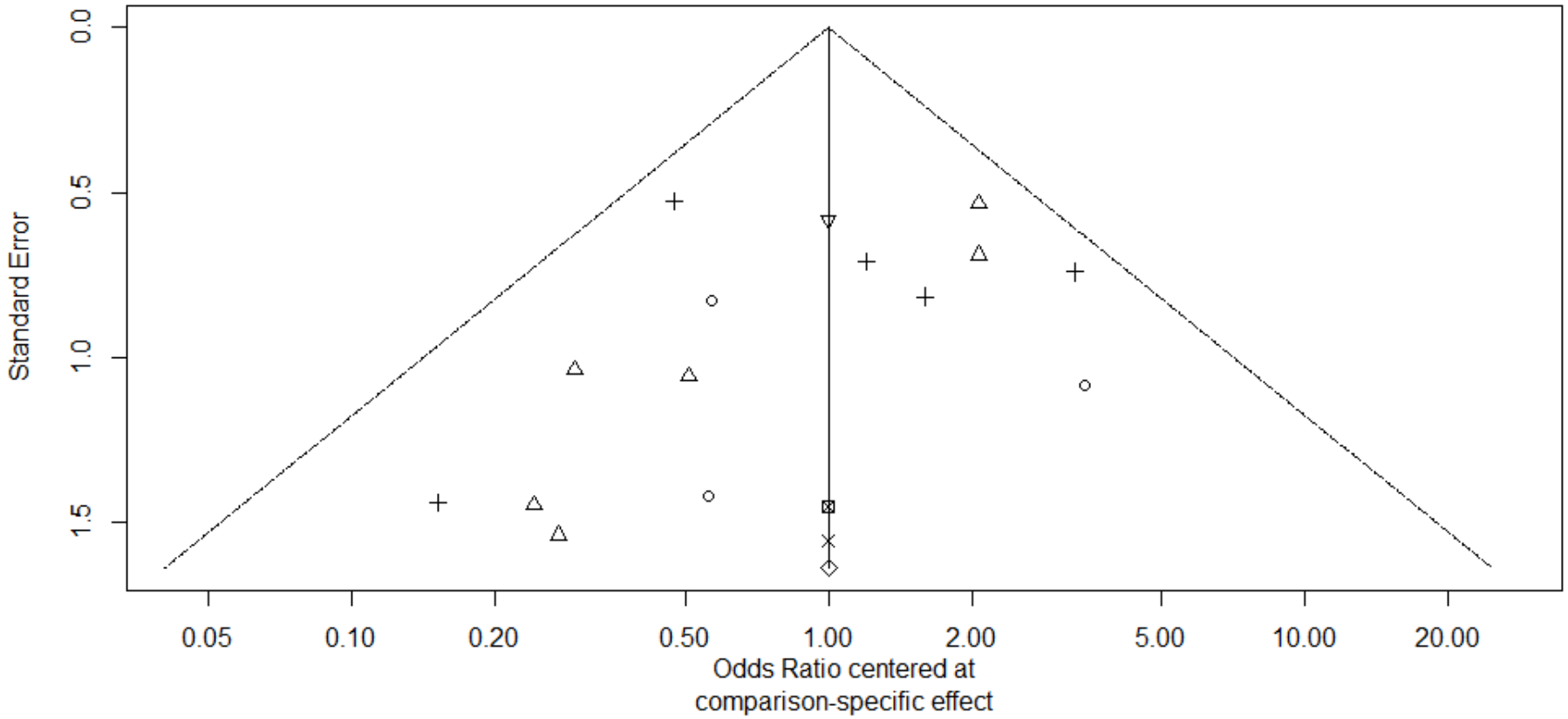
Supplementary Figure S16: Comparison-adjusted funnel plot for sweating



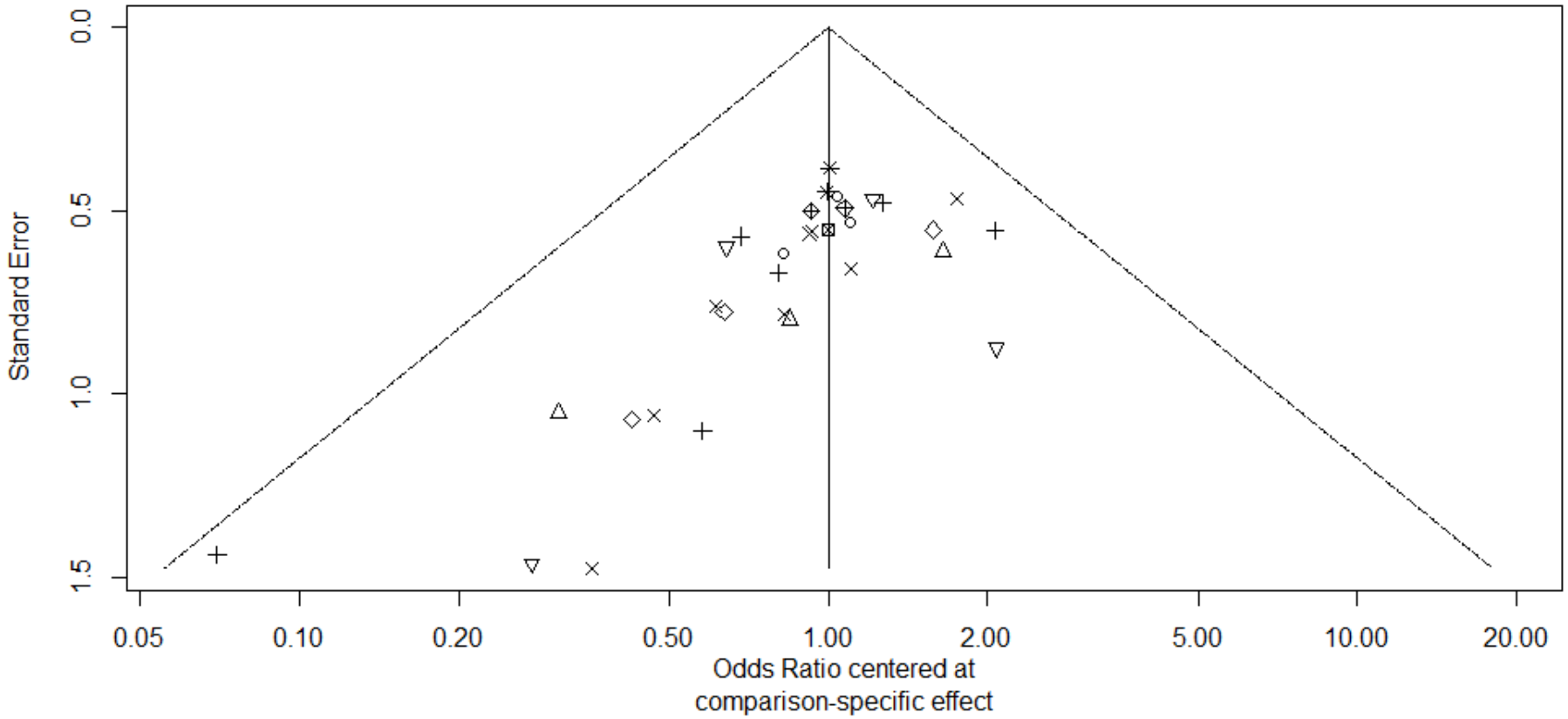
Supplementary Figure S17: Comparison-adjusted funnel plot for ejaculation dysfunction



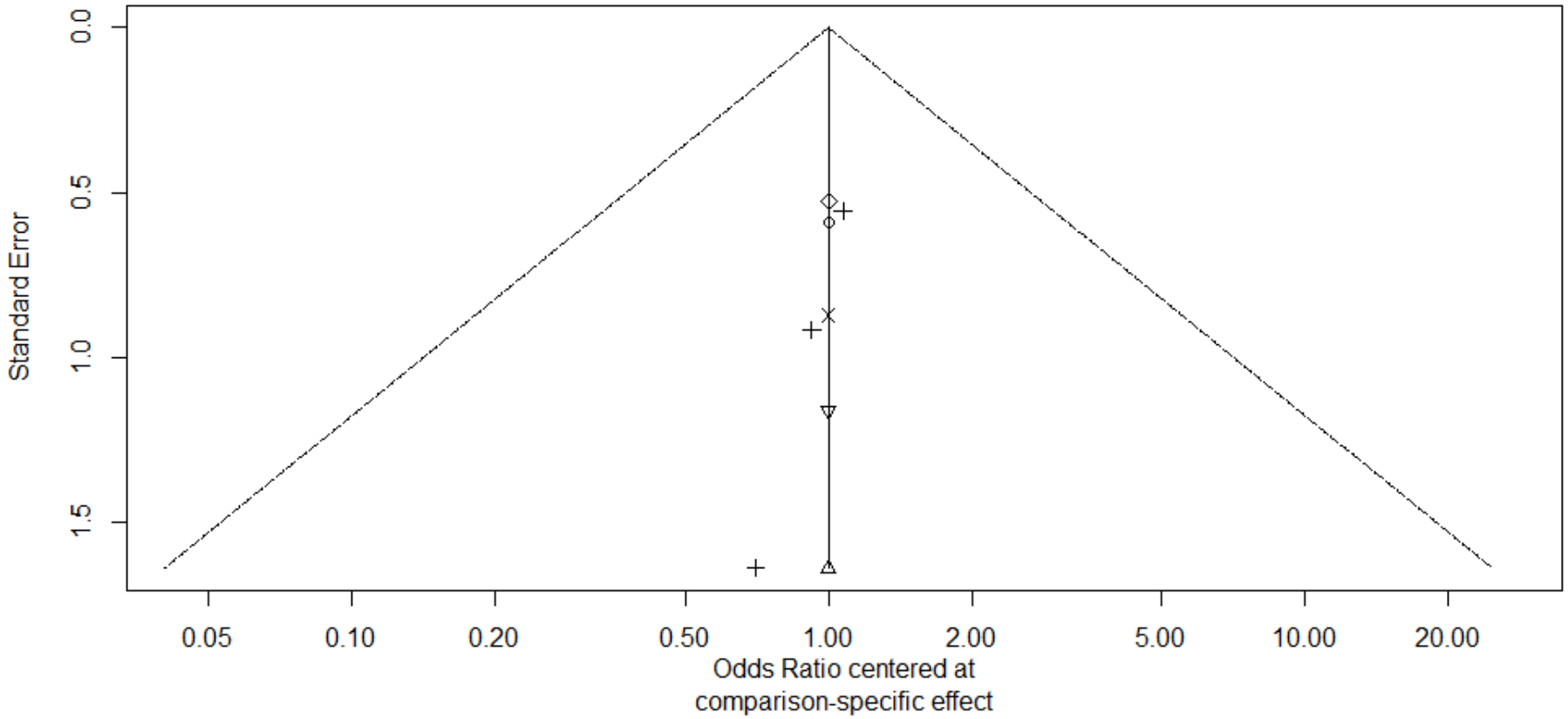
Supplementary Figure S18: Comparison-adjusted funnel plot for erectile dysfunction



Supplementary Figure S19: Comparison-adjusted funnel plot for loss of libido



Supplementary Figure S20: Comparison-adjusted funnel plot for weight change rates



Supplementary Table S6: Evaluation of certainty of evidence using CINeMA framework for overall tolerability

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Placebo	1	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High
Duloxetine:Placebo	4	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Duloxetine:Venlafaxine	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Paroxetine	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Placebo	3	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluoxetine:Placebo	3	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluvoxamine:Placebo	7	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Placebo	10	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Venlafaxine	3	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Placebo:Sertraline	4	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Placebo:Venlafaxine	10	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Citalopram:Duloxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Escitalopram	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Citalopram:Fluvoxamine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Escitalopram	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Duloxetine:Fluoxetine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Duloxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Duloxetine:Paroxetine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Duloxetine:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Escitalopram:Fluoxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluoxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluoxetine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High

Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluvoxamine:Venlafaxine	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Paroxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Sertraline:Venlafaxine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate

Supplementary Table S7: Evaluation of certainty of evidence using CINeMA framework for the aggregate measure of all adverse events

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Escitalopram	7	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Placebo	24	No concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Moderate
Citalopram:Sertraline	6	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Placebo	35	Major concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine:Venlafaxine	14	Major concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
Escitalopram:Paroxetine	26	No concerns	Some concerns	No concerns	No concerns	Major concerns	Some concerns	Low
Escitalopram:Placebo	50	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Low
Fluoxetine:Placebo	29	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low
Fluvoxamine:Placebo	66	Some concerns	Some concerns	No concerns	No concerns	No concerns	Major concerns	Moderate
Paroxetine:Placebo	136	No concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Venlafaxine	28	Major concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Low
Placebo:Sertraline	109	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Moderate
Placebo:Venlafaxine	128	Major concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate

Citalopram:Duloxetine	0	No concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Low
Citalopram:Fluoxetine	0	No concerns	Some concerns	No concerns	Some concerns	Some concerns	Major concerns	Low
Citalopram:Fluvoxamine	0	No concerns	Some concerns	No concerns	Some concerns	Some concerns	Major concerns	Low
Citalopram:Paroxetine	0	No concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Low
Citalopram:Venlafaxine	0	No concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Low
Duloxetine:Escitalopram	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	Major concerns	Low
Duloxetine:Fluoxetine	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	Major concerns	Low
Duloxetine:Fluvoxamine	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low
Duloxetine:Paroxetine	0	Major concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low
Duloxetine:Sertraline	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Low
Escitalopram:Fluoxetine	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	Major concerns	Low
Escitalopram:Fluvoxamine	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	Major concerns	Low
Escitalopram:Sertraline	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	Major concerns	Low
Escitalopram:Venlafaxine	0	No concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Low
Fluoxetine:Fluvoxamine	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low
Fluoxetine:Paroxetine	0	No concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Low
Fluoxetine:Sertraline	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	Major concerns	Very low
Fluoxetine:Venlafaxine	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	Major concerns	High

Fluvoxamine:Paroxetine	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	Major concerns	Very low
Fluvoxamine:Sertraline	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	Major concerns	Very low
Fluvoxamine:Venlafaxine	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low
Paroxetine:Sertraline	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low
Sertraline:Venlafaxine	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low

Supplementary Table S8: Evaluation of certainty of evidence using CINeMA framework for the aggregate measure of autonomic adverse events

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Escitalopram	3	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Placebo	9	No concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Moderate
Citalopram:Sertraline	2	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Placebo	9	Major concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine:Venlafaxine	3	Major concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
Escitalopram:Paroxetine	9	No concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Low
Escitalopram:Placebo	15	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Some concerns	Low
Fluoxetine:Placebo	10	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
Fluvoxamine:Placebo	15	Some concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Low
Paroxetine:Placebo	34	No concerns	Some concerns	No concerns	No concerns	Some concerns	Some concerns	Moderate
Paroxetine:Venlafaxine	7	Major concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
Placebo:Sertraline	34	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Low
Placebo:Venlafaxine	38	Major concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate

Citalopram:Duloxetine	0	No concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Moderate
Citalopram:Fluoxetine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Fluvoxamine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Paroxetine	0	No concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram:Venlafaxine	0	No concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Moderate
Duloxetine:Escitalopram	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Moderate
Duloxetine:Fluoxetine	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Moderate
Duloxetine:Fluvoxamine	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Moderate
Duloxetine:Paroxetine	0	Major concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
Duloxetine:Sertraline	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Low
Escitalopram:Fluoxetine	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Fluvoxamine	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Sertraline	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
Escitalopram:Venlafaxine	0	No concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Moderate
Fluoxetine:Fluvoxamine	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine:Paroxetine	0	No concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Moderate
Fluoxetine:Sertraline	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine:Venlafaxine	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Low

Fluvoxamine:Paroxetine	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Low
Fluvoxamine:Sertraline	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
Fluvoxamine:Venlafaxine	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Moderate
Paroxetine:Sertraline	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
Sertraline:Venlafaxine	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Low

Supplementary Table S9: Evaluation of certainty of evidence using CINeMA framework for the aggregate measure of gastrointestinal adverse events

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Escitalopram	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Placebo	4	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Citalopram:Sertraline	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Placebo	11	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine:Venlafaxine	4	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Escitalopram:Paroxetine	5	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram:Placebo	11	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluoxetine:Placebo	10	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Fluvoxamine:Placebo	19	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Placebo	28	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Venlafaxine	5	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Placebo:Sertraline	34	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Placebo:Venlafaxine	27	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate

