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GABRIELA DE MORAES COSTA

EFICÁCIA, ACEITABILIDADE E TOLERABILIDADE DO TRATAMENTO FARMACOLÓGICO DO TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO E DOS ANTIDEPRESSIVOS NA QUALIDADE DO SONO DE ADULTOS COM TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO: REVISÕES SISTEMÁTICAS E METANÁLISES EM REDE

Tese de Doutorado

Santa Maria, RS
2021

GABRIELA DE MORAES COSTA

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Tese apresentada ao Curso de Doutorado do Programa de Pós-Graduação em Farmacologia, Área de Concentração Neuropsicofarmacologia, da Universidade Federal de Santa Maria (UFSM, RS), como requisito para obtenção do grau de **Doutora em Farmacologia**.

Orientador: Prof. Dr. Carlos Fernando de Mello

Coorientador: Prof. Dr. Fabricio Batistin Zanatta

Santa Maria, RS
2021

Costa, Gabriela de Moraes
Eficácia, Aceitabilidade e Tolerabilidade do Tratamento Farmacológico do Transtorno de Estresse Pós Traumático e dos Antidepressivos na Qualidade do Sono de Adultos com Transtorno de Estresse Pós-traumático: Revisões Sistemáticas e Metanálises em Rede / Gabriela de Moraes Costa.- 2021.
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GABRIELA DE MORAES COSTA

EFICÁCIA, ACEITABILIDADE E TOLERABILIDADE DO TRATAMENTO FARMACOLÓGICO DO TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO E DOS ANTIDEPRESSIVOS NA QUALIDADE DO SONO DE ADULTOS COM TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO: REVISÕES SISTEMÁTICAS E METANÁLISES EM REDE

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Aprovada em 25 de agosto de 2021.

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Santa Maria, RS,
2021

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RESUMO 1

TRATAMENTOS FARMACOLÓGICOS PARA ADULTOS COM TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO : UM METANÁLISE EM REDE DE EFICÁCIA E ACEITABILIDADE COMPARADAS

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COORIENTADOR: PROF. DR. FABRICIO BATISTIN ZANATTA

Local e Data da Defesa: Santa Maria, 25 de agosto de 2021.

Contexto: O objetivo deste estudo foi comparar a eficácia e a aceitabilidade entre os tratamentos farmacológicos para adultos com transtorno de estresse pós-traumático (TEPT) por meio de uma revisão sistemática, metanálise de efeitos randômicos e metanálise em rede. Métodos: Ensaios clínicos randomizados duplo-cegos comparando intervenções farmacológicas para adultos com TEPT foram pesquisados desde a sua inserção até 28 de agosto de 2018 nos bancos de dados: Cochrane (Central), Embase, LILACS, PILOTS, PsycINFO, PubMed e Web of Science. Registros de ensaios clínicos e sites de empresas farmacêuticas também foram pesquisados. O sistema GRADE foi usado para avaliar a qualidade das evidências. Resultados: A revisão sistemática incluiu 58 estudos envolvendo 6.766 pacientes randomizados para 26 intervenções diferentes. Em relação à eficácia, topiramato (SMD = -0,57; 95% CrI: -1,07, -0,10), risperidona (SMD = -0,53; 95% CrI: -0,93, -0,15), quetiapina (SMD = -0,59; 95% CrI: -1,06, -0,11), paroxetina (SMD = -0,35; 95% CrI: -0,48, -0,21), venlafaxina (SMD = -0,25; 95% CrI: -0,44, -0,05), fluoxetina (SMD = -0,28; 95% CrI: -0,46, -0,08) e sertralina (SMD = -0,21; 95% CrI: -0,33, -0,09) foram superiores ao placebo. Além disso, fenelzina (RR = 3,39; 95% CrI: 1,43,11,09), lamotrigina (RR = 4,39; 95% CrI: 1,18,26,38) e fluoxetina (RR = 1,28% CrI: 1,01,1,59) superaram o placebo em termos de aceitabilidade. Conclusões: A NMA apóia topiramato, risperidona, quetiapina, paroxetina, venlafaxina, fluoxetina e sertralina como opções farmacológicas eficazes para o tratamento do TEPT. A quetiapina e o topiramato têm a desvantagem de depender de poucos estudos pequenos, mas a redução clinicamente significativa nos sintomas é digna de nota e merece investigação adicional. Entre os tratamentos farmacológicos com evidência de eficácia em comparação com o placebo, a fluoxetina alcançou uma classificação relativamente elevada em aceitabilidade. Até onde sabemos, esta é a maior NMA contemporânea sobre o tema e a adição de novos medicamentos é um acréscimo importante às metanálises anteriores, possibilitando um maior número de comparações entre medicamentos.