Citalopram:Duloxetine	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Fluvoxamine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Duloxetine:Escitalopram	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Duloxetine:Fluoxetine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Duloxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Duloxetine:Paroxetine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Duloxetine:Sertraline	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Escitalopram:Fluoxetine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Moderate
Fluoxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Fluoxetine:Paroxetine	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Fluoxetine:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Fluoxetine:Venlafaxine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High

Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Fluvoxamine:Venlafaxine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Paroxetine:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Sertraline:Venlafaxine	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate

Supplementary Table S10: Evaluation of certainty of evidence using CINeMA framework for the aggregate measure of motor adverse events

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Escitalopram	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Placebo	5	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Citalopram:Sertraline	2	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Duloxetine:Placebo	5	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine:Venlafaxine	3	Major concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Escitalopram:Paroxetine	4	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Placebo	5	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluoxetine:Placebo	3	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Fluvoxamine:Placebo	5	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Placebo	23	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Venlafaxine	5	Major concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Placebo:Sertraline	10	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Placebo:Venlafaxine	18	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Citalopram:Duloxetine	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High

Citalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram:Paroxetine	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Duloxetine:Escitalopram	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Duloxetine:Fluoxetine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Duloxetine:Paroxetine	0	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Escitalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Fluoxetine:Fluvoxamine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Paroxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Sertraline:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Supplementary Table S11: Evaluation of certainty of evidence using CINeMA framework for the aggregate measure of sexual adverse events

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Placebo	1	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Placebo	3	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine:Venlafaxine	1	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Paroxetine	4	No concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram:Placebo	8	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Fluoxetine:Placebo	1	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Placebo	11	Some concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Low
Paroxetine:Placebo	24	No concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Venlafaxine	5	Major concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Low
Placebo:Sertraline	9	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Placebo:Venlafaxine	19	Major concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Citalopram:Duloxetine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Escitalopram	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate

Citalopram:Fluoxetine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Fluvoxamine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Paroxetine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Sertraline	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Venlafaxine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Escitalopram	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Fluoxetine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Fluvoxamine	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
Duloxetine:Paroxetine	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Sertraline	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Fluoxetine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Fluvoxamine	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Low
Escitalopram:Sertraline	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Venlafaxine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Fluvoxamine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Paroxetine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Sertraline	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Venlafaxine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate

Fluvoxamine:Paroxetine	0	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Fluvoxamine:Sertraline	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Moderate
Fluvoxamine:Venlafaxine	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Low
Paroxetine:Sertraline	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Sertraline:Venlafaxine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate

Supplementary Table S12: Evaluation of certainty of evidence using CINeMA framework for the aggregate measure of sleep related adverse events

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Escitalopram	2	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Citalopram:Placebo	5	No concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	High
Citalopram:Sertraline	1	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
Duloxetine:Placebo	7	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Low
Duloxetine:Venlafaxine	3	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram:Paroxetine	4	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Escitalopram:Placebo	10	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluoxetine:Placebo	5	Some concerns	Low risk	No concerns	Some concerns	No concerns	Major concerns	Low
Fluvoxamine:Placebo	15	Some concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	Moderate
Paroxetine:Placebo	24	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Venlafaxine	5	Major concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Placebo:Sertraline	21	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Placebo:Venlafaxine	25	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Citalopram:Duloxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low

Citalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low
Citalopram:Fluvoxamine	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Low
Citalopram:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low
Citalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low
Duloxetine:Escitalopram	0	Some concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	Moderate
Duloxetine:Fluoxetine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Major concerns	Low
Duloxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low
Duloxetine:Paroxetine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Major concerns	Low
Duloxetine:Sertraline	0	Some concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	Moderate
Escitalopram:Fluoxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	Moderate
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low
Escitalopram:Venlafaxine	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	Major concerns	Moderate
Fluoxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Major concerns	Moderate
Fluoxetine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low
Fluoxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low
Fluoxetine:Venlafaxine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Low
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	Major concerns	Low

Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	High
Fluvoxamine:Venlafaxine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Low
Paroxetine:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Major concerns	Low
Sertraline:Venlafaxine	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	Major concerns	Low

Supplementary Table S13: Evaluation of certainty of evidence using CINeMA framework for agitation

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Escitalopram:Paroxetine	1	No concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Low
Fluoxetine:Placebo	1	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Very low
Fluvoxamine:Placebo	3	Major concerns	Some concerns	No concerns	No concerns	No concerns	Major concerns	Low
Paroxetine:Placebo	3	Some concerns	Some concerns	No concerns	Some concerns	No concerns	Major concerns	Low
Placebo:Sertraline	4	Some concerns	Some concerns	No concerns	No concerns	No concerns	Major concerns	Low
Placebo:Venlafaxine	3	Major concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Very low
Escitalopram:Fluoxetine	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	High
Escitalopram:Fluvoxamine	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	High
Escitalopram:Placebo	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	High
Escitalopram:Sertraline	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	High
Escitalopram:Venlafaxine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	High
Fluoxetine:Fluvoxamine	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	High
Fluoxetine:Paroxetine	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	High

Fluoxetine:Sertraline	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	High
Fluoxetine:Venlafaxine	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	High
Fluvoxamine:Paroxetine	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	Major concerns	High
Fluvoxamine:Sertraline	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	High
Fluvoxamine:Venlafaxine	0	Major concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	High
Paroxetine:Sertraline	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	Major concerns	High
Paroxetine:Venlafaxine	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	High
Sertraline:Venlafaxine	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	High

Supplementary Table S14: Evaluation of certainty of evidence using CINeMA framework for asthenia

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Escitalopram	1	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram:Placebo	3	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Citalopram:Sertraline	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Placebo	4	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Duloxetine:Venlafaxine	2	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Escitalopram:Paroxetine	2	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Placebo	3	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluoxetine:Placebo	2	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Placebo	5	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Placebo	13	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Venlafaxine	2	Major concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Placebo:Sertraline	6	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Placebo:Venlafaxine	9	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Citalopram:Duloxetine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High

Citalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Citalopram:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Duloxetine:Escitalopram	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Duloxetine:Fluoxetine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Duloxetine:Paroxetine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Duloxetine:Sertraline	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Escitalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate

Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluvoxamine:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Paroxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Sertraline:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Supplementary Table S15: Evaluation of certainty of evidence using CINeMA framework for constipation

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Duloxetine:Placebo	4	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Duloxetine:Venlafaxine	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Paroxetine	1	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Escitalopram:Placebo	2	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluoxetine:Placebo	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Placebo	4	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Paroxetine:Placebo	9	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Venlafaxine	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Placebo:Sertraline	3	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Placebo:Venlafaxine	10	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Duloxetine:Escitalopram	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Duloxetine:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Duloxetine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Duloxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluoxetine:Fluvoxamine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Venlafaxine	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Sertraline:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Supplementary Table S16: Evaluation of certainty of evidence using CINeMA framework for diarrhea

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Placebo	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Placebo	2	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Paroxetine	2	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Placebo	3	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluoxetine:Placebo	3	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High
Fluvoxamine:Placebo	5	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Placebo	5	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Venlafaxine	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Placebo:Sertraline	11	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Placebo:Venlafaxine	3	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Duloxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Escitalopram	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Fluvoxamine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Citalopram:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Escitalopram	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Fluoxetine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Fluvoxamine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Paroxetine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Sertraline	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Venlafaxine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Fluoxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Venlafaxine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate

Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Venlafaxine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Paroxetine:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Sertraline:Venlafaxine	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate

Supplementary Table S17: Evaluation of certainty of evidence using CINeMA framework for dizziness

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Escitalopram	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Placebo	3	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Sertraline	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Placebo	3	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Escitalopram:Paroxetine	2	No concerns	Low risk	No concerns	Some concerns	No concerns	Major concerns	Moderate
Escitalopram:Placebo	4	Some concerns	Low risk	No concerns	Some concerns	No concerns	Major concerns	Low
Fluoxetine:Placebo	2	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Placebo	3	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Placebo	6	No concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	Moderate
Paroxetine:Venlafaxine	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Placebo:Sertraline	5	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Placebo:Venlafaxine	9	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Citalopram:Duloxetine	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Citalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Citalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Citalopram:Paroxetine	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Citalopram:Venlafaxine	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High
Duloxetine:Escitalopram	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Duloxetine:Fluoxetine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Paroxetine	0	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Duloxetine:Sertraline	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Duloxetine:Venlafaxine	0	Major concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Escitalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Fluoxetine:Fluvoxamine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Paroxetine:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Sertraline:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Supplementary Table S18: Evaluation of certainty of evidence using CINeMA framework for dry mouth

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Escitalopram	1	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram:Placebo	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Duloxetine:Placebo	4	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine:Venlafaxine	2	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Paroxetine	2	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Placebo	3	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluoxetine:Placebo	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Placebo	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Paroxetine:Placebo	11	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Venlafaxine	3	Major concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Low
Placebo:Sertraline	12	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High
Placebo:Venlafaxine	12	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Moderate
Citalopram:Duloxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Citalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Citalopram:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Sertraline	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Citalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Escitalopram	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Duloxetine:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Duloxetine:Paroxetine	0	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Duloxetine:Sertraline	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High
Escitalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluoxetine:Fluvoxamine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Venlafaxine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Paroxetine:Sertraline	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Sertraline:Venlafaxine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High

Supplementary Table S19: Evaluation of certainty of evidence using CINeMA framework for dyspepsia

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Duloxetine:Placebo	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
Fluvoxamine:Placebo	2	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Low
Paroxetine:Placebo	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low
Placebo:Sertraline	3	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Low
Duloxetine:Fluvoxamine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
Duloxetine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low
Duloxetine:Sertraline	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low
Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low
Paroxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low

Supplementary Table S20: Evaluation of certainty of evidence using CINeMA framework for ejaculation dysfunction

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Placebo	1	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Paroxetine	1	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Placebo	4	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Fluvoxamine:Placebo	5	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Paroxetine:Placebo	11	No concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Venlafaxine	2	Major concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Placebo:Sertraline	5	No concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	High
Placebo:Venlafaxine	7	Major concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Citalopram:Escitalopram	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Fluvoxamine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Paroxetine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Sertraline	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Venlafaxine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate

Escitalopram:Fluvoxamine	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Sertraline	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	Major concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Fluvoxamine:Paroxetine	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
Fluvoxamine:Sertraline	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Fluvoxamine:Venlafaxine	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine:Sertraline	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Sertraline:Venlafaxine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate

Supplementary Table S21: Evaluation of certainty of evidence using CINeMA framework for headache

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Escitalopram	1	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram:Placebo	2	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High
Duloxetine:Placebo	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Paroxetine	2	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Escitalopram:Placebo	6	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluoxetine:Placebo	5	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Placebo	7	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Paroxetine:Placebo	4	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Placebo:Sertraline	9	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Placebo:Venlafaxine	5	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Citalopram:Duloxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Fluvoxamine	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Citalopram:Paroxetine	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High

Citalopram:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Escitalopram	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Fluoxetine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Fluvoxamine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Paroxetine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Sertraline	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Venlafaxine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Fluoxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Fluvoxamine:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Paroxetine:Sertraline	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Paroxetine:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Sertraline:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Supplementary Table S22: Evaluation of certainty of evidence using CINeMA framework for erectile dysfunction

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Escitalopram:Paroxetine	1	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High
Escitalopram:Placebo	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Placebo	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Placebo	3	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Paroxetine:Placebo	5	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Venlafaxine	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Placebo:Sertraline	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Placebo:Venlafaxine	6	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Escitalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Fluvoxamine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High
Fluoxetine:Fluvoxamine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Fluoxetine:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluvoxamine:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Venlafaxine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Sertraline:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Supplementary Table S23: Evaluation of certainty of evidence using CINeMA framework for insomnia

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Escitalopram	1	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram:Placebo	3	No concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	High
Citalopram:Sertraline	1	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Moderate
Duloxetine:Placebo	3	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Duloxetine:Venlafaxine	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Paroxetine	2	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram:Placebo	4	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
Fluoxetine:Placebo	4	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Moderate
Fluvoxamine:Placebo	8	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Moderate
Paroxetine:Placebo	10	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Venlafaxine	2	Major concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Placebo:Sertraline	13	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Placebo:Venlafaxine	13	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Citalopram:Duloxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Moderate

Citalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Moderate
Citalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
Citalopram:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Moderate
Citalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Moderate
Duloxetine:Escitalopram	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Low
Duloxetine:Fluoxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
Duloxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
Duloxetine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
Duloxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
Escitalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Moderate
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Moderate
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Low
Escitalopram:Venlafaxine	0	No concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	High
Fluoxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Low
Fluoxetine:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Moderate
Fluoxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
Fluoxetine:Venlafaxine	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Moderate

Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Moderate
Fluvoxamine:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
Paroxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
Sertraline:Venlafaxine	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Moderate

Supplementary Table S24: Evaluation of certainty of evidence using CINeMA framework for loss of libido

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Duloxetine:Placebo	3	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	High
Duloxetine:Venlafaxine	1	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Paroxetine	2	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Placebo	3	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Fluvoxamine:Placebo	3	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Paroxetine:Placebo	8	Major concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Paroxetine:Venlafaxine	2	Major concerns	Some concerns	No concerns	Some concerns	No concerns	No concerns	Low
Placebo:Sertraline	3	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Placebo:Venlafaxine	6	Major concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine:Escitalopram	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Fluvoxamine	0	Some concerns	Some concerns	No concerns	Some concerns	No concerns	No concerns	Moderate
Duloxetine:Paroxetine	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Sertraline	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low

Escitalopram:Fluvoxamine	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
Escitalopram:Sertraline	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Venlafaxine	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	High
Fluvoxamine:Paroxetine	0	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Fluvoxamine:Sertraline	0	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Fluvoxamine:Venlafaxine	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine:Sertraline	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Sertraline:Venlafaxine	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low

Supplementary Table S25: Evaluation of certainty of evidence using CINeMA framework for nausea

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Escitalopram	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Placebo	3	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Citalopram:Sertraline	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Placebo	4	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine:Venlafaxine	2	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Escitalopram:Paroxetine	2	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram:Placebo	6	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluoxetine:Placebo	6	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Placebo	8	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Placebo	13	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Venlafaxine	2	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Placebo:Sertraline	17	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Placebo:Venlafaxine	14	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Citalopram:Duloxetine	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High

Citalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Duloxetine:Escitalopram	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Duloxetine:Fluoxetine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Duloxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Duloxetine:Paroxetine	0	Major concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Duloxetine:Sertraline	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Escitalopram:Fluoxetine	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Fluoxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluoxetine:Paroxetine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluoxetine:Sertraline	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Fluoxetine:Venlafaxine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate

Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Fluvoxamine:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Paroxetine:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Sertraline:Venlafaxine	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate

Supplementary Table S26: Evaluation of certainty of evidence using CINeMA framework for somnolence

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Escitalopram	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Placebo	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Duloxetine:Placebo	4	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine:Venlafaxine	2	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Escitalopram:Paroxetine	2	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Escitalopram:Placebo	6	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluoxetine:Placebo	1	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Fluvoxamine:Placebo	7	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Placebo	14	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Paroxetine:Venlafaxine	3	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Placebo:Sertraline	8	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Placebo:Venlafaxine	12	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Citalopram:Duloxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Fluoxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Citalopram:Fluvoxamine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Escitalopram	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Duloxetine:Fluoxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	High
Duloxetine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	High
Duloxetine:Sertraline	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Escitalopram:Fluoxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluoxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate

Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluvoxamine:Venlafaxine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Paroxetine:Sertraline	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Sertraline:Venlafaxine	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High

Supplementary Table S27: Evaluation of certainty of evidence using CINeMA framework for sweating

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Placebo	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Citalopram:Sertraline	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Placebo	1	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine:Venlafaxine	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Paroxetine	2	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram:Placebo	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluoxetine:Placebo	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Paroxetine:Placebo	10	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Paroxetine:Venlafaxine	3	Major concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Placebo:Sertraline	4	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Placebo:Venlafaxine	9	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Citalopram:Duloxetine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram:Escitalopram	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Citalopram:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Escitalopram	0	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Duloxetine:Fluoxetine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Paroxetine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Sertraline	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Fluoxetine:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Paroxetine:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Sertraline:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Supplementary Table S28: Evaluation of certainty of evidence using CINeMA framework for tremor

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Placebo	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Citalopram:Sertraline	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Placebo	1	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine:Venlafaxine	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Paroxetine	2	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram:Placebo	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Fluoxetine:Placebo	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Paroxetine:Placebo	10	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Paroxetine:Venlafaxine	3	Major concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Placebo:Sertraline	4	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Placebo:Venlafaxine	9	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Citalopram:Duloxetine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram:Escitalopram	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Citalopram:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Escitalopram	0	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Duloxetine:Fluoxetine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Paroxetine	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine:Sertraline	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Fluoxetine:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Paroxetine:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Sertraline:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Supplementary Table S29: Evaluation of certainty of evidence using CINeMA framework for weight change

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Escitalopram:Placebo	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Placebo	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Paroxetine:Placebo	3	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Paroxetine:Venlafaxine	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Placebo:Sertraline	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Placebo:Venlafaxine	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Paroxetine:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate

Sertraline:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

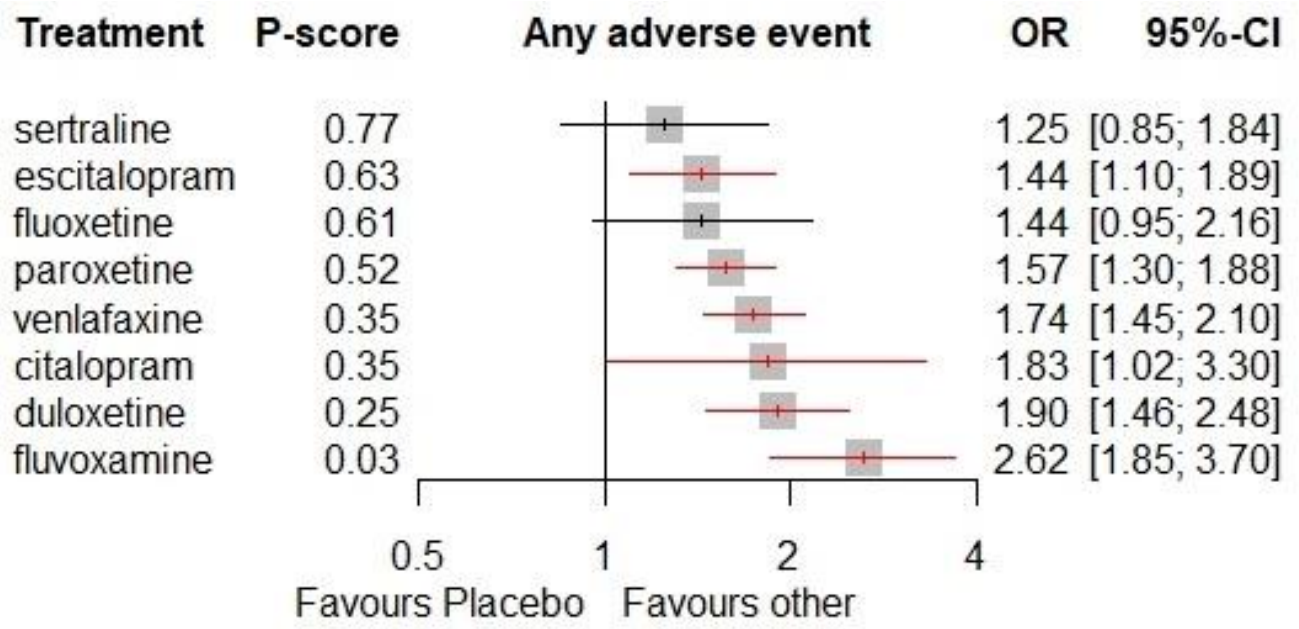
Supplementary Table S30: Evaluation of certainty of evidence using CINeMA framework for suicidal ideation

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Escitalopram	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Placebo	3	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Sertraline	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Placebo	4	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Venlafaxine	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Paroxetine	2	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Placebo	6	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Placebo	6	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Placebo	10	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Paroxetine:Placebo	18	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Paroxetine:Venlafaxine	4	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Placebo:Sertraline	17	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Placebo:Venlafaxine	17	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Duloxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Citalopram:Fluoxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:Venlafaxine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Escitalopram	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Fluoxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Fluvoxamine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Paroxetine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine:Sertraline	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Fluoxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

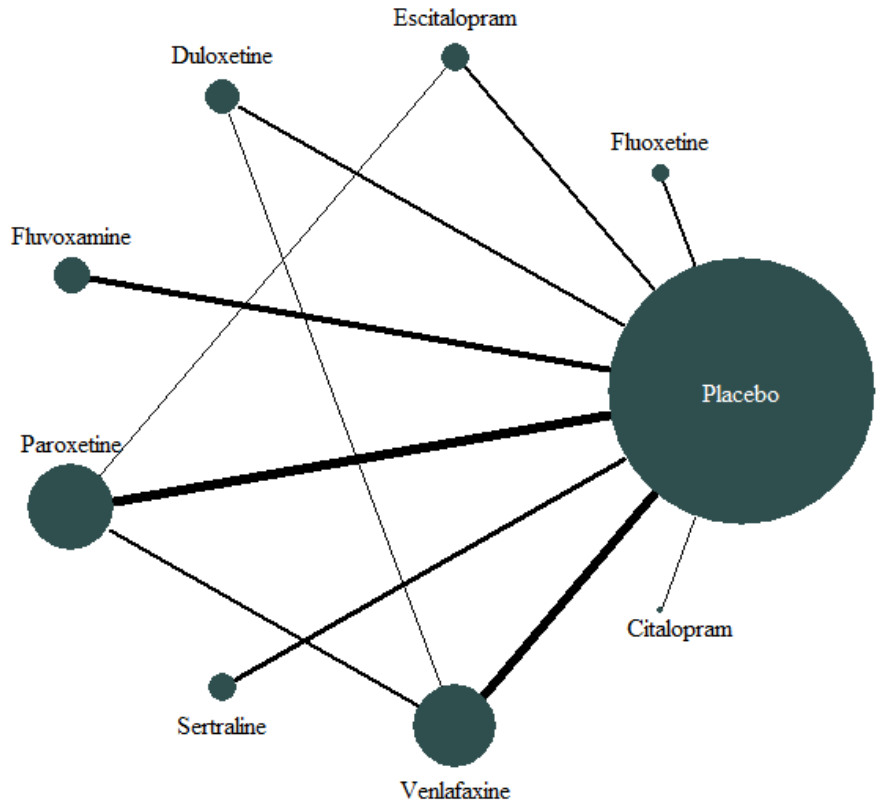
Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluvoxamine:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Paroxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate
Sertraline:Venlafaxine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate

Supplementary Figure S21. Forest plot of network meta-analysis for overall tolerability



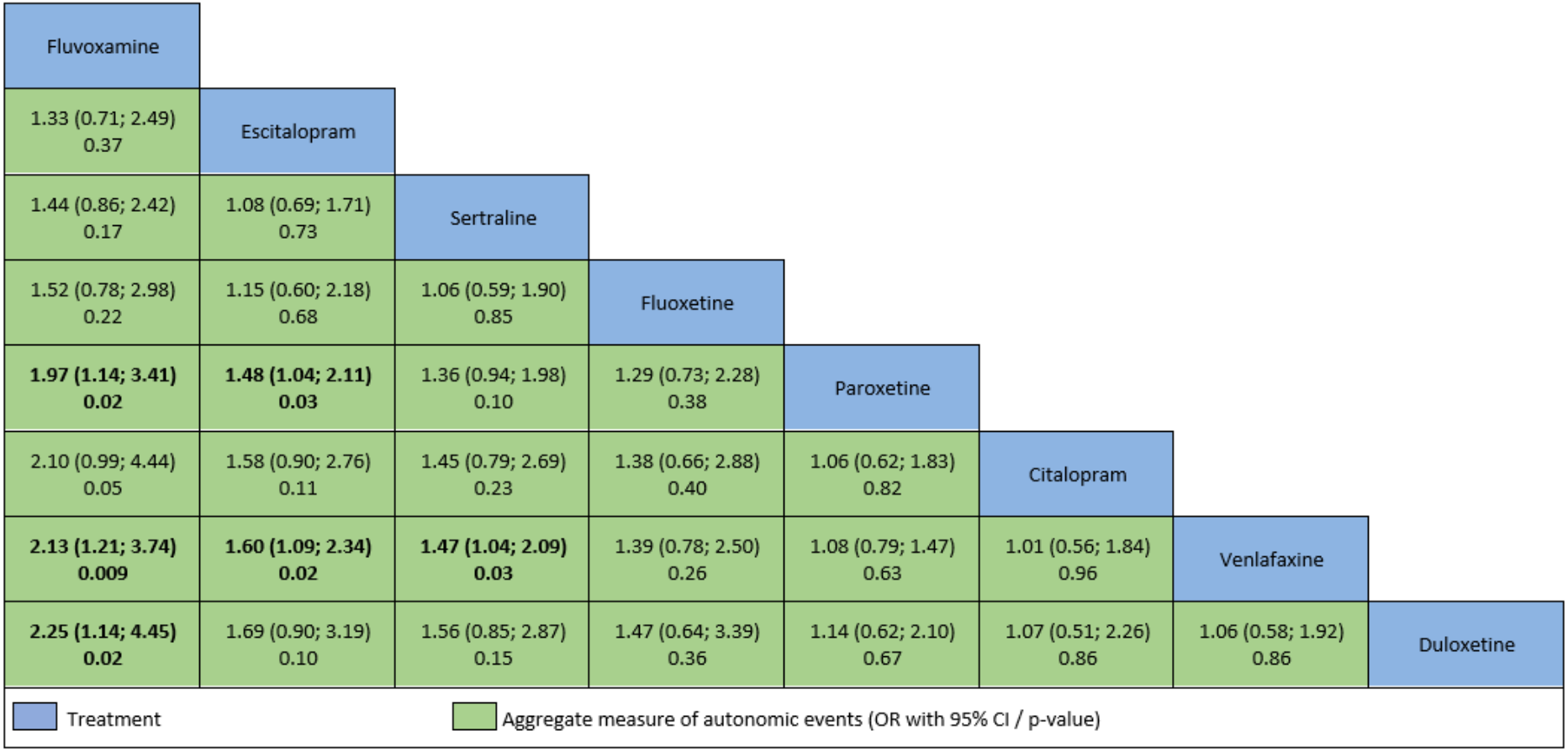
Legend: OR, odds ratio; CI, Confidence Interval. Medications are ordered from best to worst according to treatment rankings based on P-scores. Antidepressants were compared to placebo, which was the reference intervention.

Supplementary Figure S22: Network meta-analysis of available comparisons



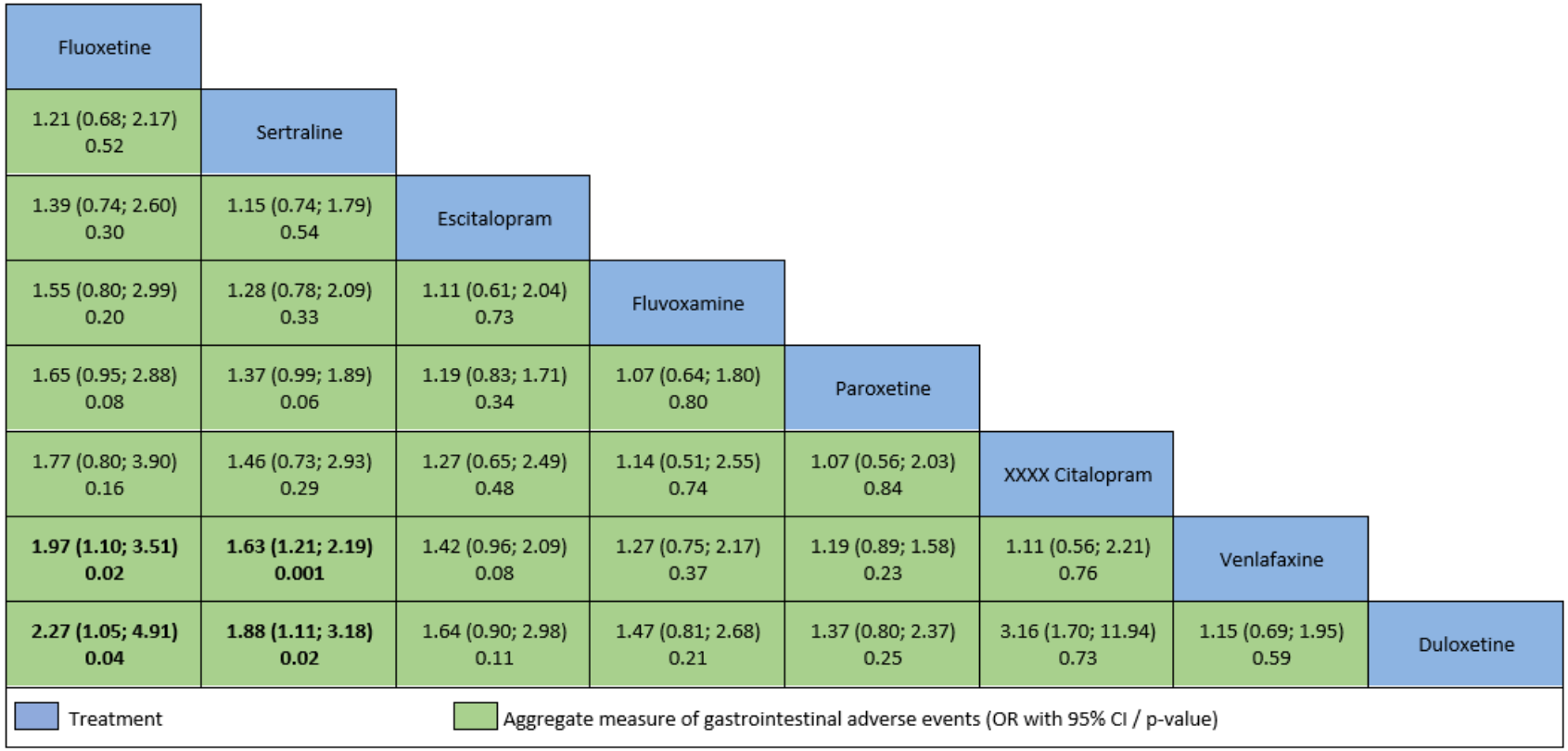
Legend: Line width is proportional to the number of trials including every pair of treatments (direct comparisons). Circle size is proportional to the total number of participants randomly assigned for each treatment in the network

Supplementary Figure S23: Comparisons of all SSRIs and SNRIs for the aggregate measure of autonomic adverse events in the multiple meta-regression model



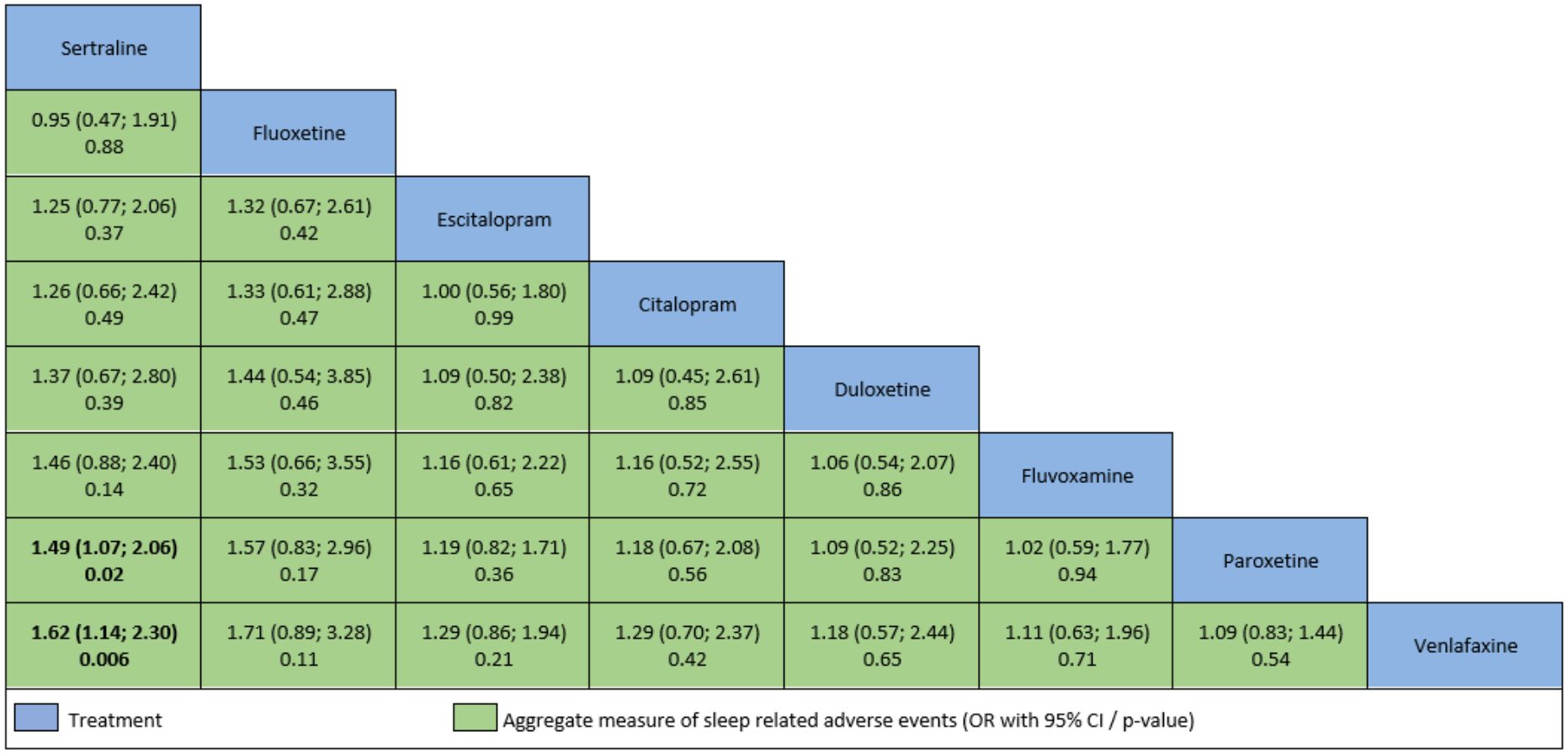
Legend: SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; OR, odds ratio; CI, Confidence Interval. Medications are ordered from best to worst according to treatment rankings based on P-scores. Comparisons between treatments should be read from left 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.