Palavras-chave: Transtornos de Estresse Pós-Traumáticos; Metanálise em Rede; Meta-Análise de Comparação de Múltiplos Tratamentos; Psicofarmacologia.

ABSTRACT 1

Pharmacological treatments for adults with post-traumatic stress disorder: A network meta-analysis of comparative efficacy and acceptability

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Place and Date: Santa Maria, August 25th, 2021.

Background: The purpose of this study was to compare efficacy and acceptability among drug treatments for adults with post-traumatic stress disorder (PTSD) through a systematic review, random-effects pairwise and network meta-analyses. Methods: Double-blind randomized controlled trials comparing pharmacological interventions for adults with PTSD were searched from database inception through Aug. 28, 2018, on Cochrane (Central), Embase, LILACS, PILOTS, PsycINFO, PubMed, and Web of Science. Clinical trial registries and the websites of pharmaceutical companies were also searched. The GRADE system was used to assess the quality of the evidence. Results: The systematic review included 58 studies comprising 6766 patients randomized to 26 different interventions. Regarding efficacy, topiramate (SMD=-0.57;95%CrI: -1.07,-0.10), risperidone (SMD=-0.53;95%CrI: -0.93,-0.15), quetiapine (SMD=-0.59;95%CrI: -1.06,-0.11), paroxetine (SMD=-0.35;95%CrI: -0.48,-0.21), venlafaxine (SMD=-0.25;95%CrI: -0.44,-0.05), fluoxetine (SMD=-0.28;95%CrI: -0.46,-0.08), and sertraline (SMD=-0.21;95%CrI: -0.33,-0.09) outperformed placebo. Moreover, phenelzine (RR=3.39;95%CrI: 1.43,11.09), lamotrigine (RR=4.39;95%CrI: 1.18,26.38), and fluoxetine (RR=1.28%CrI: 1.01,1.59) outperformed placebo in terms of acceptability. Conclusions: The NMA supports topiramate, risperidone, quetiapine, paroxetine, venlafaxine, fluoxetine and sertraline as effective pharmacological choices for the treatment of PTSD. Quetiapine and topiramate have the shortcoming of relying on a few small studies, but the clinically meaningful change in symptoms is noteworthy and merits further investigation. Among the pharmacological treatments with evidence of efficacy compared to placebo, fluoxetine achieved a relatively high rank regarding acceptability. To the best of our knowledge, this is the largest contemporary NMA on the subject and the addition of new medications is an important extension of previous meta-analyses, enabling a larger number of drug comparisons.

Keywords: Stress Disorders, Post-Traumatic; Network Meta-Analysis; Multiple Treatment Comparison Meta-Analysis; Psychopharmacology.

RESUMO 2

EFICÁCIA, ACEITABILIDADE E TOLERABILIDADE DOS ANTIDEPRESSIVOS PARA DISTÚRBIOS DO SONO NO TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO: REVISÃO SISTEMÁTICA E METANÁLISE EM REDE

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Local e Data da Defesa: Santa Maria, 25 de agosto de 2021.