Supplementary Figure S24: Comparisons of all SSRIs and SNRIs for the aggregate measure of gastrointestinal adverse events in the multiple meta-regression model



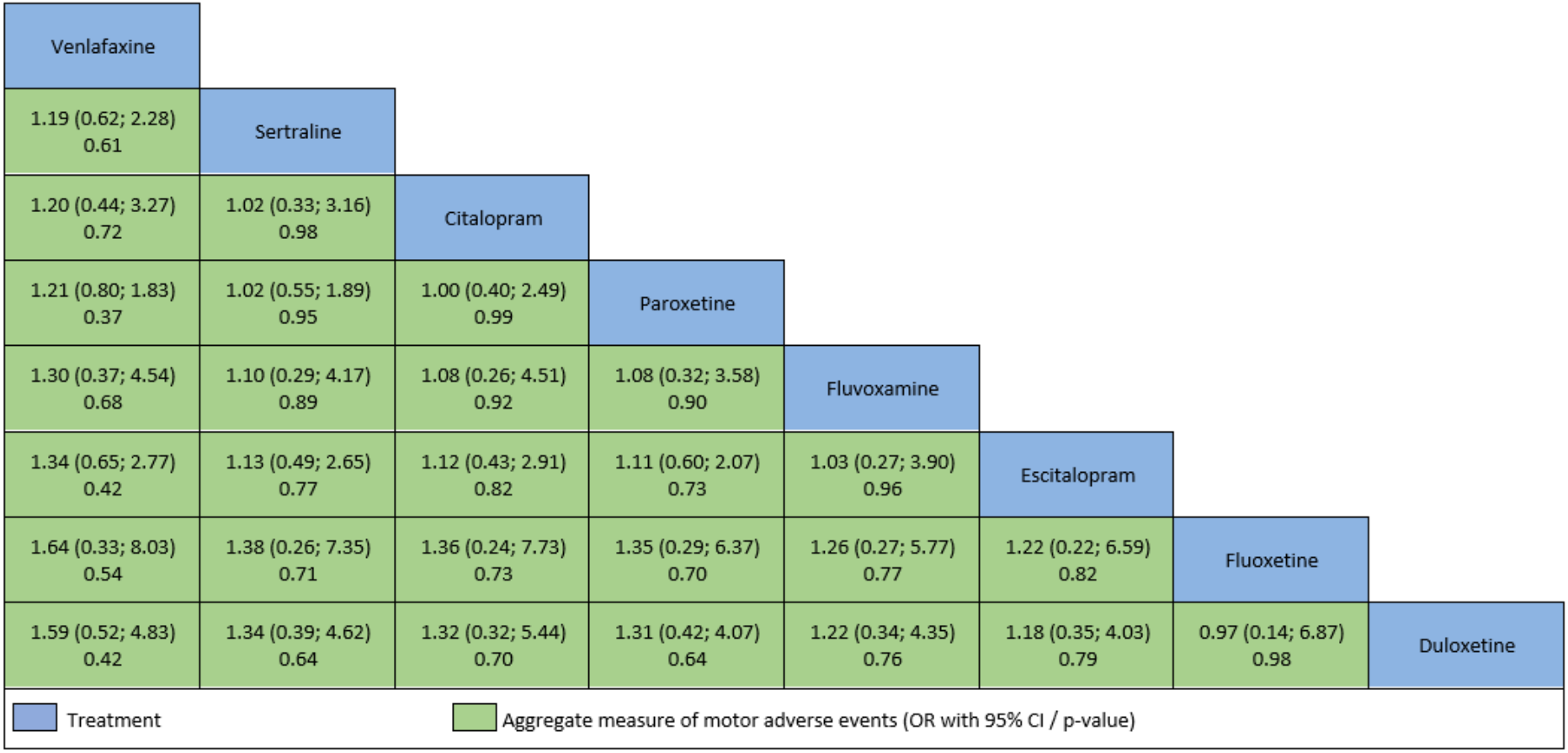
Legend: SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; OR, odds ratio; CI, Confidence Interval. Medications are ordered from best to worst according to treatment rankings based on P-scores. Comparisons between treatments should be read from left 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.

Supplementary Figure S25: Comparisons of all SSRIs and SNRIs for the aggregate measure of sleep related adverse events in the multiple meta-regression model



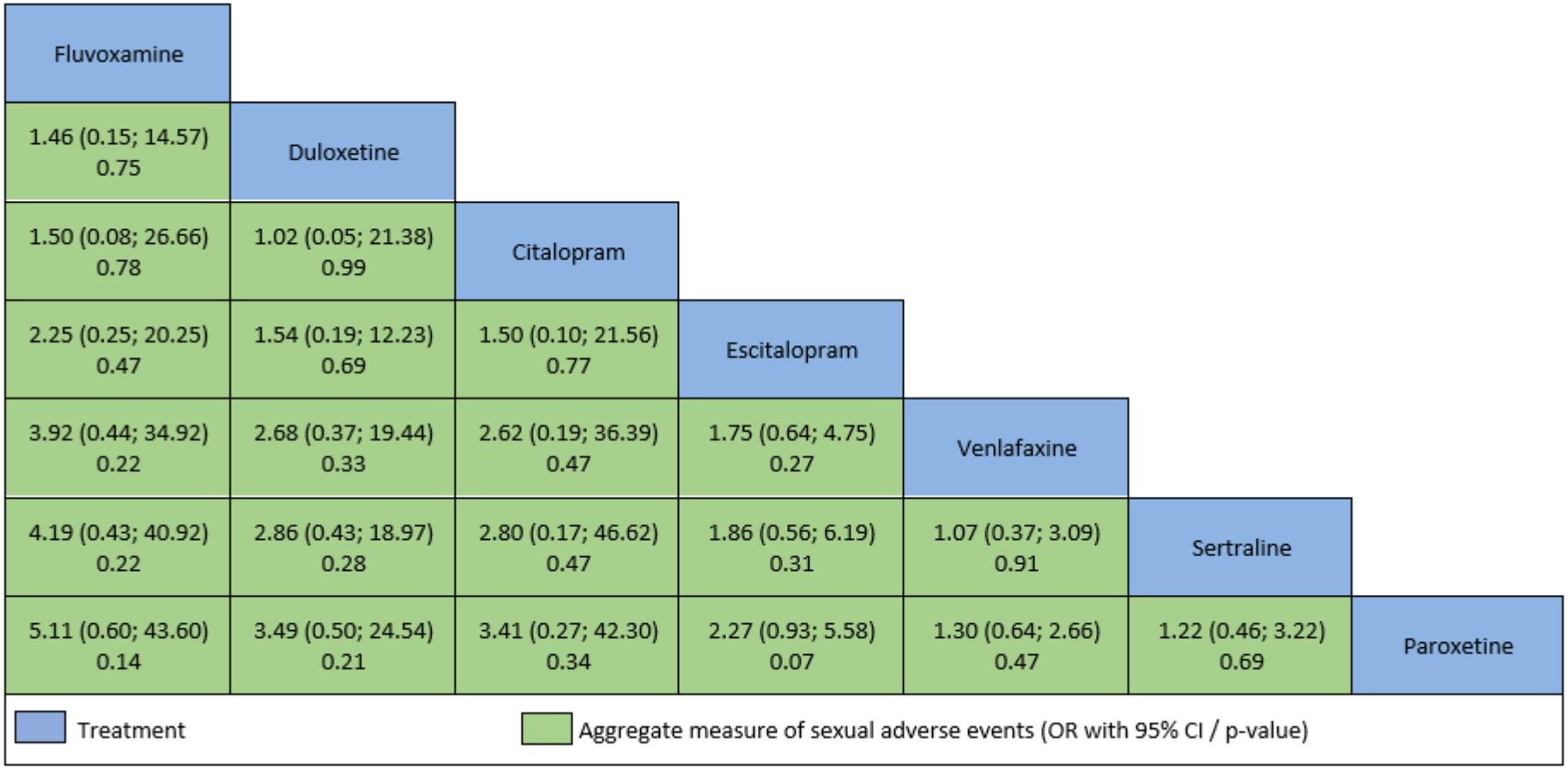
Legend: SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; OR, odds ratio; CI, Confidence Interval. Medications are ordered from best to worst according to treatment rankings based on P-scores. Comparisons between treatments should be read from left 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.

Supplementary Figure S26: Comparisons of all SSRIs and SNRIs for the aggregate measure of motor adverse events in the multiple meta-regression model



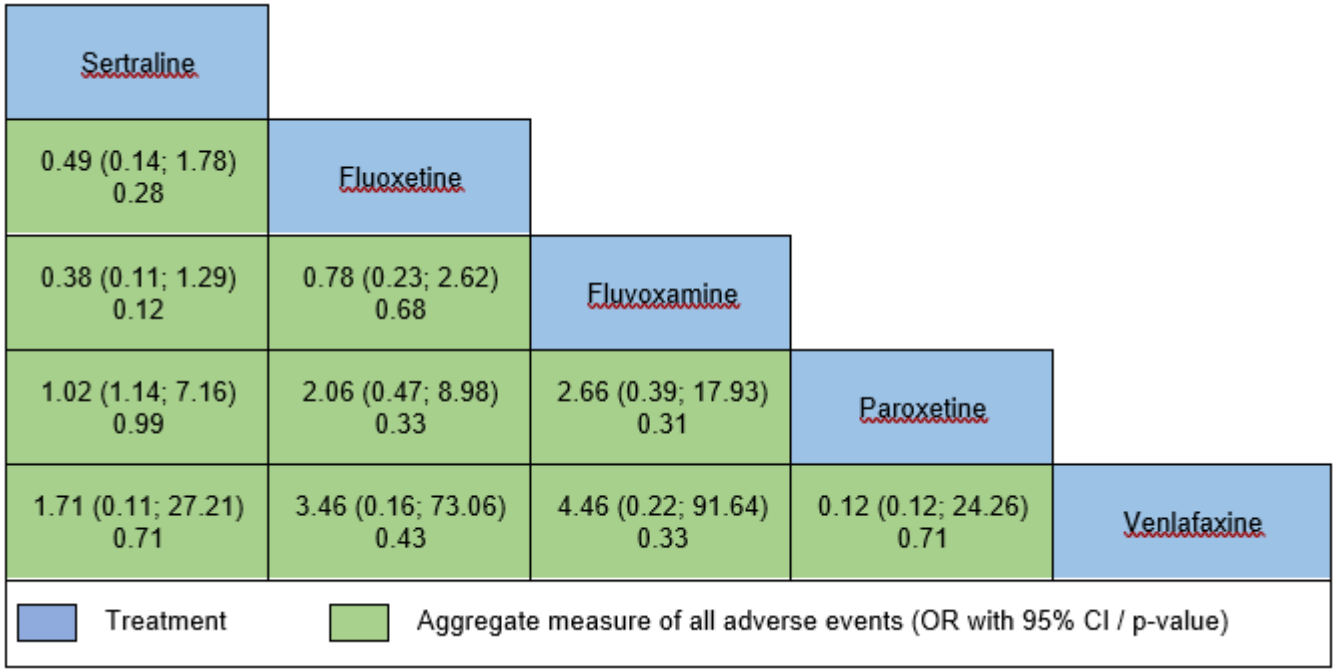
Legend: SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; OR, odds ratio; CI, Confidence Interval. Medications are ordered from best to worst according to treatment rankings based on P-scores. Comparisons between treatments should be read from left 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.

Supplementary Figure S27: Comparisons of all SSRIs and SNRIs for the aggregate measure of sexual adverse events in the multiple meta-regression model



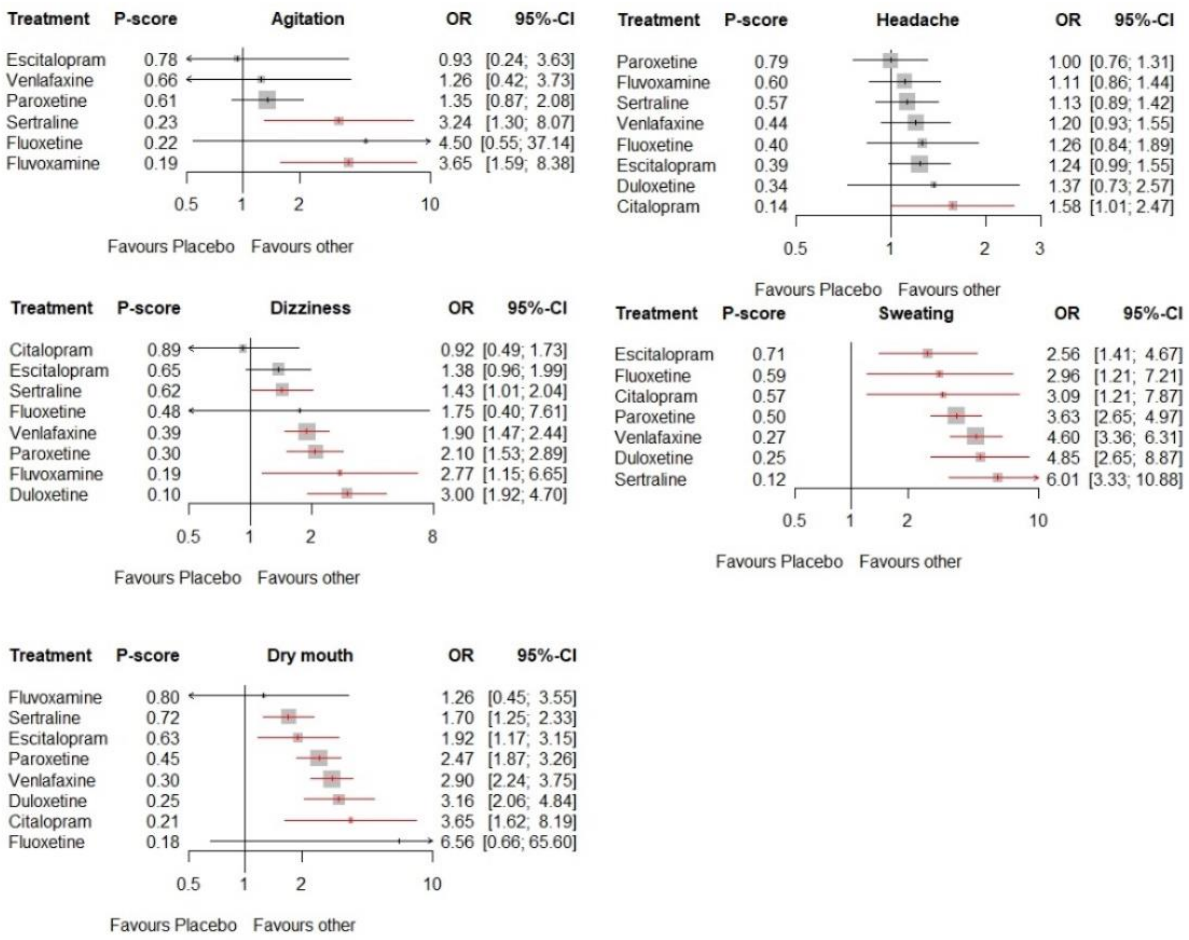
Legend: SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; OR, odds ratio; CI, Confidence Interval. Medications are ordered from best to worst according to treatment rankings based on P-scores. Comparisons between treatments should be read from left 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.

Supplementary Figure S28. Comparisons of SSRIs and SNRIs for the aggregate measure of all adverse events in children and adolescents using the multiple meta-regression model



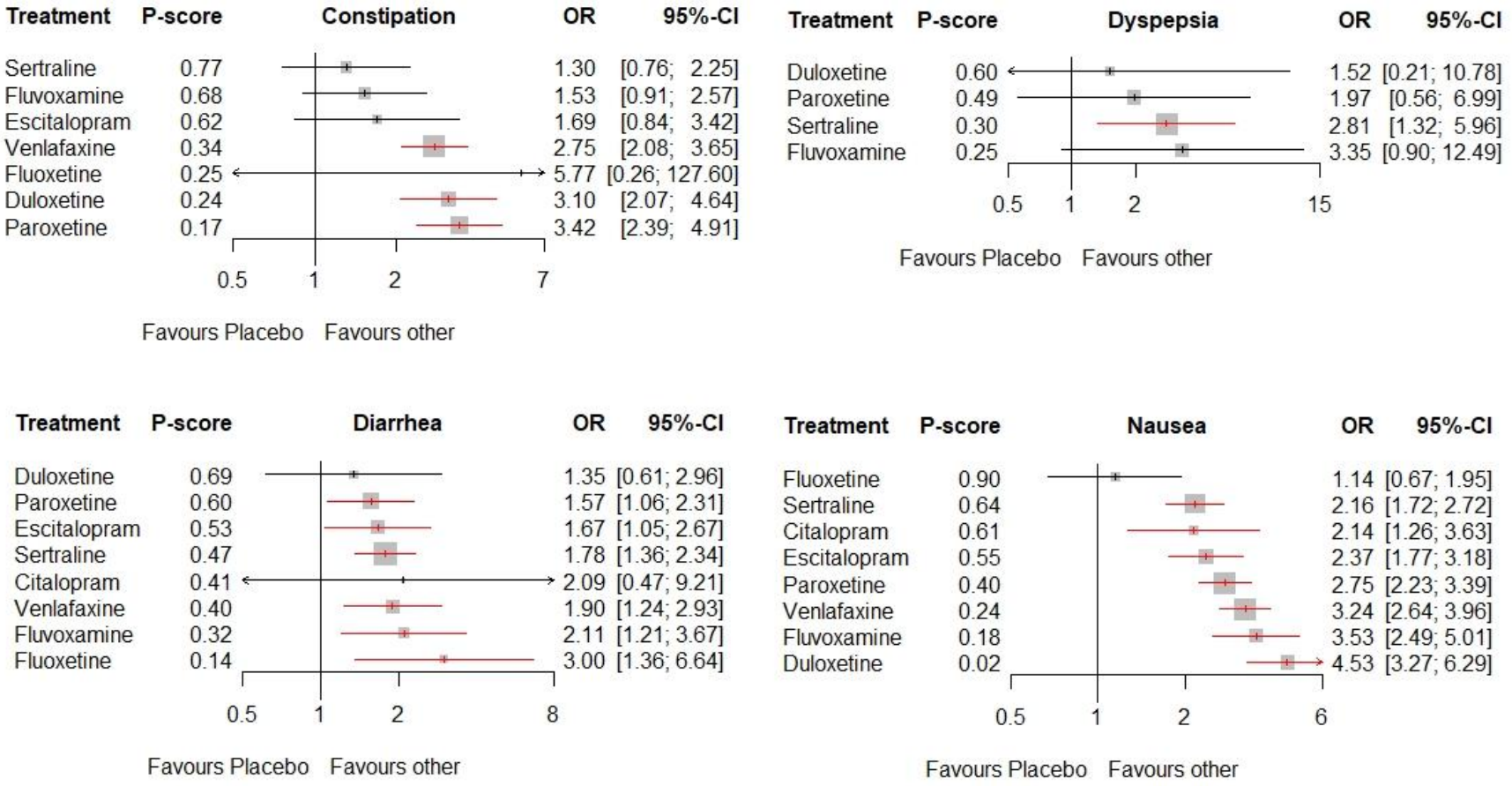
Legend: SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; OR, odds ratio; CI, Confidence Interval. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. ORs above 1 indicate better tolerability for the column-defining treatment. Significant results are in bold.

Supplementary Figure S28: Forest plots of network meta-analysis for autonomic adverse events



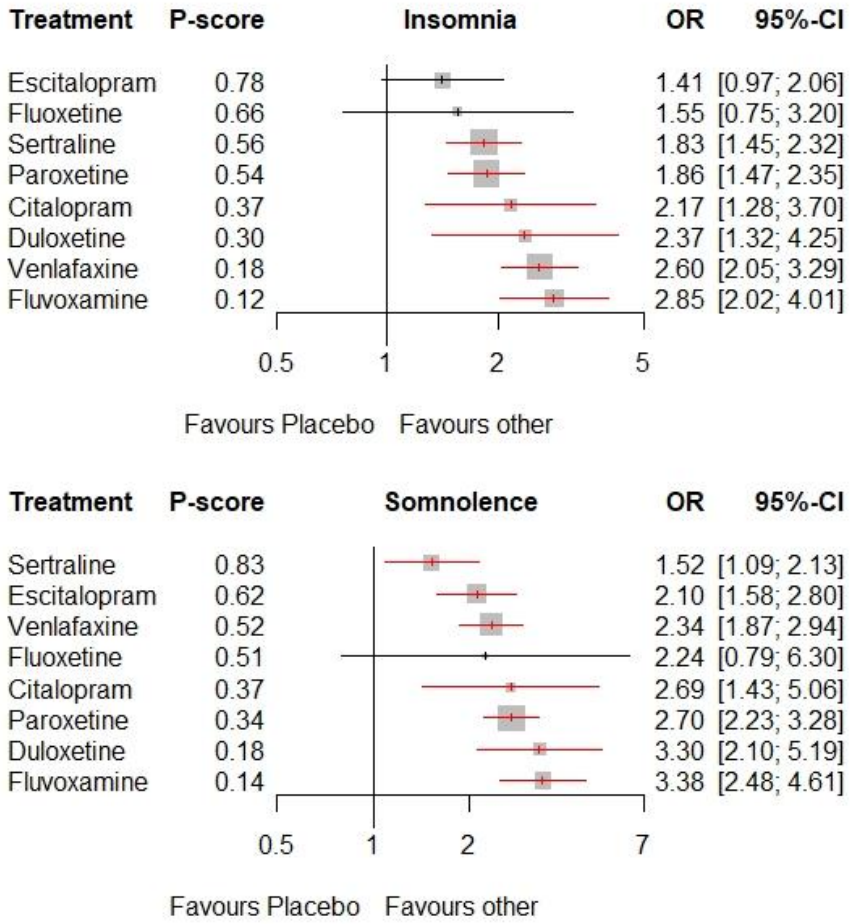
Legend: OR, odds ratio; CI, Confidence Interval. Medications are ordered from best to worst according to treatment rankings based on P-scores. Antidepressants were compared to placebo, which was the reference intervention. Significant differences are highlighted in red.

Supplementary Figure S29: Forest plots of network meta-analysis for gastrointestinal adverse events



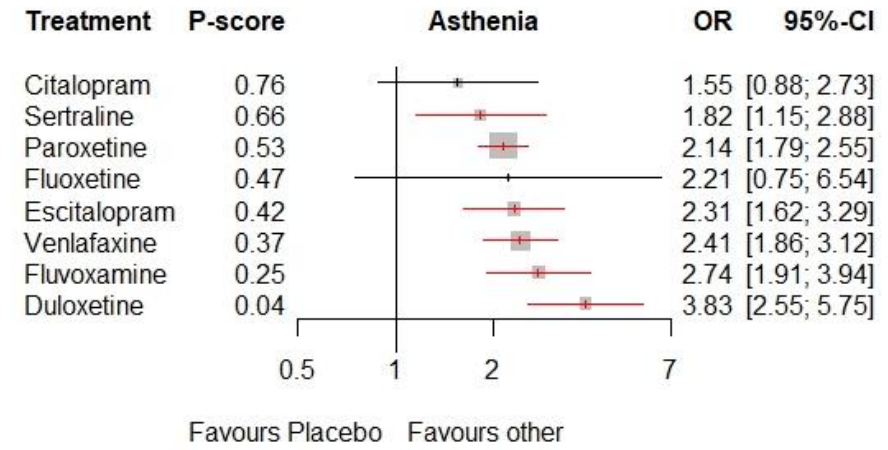
Legend: OR, odds ratio; CI, Confidence Interval. Medications are ordered from best to worst according to treatment rankings based on P-scores. Antidepressants were compared to placebo, which was the reference intervention. Significant differences are highlighted in red.

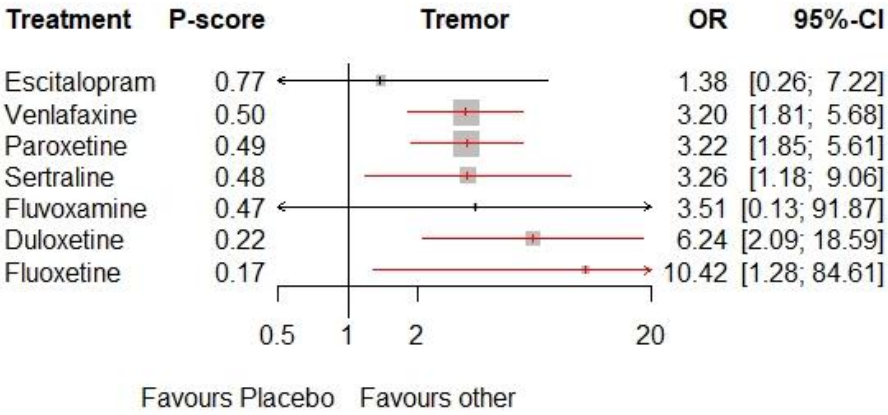
Supplementary Figure S30: Forest plots of network meta-analysis for sleep related adverse events



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. Significant differences are highlighted in red.

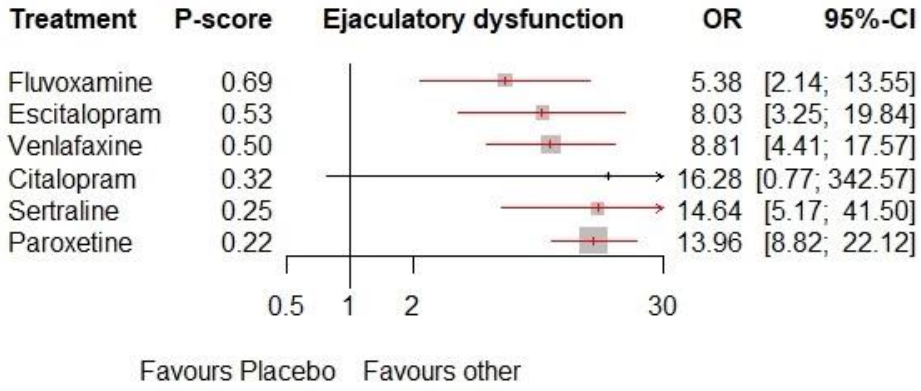
Supplementary Figure S31: Forest plots of network meta-analysis for motor adverse events

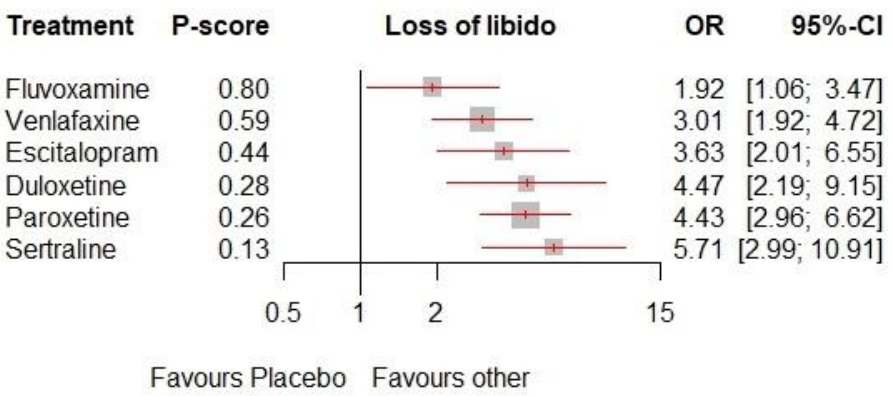


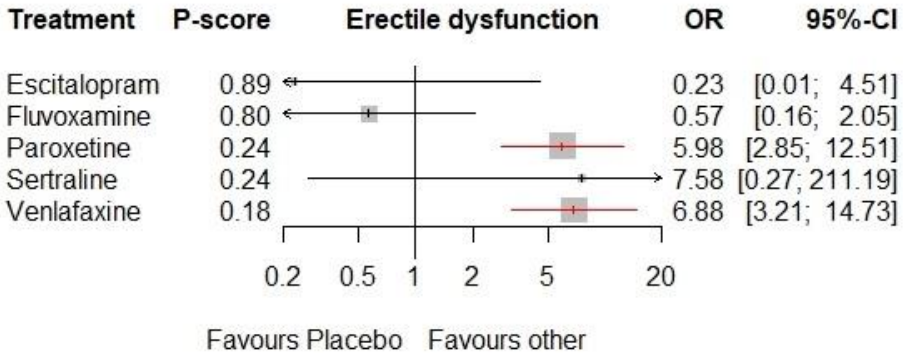


Legend: OR, odds ratio; CI, Confidence Interval. Medications are ordered from best to worst according to treatment rankings based on P-scores. Antidepressants were compared to placebo, which was the reference intervention. Significant differences are highlighted in red.