Queixas de sono são uma ocorrência comum no transtorno de estresse pós-traumático (TEPT) e podem persistir mesmo após a implementação do tratamento baseado em evidências para o transtorno. Se não for tratada, a perturbação do sono pode perpetuar ou agravar o TEPT. Nós conduzimos uma revisão sistemática e meta-análise em rede (NMA) de ensaios clínicos randomizados (ECRs) comparando eficácia, aceitabilidade e tolerabilidade entre antidepressivos para distúrbios do sono em adultos com TEPT e usamos o RoB2.0 da Cochane e o GRADE para NMA para a interpretação dos resultados. As bases de dados Cochrane, LILACS, PsycINFO, PTSDpubs e PubMed Central foram pesquisadas desde a introdução até 29 de novembro de 2020, levando à recuperação de 3.733 estudos. Sete ECRs foram incluídos na revisão (N=600) mediante a aplicação dos critérios de elegibilidade. Encontramos baixa certeza da evidência (LCE) de que a sertralina pode melhorar a qualidade do sono (medida pela escala PSQI) em pacientes com TEPT (MD –0,48, 95% CrI –0,63 a –0,32). A sertralina apresentou aceitabilidade (RR 1,12, 95% CrI -0,83 a 1,52, certeza muito baixa [VLCE]) e tolerabilidade (RR 0,58, 95% CrI 0,28 a 1,14, LCE) semelhantes ao placebo. Mirtazapina (MD -3,35, 95% CrI –9,06 a 2,39, LCE), paroxetina (MD –3,13, 95% CrI –7,47 a 1,26, VLCE), nefazodona (MD –0,25, 95% CrI –5,95 a 5,38, VLCE) e bupropiona (MD –2,28, 95% CrI –4,75 a 0,21, VLCE) foram semelhantes ao placebo para melhorar a qualidade do sono. Esses antidepressivos resultaram em pouco ou nenhum benefício para os distúrbios do sono no TEPT. Embora a NMA tenha sugerido que a sertralina pode melhorar o sono no TEPT em comparação com o placebo, devido à baixa certeza, essas estimativas não são robustas o suficiente para guiar decisões clínicas.

Palavras-chave: Transtornos de Estresse Pós-Traumáticos; Metanálise em Rede; Meta-Análise de Comparação de Múltiplos Tratamentos; Sono.

ABSTRACT 2

Efficacy, Acceptability, and Tolerability of Antidepressants for Sleep Disturbance in Post-Traumatic Stress Disorder: a Systematic Review and Network Meta-Analysis

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ADVISOR: PROF. DR. Carlos Fernando Mello
CO-ADVISOR: PROF. DR. Fabricio Batistin Zanatta

Place and Date: Santa Maria, August 25th, 2021.

Sleep complaints are a common occurrence in post-traumatic stress disorder (PTSD) and may remain after evidence-based treatment for PTSD has been implemented. If left untreated, sleep disturbance can perpetuate or aggravate the disorder. A systematic review and network meta-analysis (NMA) of randomized controlled trials (RCTs) was conducted comparing efficacy, acceptability, and tolerability among antidepressants for sleep disturbance in adults with PTSD, using Cochane's RoB2.0 and GRADE approach for NMA. The Cochrane Library, LILACS, PsycINFO, PTSDpubs, and PubMed Central databases were searched from inception to November 29, 2020, leading to the retrieval of 3,733 reports. After the selection process, seven RCTs were included in the review (N=600). We found low certainty of evidence (LCE) that sertraline may improve sleep quality (measured by PSQI) in patients with PTSD (MD –0.48, 95% CrI –0.63 to –0.32). Sertraline was as well accepted (RR 1.12, 95% CrI –0.83 to 1.52, very low certainty [VLCE]) and as well tolerated as placebo (RR 0.58, 95% CrI 0.28 to 1.14, LCE). Mirtazapine (MD –3.35, 95% CrI –9.06 to 2.39, LCE), paroxetine (MD –3.13, 95% CrI –7.47 to 1.26, VLCE), nefazodone (MD –0.25, 95% CrI –5.95 to 5.38, VLCE), and bupropion (MD –2.28, 95% CrI –4.75 to 0.21, VLCE) were sim to placebo for improving sleep quality. These antidepressants resulted in little or no ben for sleep disturbances in PTSD. Although the NMA suggested that sertraline may improve sleep in PTSD compared to placebo, due to the low certainty, these estimates are not robust enough to guide clinical decisions.

Keywords: Stress Disorders, Post-Traumatic; Network Meta-Analysis; Multiple Treatment Comparison Meta-Analysis; Sleep.

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LISTA DE ABREVIATURAS E SIGLAS

5-HTTLPR S – Alelo curto do gene transportador da serotonina
APA – Associação Psiquiátrica Americana
COVID-19 – Doença por coronavírus 2019
DSM-5 - Manual diagnóstico e estatístico dos transtornos mentais, 5ª edição
DSM-III – Manual diagnóstico e estatístico dos transtornos mentais, 3ª edição
FKBP5 – Variante funcional em gene que codifica uma co-chaperona do receptor glicocorticóide
HPA – Eixo hipotálamo-hipófise-adrenal
ISRS – Inibidores seletivos de recaptação da serotonina
ISRSN – Inibidore seletivo de recaptação da serotonina e noradrenalina
NMA – Network meta-analysis
OMS – Organização Mundial da Saúde
PSQI – Índice de qualidade do sono de Pittsburgh
PTSD – Post-traumatic stress disorder
RCT – Randomized controlled trial
SARS-CoV-2 – Síndrome respiratória aguda grave causada pelo coronavírus 2
REM – movimento rápido dos olhos
SLC6A4 – Polimorfismo funcional na região promotora do gene do transportador de serotonina
SNC – Sistema nervoso central
TEPT – Transtorno de estresse pós-traumático