Supplementary Figure S32: Forest plots of network meta-analysis for sexual adverse events

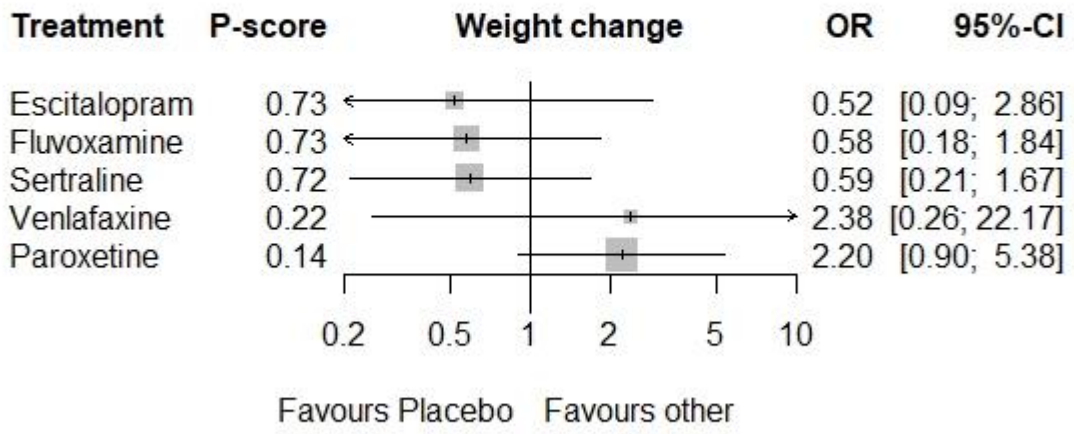






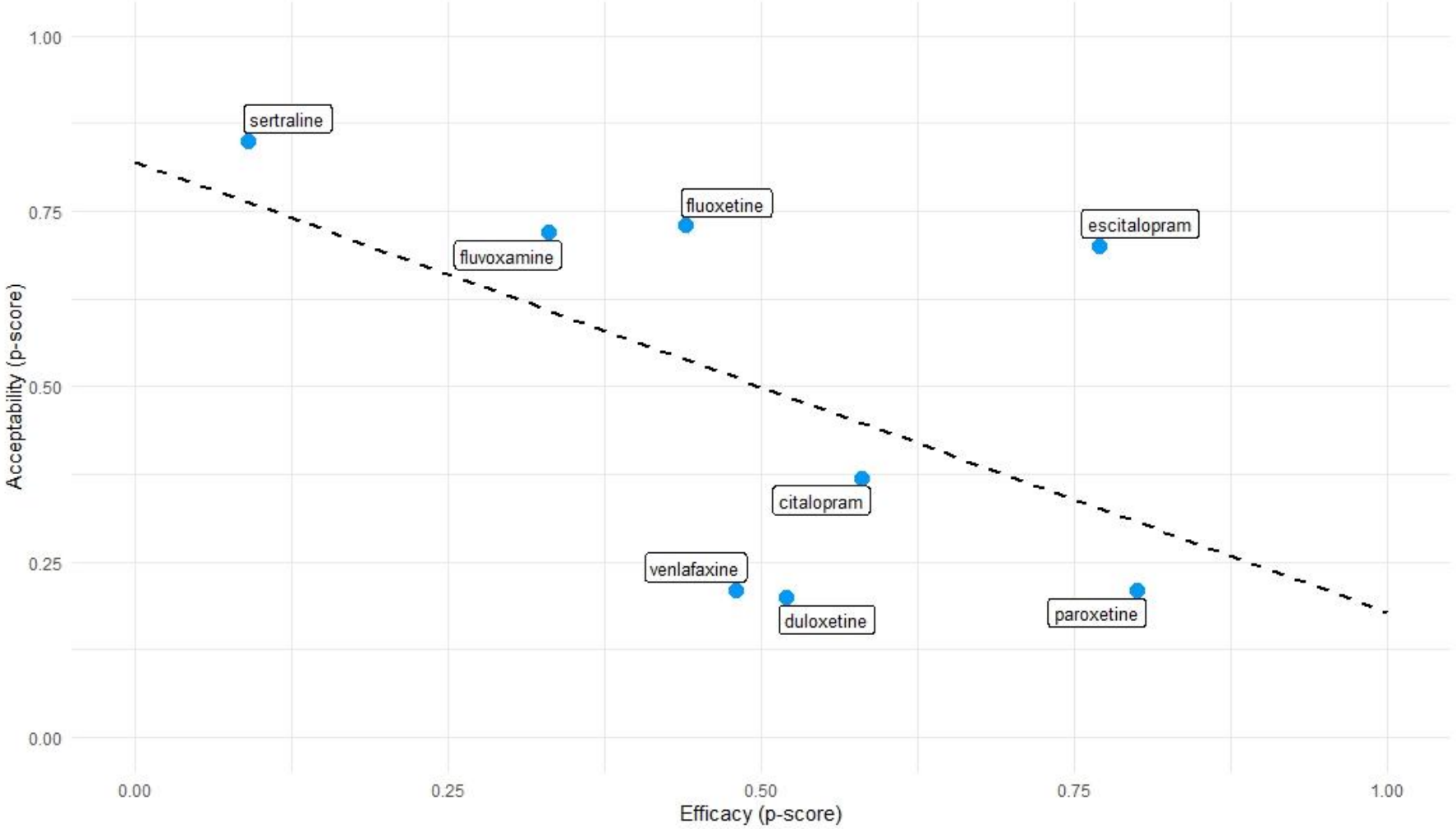
Legend: OR, odds ratio; CI, Confidence Interval. Medications are ordered from best to worst according to treatment rankings based on P-scores. Antidepressants were compared to placebo, which was the reference intervention. Significant differences are highlighted in red.

Supplementary Figure S33: Forest plots of network meta-analysis for weight change rates

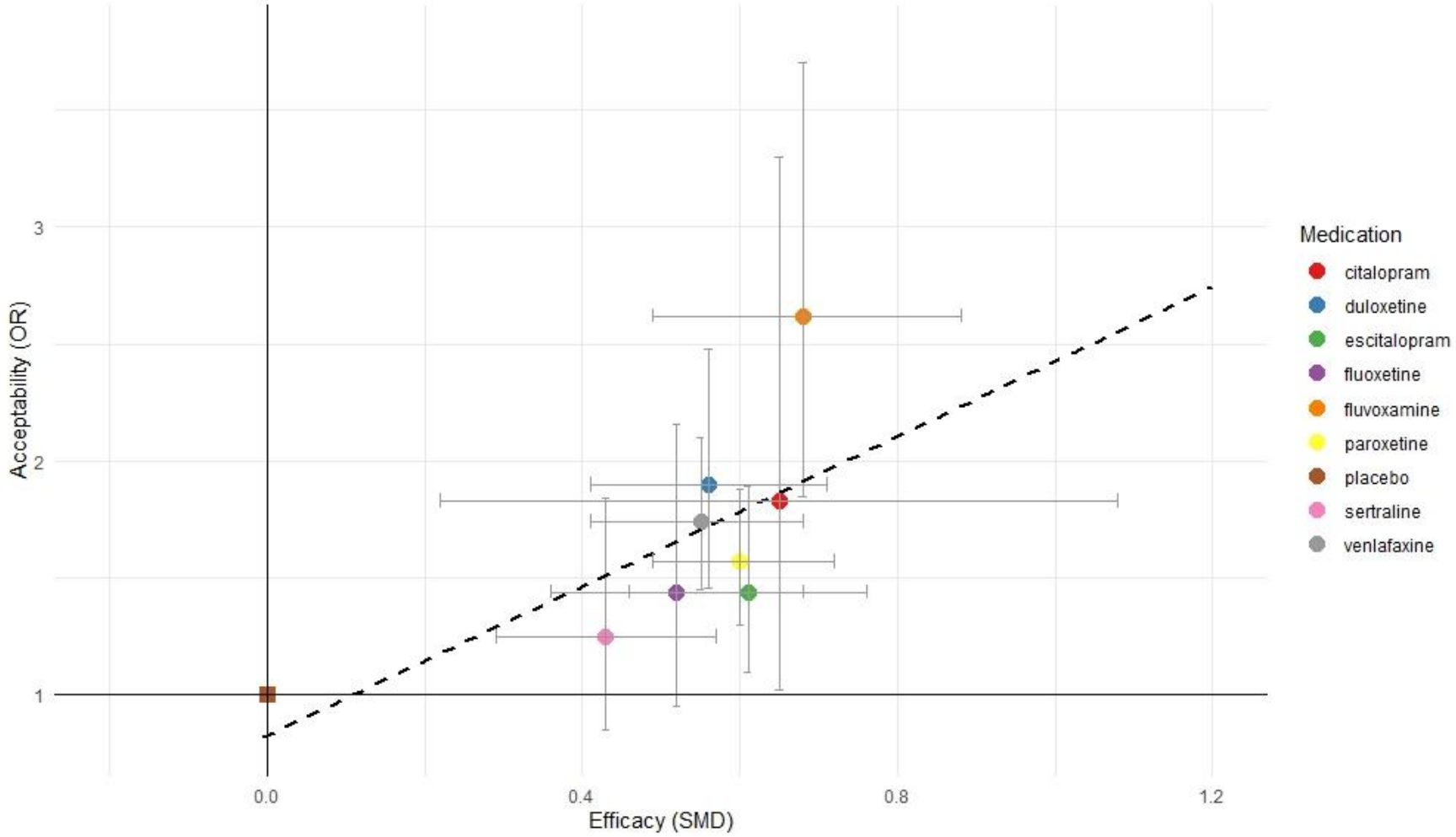


Legend: OR, odds ratio; CI, Confidence Interval. Medications are ordered from best to worst according to treatment rankings based on P-scores. Antidepressants were compared to placebo, which was the reference intervention. Significant differences are highlighted in red.

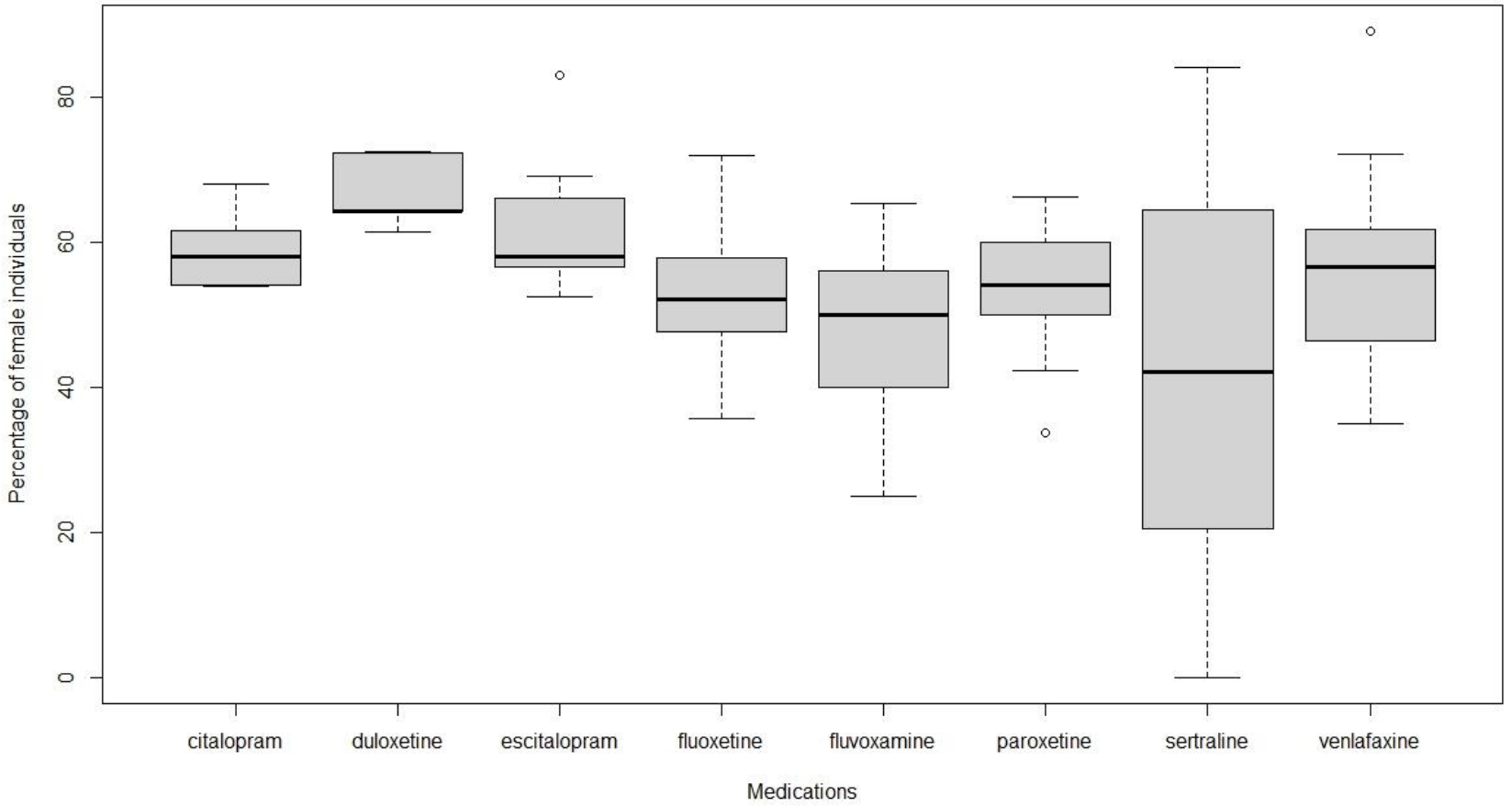
Supplementary Figure S34: Correlation between treatment rankings in multiple meta-regression models for acceptability and efficacy



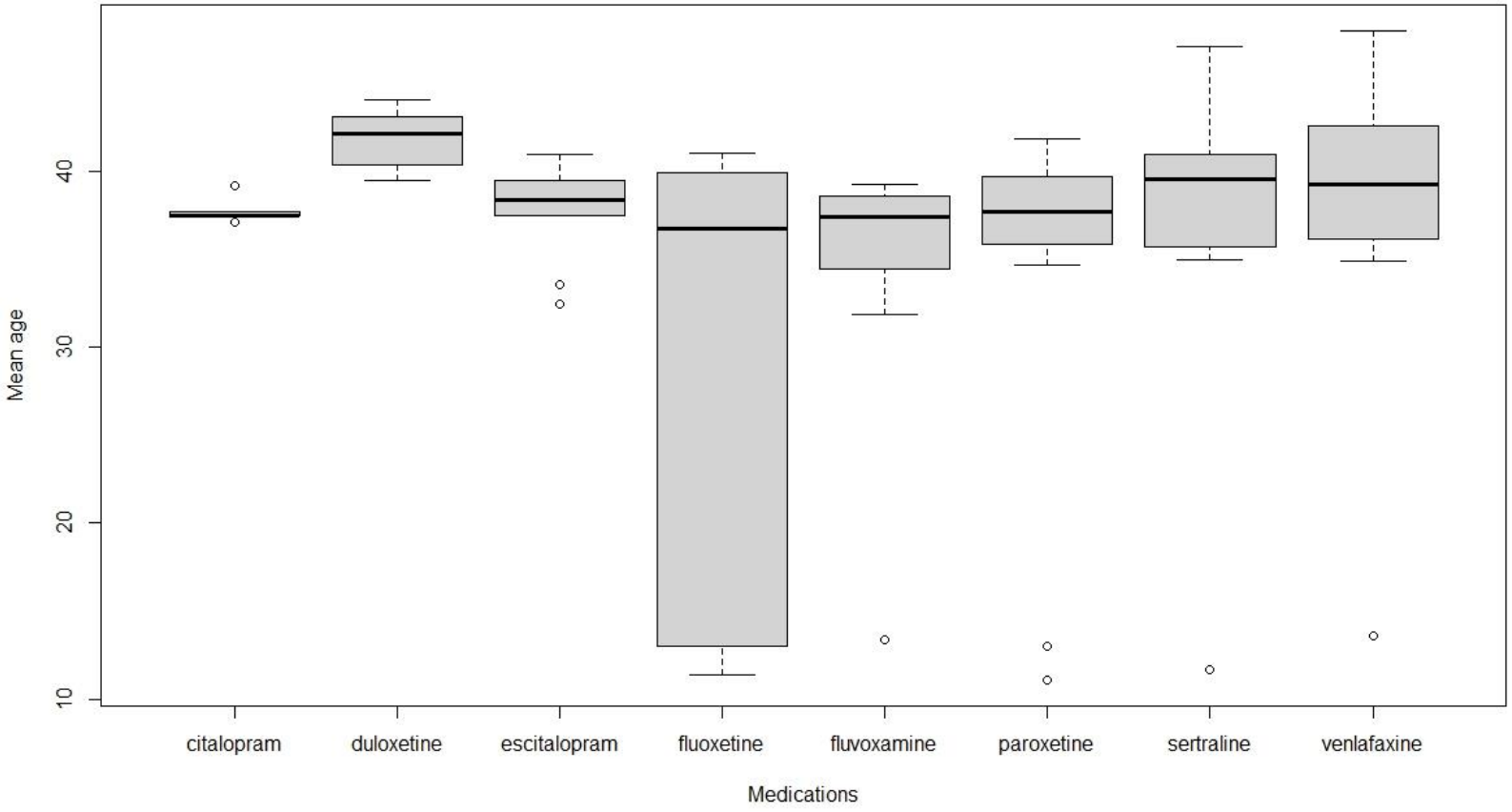
Supplementary Figure S35: Correlation between effect size estimates for acceptability and efficacy



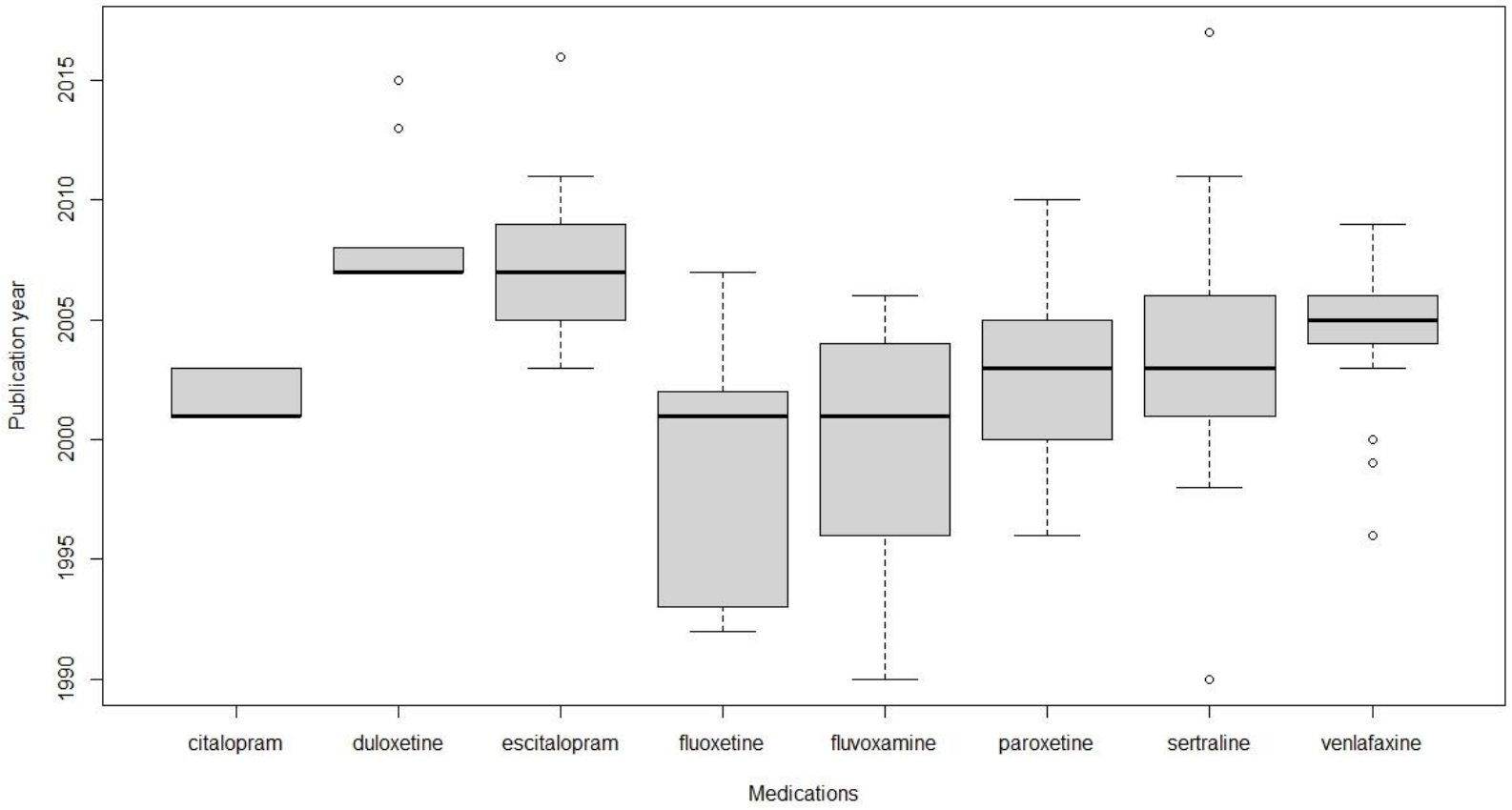
Supplementary Figure S36: Distribution of the percentage of female individuals by medication



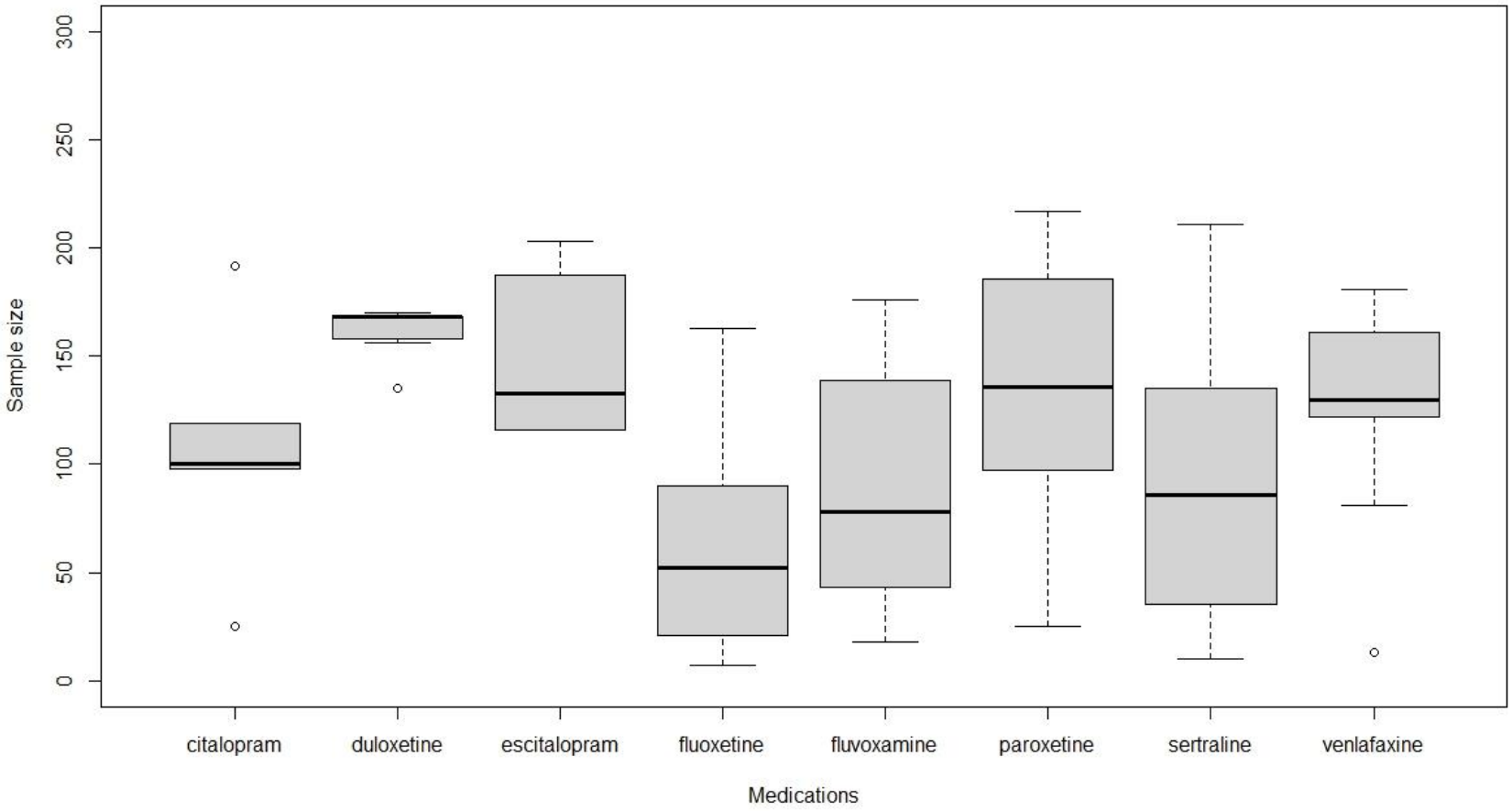
Supplementary Figure S37: Distribution of mean age by medication



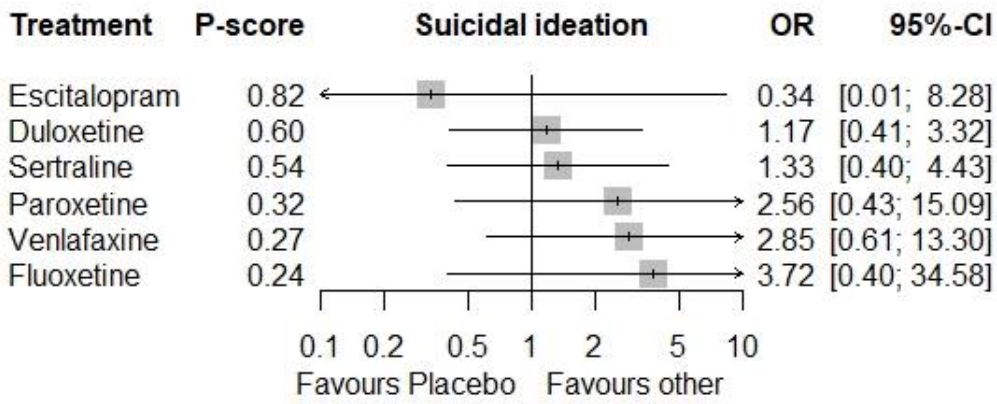
Supplementary Figure S38: Distribution of publication year by medication



Supplementary Figure S39: Distribution of sample size by medication



Supplementary Figure S40: Forest plots of network meta-analysis for suicidal ideation



Supplementary Table S31: Multiple meta-regression for the aggregate measure of all adverse events comparing medication versus placebo

	o/k (n)	Odds ratio (95%CI)	SE	p-value	Test of moderators (QM)	p-value
Publication year	799/80 (21 338)	1.00 (0.98 to 1.02)	0.01	0.96	0.0021	0.96
Medication Sertraline	124/19 (3031)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
Fluoxetine	44/7 (1028)	1.07 (0.70 to 1.63)	0.22	0.75	24.1682	**0.001**
Paroxetine	203/19 (5773)	1.51 (1.19 to 1.92)	0.12	**<0.001**		
Fluvoxamine	68/10 (1639)	1.09 (0.77 to 1.53)	0.17	0.63		
Citalopram	43/3 (699)	1.38 (0.90 to 2.11)	0.22	0.15		
Escitalopram	79/7 (2352)	1.11 (0.82 to 1.52)	0.16	0.50		
Venlafaxine	186/20 (5311)	1.52 (1.22 to 1.91)	0.11	**<0.001**		
Duloxetine	52/5 (1505)	1.57 (1.06 to 2.31)	0.20	**0.02**		
Comparator Head-to-head	179/10 (3969)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
Different dose	189/11 (4183)	1,06 (0.80 to 1.39)	0.14	0.69	4.8933	0.09
Placebo	431/59 (13 186)	1.25 (0.99 to 1.57)	0.12	0.06		

	o/k (n)	Odds ratio (95%CI)	SE	p-value	Test of moderators (QM)	p-value
Equivalent dose 1 – 1.99	254/35 (7937)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
2 – 2.99	372/43 (9286)	1,33 (1.15 to 1.55)	0.08	**<.001**	17.1740	**<.001**
3 – 3.99	122/17 (2999)	1.45 (1.15 to 1.82)	0.12	**0.001**		
>= 4	51/7 (1116)	1,68 (1.13 to 2.49)	0.20	**0.01**		
Trial duration 12-15 weeks	309/29 (8947)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
5-8 weeks	163/18 (4223)	1,00 (0.74 to 1.34)	0.15	0.99	0.2740	0.96
9-11 weeks	229/25 (5773)	0.95 (0.73 to 1.23)	0.13	0.68		
16-26 weeks	98/8 (2395)	1.00 (0.76 to 1.32)	0.14	0.98		
Main diagnosis GAD	228/21 (6992)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
Social anxiety	189/18 (5590)	1.03 (0.78 to 1.37)	0.14	0.82	10.3090	**0.04**
Panic	122/12 (3466)	0.71 (0.54 to 0.94)	0.14	**0.02**		
PTSD	97/14 (2629)	0.76 (0.55 to 1.06)	0.17	0.11		
OCD	163/15 (2661)	0.84 (0.59 to 1.20)	0.18	0.33		
Sample age Adults/Elderly	742/69 (19 854)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
Children/Adolescents	57/11 (1484)	-0.97 (0.68 to 1.39)	0.18	0.89	0.0203	0.89

	o/k (n)	Odds ratio (95%CI)	SE	p-value	Test of moderators (QM)	p-value
Benzodiazepine use No	499/44 (13 567)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
Yes	110/12 (1886)	0.82 (0.63 to 1.08)	0.14	0.15	3.1193	0.37
Not informed	172/22 (5348)	1.01 (0.83 to 1.22)	0.10	0.92		
Unclear	18/2 (537)	0.76 (0.47 to 1.24)	0.25	0.27		
Placebo lead-in No	270/28 (6141)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
Yes	445/41 (12 182)	1.26 (1.02 to 1.56)	0.11	**0.03**	5.5732	0.13
Not informed	72/9 (2465)	1.15 (0.83 to 1.58)	0.16	0.41		
Unclear	12/2 (550)	1,60 (0.91 to 2.82)	0.29	0.10		
Funding Academic	29/4 (226)	[Ref]	[Ref]	[Ref]	[Ref]	[Ref]
Governmental or non-profit	13/3 (92)	1.17 (0.49 to 2.77)	0.44	0.72	3.5035	0.32
Industry	691/65 (19 193)	0.77 (0.49 to 1.21)	0.23	0.26		
Unclear	66/8 (1827)	0.90 (0.54 to 1.50)	0.26	0.68		

o, number of outcomes; k, number of studies; n, sample size; SE, standard error; QM, Cochran's Q test of moderators; GAD, generalized anxiety disorder; PTSD, post-traumatic stress disorder; OCD, obsessive-compulsive disorder; QE, Cochran's Q test for residual heterogeneity; test of moderators of the multiple meta-regression model [QM]=95.3400, p value<.001; test for residual heterogeneity of the multiple meta-regression model [QE]=894.1531, p value=0.001

6 FINAL CONSIDERATIONS AND CONCLUSION

This thesis had the main aim to investigate the efficacy, acceptability, and tolerability of SSRIs, SNRIs, and placebo for the treatment of children and adults diagnosed with anxiety, obsessive-compulsive, or stress-related disorders, and also to explore moderators of these estimates. This is the first three-level network meta-analysis in the field of psychiatry and the largest meta-analysis to date to evaluate the efficacy of antidepressants on mental health symptoms of patients diagnosed with anxiety, obsessive-compulsive or stress-related disorders, due to full inclusion of all available outcome measures in this field, and extensive search for both published and unpublished trials with no restriction regarding symptom domains, assessment instruments, participants' age, date of publication, or study language. This study also is the most comprehensive to date to evaluate the tolerability of antidepressants for the treatment of patients diagnosed with anxiety, obsessive-compulsive, or stress-related disorders, considering the inclusion of 799 outcomes measures of 17 types of adverse events related to autonomic, gastrointestinal, sexual, motor, and sleep-related side effects.

Findings from article #1 revealed higher efficacy of SSRIs and SNRIs in comparison with placebo on the aggregate measure of internalizing symptoms. Effect sizes were small to moderate in overall psychopathology, for all considered diagnoses and in all symptom domains. We also found significant results when restricting to most used assessment instruments in each diagnosis, as commonly performed in previous meta-analyses; however, this restriction has led to exclusion of 72.71% of all available outcome measures. Moreover, estimates of efficacy were moderated by patient diagnosis, treatment duration, funding, and year of publication. Finally, pairwise comparisons revealed only small differences between medications in efficacy and acceptability.

Additionally, article #2 showed high rates of adverse events for both placebo and medication groups; however, most individual medications presented higher rates of adverse events over placebo. For individuals receiving medications, the most common adverse event was nausea, while weight change was the least common. Estimates of tolerability were moderated by dose, medication, patient diagnosis, and use of placebo lead-in periods. Furthermore, head-to-head comparisons indicated significant differences for the aggregated measure of all adverse events and for the aggregated measure of autonomic, gastrointestinal, and sleep-related symptoms. When evaluating outcomes related to suicidality, no significant differences between medications and placebo were found.

These findings improve the evidence of benefits of SSRIs and SNRIs for anxiety disorders, obsessive-compulsive, and stress-related disorders by using a three-level approach, considering that previous meta-analyses were restricted to specific scales or specific symptom domains, which reduces statistical power, does not reflect clinical practice, and makes these studies vulnerable to biases related to specific assessment instruments or symptom domains. Moreover, the assessment of adverse events complements results of efficacy, considering the lack of major differences among medications. As distinct profiles of adverse events were found, tolerability should play an important role on the selection of these effective medications. This thesis presents findings that can guide clinicians and patients to better evidence-based decisions when starting treatments with SSRIs or SNRIs by incorporating preferences of each individual on the decision-making. These findings may guide psychiatrists, patients, clinicians, and policy makers on the selection of effective pharmacological agents with higher chances of adherence for the initial treatment of these disorders.

APPENDIX A –ARTICLE #1 PUBLISHED DURING THE DOCTORATE PERIOD

Article unrelated to the main project published during the doctorate period as co-author. Article entitled "*Testing the Stability and Validity of an Executive Dysfunction Classification Using Task-Based Assessment in Children and Adolescents*" published at *Journal of the American Academy of Child and Adolescent Psychiatry* on December 17, 2020.