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SUMÁRIO

APRESENTAÇÃO

Os resultados que fazem parte desta tese estão apresentados sob a forma de dois artigos científicos, os quais se encontram nos itens **ARTIGO CIENTÍFICO 1 e ARTIGO CIENTÍFICO 2**. As seções Métodos, Resultados e Discussão encontram-se no próprios artigos e representam a íntegra da presente tese. O item **CONCLUSÕES**, encontrado no final desta tese, apresenta interpretações e comentários gerais sobre os artigos científicos contidos neste trabalho. As **REFERÊNCIAS BIBLIOGRÁFICAS** referem-se somente às citações que aparecem nos itens **INTRODUÇÃO** e **CONCLUSÕES** da tese, uma vez que as referências utilizadas na elaboração de cada artigo estão mencionadas nos próprios manuscritos.

1 INTRODUÇÃO

Embora a sintomatologia do estresse traumático seja conhecida há mais de um século por terminologias que incluem “síndrome do choque de granada”, “coração de soldado”, “neurose de guerra”, foi somente a partir da década de 80 que as reações ao trauma e ao estresse foram devidamente reconhecidas na nosologia psiquiátrica (SHEPHARD, 2000). Assim, a Associação Psiquiátrica Americana (APA) introduziu o diagnóstico de transtorno de estresse pós-traumático (TEPT ou, em inglês, PTSD) na terceira edição do seu Manual Diagnóstico e Estatístico dos Transtornos Mentais (DSM-III) (AMERICAN PSYCHIATRIC ASSOCIATION, 1980). Desde o despertar de perturbações da saúde mental evidentes em combatentes que retornaram do Vietnã, o conhecimento sobre o TEPT cresceu significativamente. No entanto, as equipes de saúde ainda se confrontam com grandes desafios no manejo dos pacientes, ao passo que o tratamento mais efetivo segue alvo de intensos debates (BRYANT, 2019).

Nesse contexto, a presente tese objetiva, à luz da medicina baseada em evidências, elucidar controvérsias a respeito da eficácia, da aceitabilidade e da tolerabilade do tratamento farmacológico do TEPT, em que pese as suas repercussões na qualidade do sono dos pacientes.

1.1 DEFINIÇÕES DIAGNÓSTICAS

Os transtornos relacionados a trauma e a estressores incluem transtornos nos quais a exposição a um evento traumático ou estressante está listada explicitamente como um critério diagnóstico. O sofrimento mental decorrente de um evento traumático ou estressante é bastante variável. A fim de que sejam satisfeitos os critérios diagnósticos para TEPT segundo a mais recente edição do Manual diagnóstico e estatístico dos transtornos mentais, o DSM-5, o indivíduo precisa experimentar ou testemunhar um grande evento traumático (por exemplo: exposição a morte real ou ameaçada de morte, lesão grave ou violência sexual) (critério A). Além disso, após experimentar ou testemunhar tal evento, há quatro dimensões sintomatológicas (*clusters*) que devem se manifestar: sintomas de reexperiência ou revivência

traumática (critério B); evitação ativa de lembranças do trauma, por meio de gatilhos internos ou externos (critério C), alterações negativas persistentes no humor e na cognição (critério D), sintomas de hiperexcitabilidade (critério E). O diagnóstico de TEPT requer o início ou persistência desses sintomas por mais de um mês após a exposição traumática, evitando-se, com isso, a patologização das reações imediatas ou transitórias ao estresse. Os sintomas causam sofrimento clinicamente significativo e prejuízo social, profissional ou em outras áreas importantes da vida do indivíduo e não são devidos aos efeitos psicofisiológicos diretos de uma substância ou droga de abuso, ou então a outra condição médica (AMERICAN PSYCHIATRIC ASSOCIATION, 2013; HYLAND et al., 2018).