Journal of the American Academy of Child and Adolescent Psychiatry
December 17, 2020
doi: 10.1016/j.jaac.2020.11.016

Testing the Stability and Validity of an Executive Dysfunction Classification Using Task-Based Assessment in Children and Adolescents

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Abstract

Objective: It is unclear if pediatric executive dysfunction assessed only with cognitive tasks predicts clinically relevant outcomes independently of psychiatric diagnoses. This study tested the stability and validity of a task-based classification of executive function.

Method: A total of 2,207 individuals (6-17 years old) from the Brazilian High-Risk Cohort Study participated in this study (1,930 at baseline, 1,532 at follow-up). Executive function was measured using tests of working memory and inhibitory control. Dichotomized age- and sex-standardized performances were used as input in latent class analysis and receiver operating curves to create an executive dysfunction classification (EDC). The study tested EDC's stability over time, association with symptoms, functional impairment, a polymorphism in the CADM2 gene, polygenic risk scores (PRS), and brain structure. Analyses covaried for age, sex, social class, IQ, and psychiatric diagnoses.

Results: EDC at baseline predicted itself at follow-up (odds ratio [OR] = 5.11; 95% CI 3.41-7.64). Participants in the EDC reported symptoms spanning several domains of psychopathology and exhibited impairment in multiple settings, including more adverse school events (OR = 2.530; 95% CI 1.838-3.483). Children in the EDC presented higher attention-deficit/hyperactivity disorder and lower educational attainment PRS at baseline; higher schizophrenia PRS at follow-up; and lower chances of presenting a polymorphism in a gene previously linked to high performance in executive function (CADM2 gene). They also

exhibited smaller intracranial volumes and smaller bilateral cortical surface areas in several brain regions.

Conclusion: Task-based executive dysfunction is associated with several validators, independently of psychiatric diagnoses and intelligence. Further refinement of task-based assessments might generate clinically useful tools.

APPENDIX B –ARTICLE #2 PUBLISHED DURING THE DOCTORATE PERIOD

Article unrelated to the main project published during the doctorate period as co-author. Article entitled "*Latent structure and factor reliability of the National Health Service Community Mental Health Service User Questionnaire*" published at *Journal of Mental Health* on May 12, 2020.

Journal of Mental Health
May 12, 2020
doi: 10.1080/09638237.2021.1922655

Latent structure and factor reliability of the National Health Service Community Mental Health Service User Questionnaire

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Abstract

Background: National Health Service use the Community Mental Health Service User Questionnaire (NHS-CMH) to assess care quality. However, its reliability and internal validity is uncertain.

Aims: To test the NHS-CMH structure, reliability and item-level characteristics.

Methods: We used data from 11,373 participants who answered the 2017 NHS-CMH survey. First, we estimated the NHS-CMH structure using Exploratory Factor Analysis (EFA) in half of the dataset. Second, we tested the best EFA-derived model with Confirmatory Factor Analysis (CFA). We tested the internal validity, construct reliability (omega - ω), explained common variance of each factor (ECV), and item thresholds.

Results: EFA suggested a 4-factor solution. The structure derived from the EFA was confirmed, demonstrating good reliability for the four correlated dimensions: "Relationship with Staff" (ω = 0.952, ECV = 40.1%), "Organizing Care" (ω = 0.855, ECV = 21.4%), "Medication and Treatments" (ω = 0.837, ECV = 13.3%), and "Support and Well-being" (ω = 0.928, ECV = 25.3%). A second-order model with a high-order domain of "Quality of Care" is also supported.

Conclusions: The NHS-CMH can be used to reliably assess four user-informed dimensions of mental health care quality. This model offers an alternative for its current use (item-level and untested sum scores analysis).

APPENDIX C –ARTICLE #3 PUBLISHED DURING THE DOCTORATE PERIOD

Article unrelated to the main project published during the doctorate period as co-author. Article entitled "*Emotional eating in women with generalized anxiety disorder*" published at *Trends in Psychiatry and Psychotherapy* on February 14, 2022.

Trends in Psychiatry and Psychotherapy
February 14, 2022
doi: 10.47626/2237-6089-2021-0399

Emotional eating in women with generalized anxiety disorder

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Abstract

Introduction: Individuals diagnosed with Generalized Anxiety Disorder (GAD) search for pleasurable foods to avoid their negative emotional experiences. An ineffective regulation of negative emotions may be a risk factor for emotional eating, leading to suffering, dysfunctional behaviors and weight gain. The aim of this study is to understand the relationship between emotional dysregulation and emotional eating, investigating potential mediators as the intensity of the worry, avoidance of internal experiences, mindfulness and self-compassion in female anxious patients.

Methods: Participants from a randomized clinical trial diagnosed with GAD answered the instruments at baseline: Difficulties in Emotion Regulation Scale (DERS), Three Factor Eating Questionnaire (TFEQ-R21), Penn State Worry Questionnaire (PSWQ), Action and Acceptance Questionnaire (AAQ), Five Facet Mindfulness Questionnaire (FFMQ), and Self-Compassion Scale (SCS) in this cross-sectional study. We estimated Pearson correlation coefficients and performed mediation analyses.

Results: We evaluated 51 individuals and 34 female participants completed all the questionnaires. Our data showed that emotional eating was positively correlated with emotional dysregulation ($r=0.593$; $p<0.001$), worry trait ($r=0.402$; $p=0.018$), and avoidance of internal experiences ($r=0.565$; $p<0.001$), whereas it was negatively correlated with self-compassion ($r=-0.590$; $p<0.001$) and mindful state ($r=-0.383$; $p=0.026$). Moreover, we demonstrated that self-compassion mediates the relationship between emotional dysregulation and emotional eating (ab product estimate = 0.043, 95% CI [0.003 to 0.084]).

Conclusion: Our findings could add to the literature by identifying psychological factors that could mediate the association between emotional dysregulation and emotional eating, allowing more effective eating behavior intervention targets in patients with GAD.

APPENDIX D –ARTICLE #4 PUBLISHED DURING THE DOCTORATE PERIOD

Article unrelated to the main project published during the doctorate period as co-author. Article entitled "*Mechanisms of improvement in generalized anxiety disorder: A mediation and moderated mediation analysis from a randomized controlled trial*" published at *The British Journal of Clinical Psychology* on November 29, 2022.

The British Journal of Clinical Psychology
November 29, 2022
doi: 10.1111/bjc.12402

Mechanisms of improvement in generalized anxiety disorder: A mediation and moderated mediation analysis from a randomized controlled trial

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Abstract

Background: Generalized anxiety disorder (GAD) is associated with the lowest treatment response rate among all anxiety disorders. Understanding mechanisms of improvement may help to develop more effective and personalized treatments.

Aim: The objective of the study was to investigate different improvement mechanisms in the treatment of individuals diagnosed with GAD.

Method: Mediation analyses were performed evaluating the association between worry symptoms at baseline and anxiety scoring at the endpoint, considering self-compassion or mindfulness or its dimensions at mid-treatment as mediators for the whole sample (assessing GAD improvement mechanism) and the different interventions as moderators.

Results: Contrary to mindfulness state scoring (C = .06; 95% CI = -.05 to .20), self-compassion (C = .11; 95% CI = .01 to .28) and non-judgement of inner experience (C = .10; 95% CI = .004 to .21) mediated the association between worry symptoms at baseline and anxiety at the endpoint. When comparing BMT to FLX, the intervention modality did not moderate these associations.

Conclusion: Self-compassion and non-judgement of inner experience seem to be essential targets in GAD treatment, contrary to the mindfulness state itself. Although no difference was found considering the intervention modality, future research may assess how to boost these dimensions in specific treatments for GAD.

APPENDIX E –ARTICLE #5 PUBLISHED DURING THE DOCTORATE PERIOD

Article unrelated to the main project published during the doctorate period as co-author. Article entitled "*Translating measurement into practice: Brazilian norms for the Patient Health Questionnaire (PHQ-9) for assessing depressive symptoms*" published at *Brazilian Journal of Psychiatry* on May 19, 2023.

Brazilian Journal of Psychiatry
May 19, 2023
doi: 10.47626/1516-4446-2022-2945

Translating measurement into practice: Brazilian norms for the Patient Health Questionnaire (PHQ-9) for assessing depressive symptoms

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Abstract

Objective: To provide practical norms for measuring depressive symptoms using the Patient Health Questionnaire 9 (PHQ-9) in Brazil using a state-of-art psychometrics analysis.

Methods: We used a large and representative Brazilian dataset from the 'Pesquisa Nacional de Saúde - 2019'(PNS-2019), which includes 90,846 Brazilian citizens. First, to assess the scale structure, we assessed the unidimensional model using Confirmatory Factor Analysis (CFA). Second, we used Item Response Theory (IRT) to characterize depressive symptoms´ distribution. Then, we linked summed- and meanbased PHQ-9 scores with the IRT-based score by using generalized additive models. Finally, we generated percentiles, T scores, and a newly developed score, called D scores (decimal scores), to describe the PHQ-9 norms for Brazilian population.

Results: CFA revealed a good fit to the unidimensional model, showing to be invariant to age and sex. IRT captured item-level information of the latent trait (reliable from 1 to 3 standard deviations above the mean). Brazilian norms were presented using summed-, T-scores, and D-scores.

Conclusions: This is the first study to define Brazilian´s norms for the PHQ-9 among a large representative sample, using robust psychometric tools. More precise PHQ-9 scores are now available and may be widely used in primary and specialized clinical care settings.

APPENDIX F –ARTICLE #6 PUBLISHED AS FIRST AUTHOR DURING THE DOCTORATE PERIOD

Article unrelated to the main project published during the doctorate period first author (joint first author with Luis Souza Motta). Article entitled "*Placebo response in trials with patients with anxiety, obsessive-compulsive and stress disorders across the lifespan: a three-level meta-analysis*" published at *BMJ Mental Health* in 2023 (online ahead of print).

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Placebo response in trials with patients with anxiety, obsessive-compulsive and stress disorders across the lifespan: a three-level meta-analysis

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Abstract

Question: Randomised controlled trials assessing treatments for anxiety, obsessive-compulsive and stress-related disorders often present high placebo response rates in placebo groups. Understanding the placebo response is essential in accurately estimating the benefits of pharmacological agents; nevertheless, no studies have evaluated the placebo response across these disorders using a lifespan approach.

Study Selection and Analysis: We searched MEDLINE, PsycINFO, Embase, Cochrane, websites of regulatory agencies and international registers from inception to 9 September 2022. The primary outcome was the aggregate measure of internalising symptoms of participants in the placebo arms of randomised controlled trials designed to assess the efficacy of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) in individuals diagnosed with anxiety, obsessive-compulsive or stress-related disorders. The secondary outcomes were placebo response and remission rates. Data were analysed through a three-level meta-analysis.

Findings: We analysed 366 outcome measures from 135 studies (n=12 583). We found a large overall placebo response (standardised mean difference (SMD)=-1.11, 95% CI -1.22 to -1.00). The average response and remission rates in placebo groups were 37% and 24%, respectively. Larger placebo response was associated with a diagnosis of generalised anxiety disorder and post-traumatic stress disorder, when compared with panic, social anxiety and obsessive-compulsive disorder (SMD range, 0.40-0.49), and with absence of a placebo lead-in period

(SMD=0.44, 95% CI 0.10 to 0.78). No significant differences were found in placebo response across age groups. We found substantial heterogeneity and moderate risk of bias.

Conclusions: Placebo response is substantial in SSRI and SNRI trials for anxiety, obsessive-compulsive and stress-related disorders. Clinicians and researchers should accurately interpret the benefits of pharmacological agents in contrast to placebo response.

APPENDIX G –ARTICLE #7 PUBLISHED DURING THE DOCTORATE PERIOD

Article unrelated to the main project published during the doctorate period as co-author. Article entitled "*The science of child and adolescent mental health in Greece: a nationwide systematic review*" published at *European Child & Adolescent Psychiatry* on May 14, 2023.

European Child & Adolescent Psychiatry
May 14, 2023
doi: 10.1007/s00787-023-02213-9

The science of child and adolescent mental health in Greece: a nationwide systematic review

Natan Pereira Gosmann, Marianna de Abreu Costa, Marianna de Barros Jaeger, Luis Souza Motta, Júlia Frozi, Lucas Spanemberg, Gisele Gus Manfro, Pim Cuijpers, Daniel Samuel Pine, Anastasia Koumoula, Lauro Estivalete Marchionatti, Arthur Caye, Vasiliki Eirini Karagiorga, Panagiota Balikou, Katerina Lontou, Vicky Arkoulaki, André Simioni, Aspasia Serdari, Konstantinos Kotsis, Maria Basta, Efi Kapsimali, Andromachi Mitropoulou, Nikanthi Klavdianou, Domna Zeleni, Sotiria Mitroulaki, Anna Botzaki, Giorgos Gerostergios, Giorgos Samiotakis, Giorgos Moschos, Ioanna Giannopoulou, Katerina Papanikolaou, Katerina Aggeli, Nikolaos Scarmeas, Panagiotis Koulouvaris, Jill Emanuele, Kenneth Schuster, Eirini Karyotaki, Lily Kalikow, Katerina Pronoiti, **Natan Pereira Gosmann**, Julia Luiza Schafer, Kathleen Ries Merikangas, Peter Szatmari, Pim Cuijpers, Katholiki Georgiades, Michael Peter Milham, Mimi Corcoran, Sarah Burke, Harold Koplewicz, Giovanni Abrahão Salum

Abstract

Evidence-based information is essential for effective mental health care, yet the extent and accessibility of the scientific literature are critical barriers for professionals and policymakers. To map the necessities and make validated resources accessible, we undertook a systematic review of scientific evidence on child and adolescent mental health in Greece encompassing three research topics: prevalence estimates, assessment instruments, and interventions. We searched Pubmed, Web of Science, PsycINFO, Google Scholar, and IATPOTEK from inception to December 16th, 2021. We included studies assessing the prevalence of conditions, reporting data on assessment tools, and experimental interventions. For each area, manuals informed data extraction and the methodological quality were ascertained using validated tools. This review was registered in protocols.io [68583]. We included 104 studies reporting 533

prevalence estimates, 223 studies informing data on 261 assessment instruments, and 34 intervention studies. We report the prevalence of conditions according to regions within the country. A repository of locally validated instruments and their psychometrics was compiled. An overview of interventions provided data on their effectiveness. The outcomes are made available in an interactive resource online [https://rpubs.com/camhi/sysrev_table]. Scientific evidence on child and adolescent mental health in Greece has now been cataloged and appraised. This timely and accessible compendium of up-to-date evidence offers valuable resources for clinical practice and policymaking in Greece and may encourage similar assessments in other countries.

APPENDIX H –ARTICLE #8 PUBLISHED DURING THE DOCTORATE PERIOD

Article unrelated to the main project published during the doctorate period as co-author. Article entitled "*Efficacy of telemedicine interventions for depression and anxiety in older people: A systematic review and meta-analysis*" published at *International Journal of Geriatric Psychiatry* in 2023 (online ahead of print).

International Journal of Geriatric Psychiatry
Online ahead of print, 2023
doi: 10.1002/gps.5920

Efficacy of telemedicine interventions for depression and anxiety in older people: A systematic review and meta-analysis

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Abstract

Background: Anxiety and depression are prevalent in the elderly and lead to loss of functionality and increased mortality. Although the use of antidepressants and face-to-face psychotherapies are indicated, the current context of telemedicine provides an alternative, with the advantage of facilitating access to care. The study aimed to evaluate the efficacy of telemedicine interventions to reduce anxiety and depression in the elderly through a systematic review with meta-analysis.

Methods: The systematic review, through a search in 7 databases, included studies that evaluated the use of telemedicine interventions for depressive or anxious symptoms in the elderly, compared with usual care or waiting list or with another telemedicine intervention. Quantitative assessment was performed through meta-analysis.

Results: A total of 31 articles identified in the search met the eligibility criteria and four were included for meta-analysis. Studies showed that telemedicine interventions are feasible and several studies demonstrated significant improvement in depressive or anxiety symptoms. Four studies evaluated the efficacy of internet-delivered cognitive behavioral therapy for depression and anxiety in older adults, compared with a waitlist, and found pooled effect sizes of -1.20 (95% CI -1.60 to -0.81) and -1.14 (95% CI -1.56 to -0.72), respectively, with low heterogeneity.

Conclusions: Telemedicine interventions can be an alternative for the treatment of mood and anxiety symptoms in the elderly. However, more studies are needed to prove their clinical effectiveness, especially in countries with lower incomes and diverse culture and education.