Tabela 1- Critérios diagnósticos do DSM-5 para o Transtorno de Estresse Pós-traumático

Transtorno de Estresse Pós-traumático	
A. Exposição a episódio concreto ou ameaça de morte, lesão grave ou violência sexual em uma (ou mais) das seguintes formas	1. Vivenciar diretamente o evento traumático. 2. Testemunhar pessoalmente o evento traumático ocorrido com outras pessoas. 3. Saber que o evento traumático ocorreu com familiar ou amigo próximo. Nos casos de episódio concreto ou ameaça de morte envolvendo um familiar ou amigo, é preciso que o evento tenha sido violento ou acidental. 4. Ser exposto[a] de forma repetida ou extrema a detalhes aversivos do evento traumático (p. ex., socorristas que recolhem restos de corpos humanos; policiais repetidamente expostos a detalhes de abuso infantil).
B. Presença de um (ou mais) dos seguintes sintomas intrusivos associados ao evento traumático, começando depois de sua ocorrência	1. Lembranças intrusivas angustiantes, recorrentes e involuntárias do evento traumático. 2. Sonhos angustiantes recorrentes nos quais o conteúdo e/ou o sentimento do sonho estão relacionados ao evento traumático. 3. Reações dissociativas (p. ex., flashbacks) nas quais o indivíduo sente ou age como se o evento traumático estivesse ocorrendo novamente. Essas reações podem ocorrer em um continuum, com a expressão mais extrema na forma de uma perda completa de percepção do ambiente ao redor. 4. Sofrimento psicológico intenso ou prolongado ante a exposição a sinais internos ou externos que simbolizem ou se assemelhem a algum aspecto do evento traumático. 5. Reações fisiológicas intensas a sinais internos ou externos que simbolizem ou se assemelhem a algum aspecto do evento traumático.
C. Evitação persistente de estímulos associados ao evento traumático, começando após a ocorrência do evento, conforme evidenciado por um ou ambos dos seguintes aspectos	1. Evitação ou esforços para evitar recordações, pensamentos ou sentimentos angustiantes acerca de ou associados de perto ao evento traumático. 2. Evitação ou esforços para evitar lembranças externas (pessoas, lugares, conversas, atividades, objetos, situações) que despertem recordações, pensamentos ou sentimentos angustiantes acerca de ou associados de perto ao evento traumático.
D. Alterações negativas em cognições e no humor	1. Incapacidade de recordar algum aspecto importante do evento traumático (geralmente devido a amnésia dissociativa, e não a outros fatores, como

associadas ao evento traumático começando ou piorando depois da ocorrência de tal evento, conforme evidenciado por dois (ou mais) dos seguintes aspectos	traumatismo craniano, álcool ou drogas). 2. Crenças ou expectativas negativas persistentes e exageradas a respeito de si mesmo, dos outros e do mundo (p. ex., "Sou mau", "Não se deve confiar em ninguém", "O mundo é perigoso", "Todo o meu sistema nervoso está arruinado para sempre"). 3. Cognições distorcidas persistentes a respeito da causa ou das consequências do evento traumático que levam o indivíduo a culpar a si mesmo ou os outros. 4. Estado emocional negativo persistente (p. ex., medo, pavor, raiva, culpa ou vergonha). 5. Interesse ou participação bastante diminuída em atividades significativas. 6. Sentimentos de distanciamento e alienação em relação aos outros. 7. Incapacidade persistente de sentir emoções positivas (p. ex., incapacidade de vivenciar sentimentos de felicidade, satisfação ou amor).
E. Alterações marcantes na excitação e na reatividade associadas ao evento traumático, começando ou piorando após o evento, conforme evidenciado por dois (ou mais) dos seguintes aspectos	1. Comportamento irritadiço e surtos de raiva (com pouca ou nenhuma provocação) geralmente expressos sob a forma de agressão verbal ou física em relação a pessoas e objetos. 2. Comportamento imprudente ou autodestrutivo. 3. Hipervigilância. 4. Resposta de sobressalto exagerada. 5. Problemas de concentração. 6. Perturbação do sono (p. ex., dificuldade para iniciar ou manter o sono, ou sono agitado).

Fonte: Adaptado de AMERICAN PSYCHIATRIC ASSOCIATION, 2013.
[a]O Critério A4 não se aplica à exposição por meio de mídia eletrônica, televisão, filmes ou fotografias, a menos que tal exposição esteja relacionada ao trabalho.
Nota: A perturbação (critérios B, C, D e E) dura mais de um mês.

A característica essencial do TEPT é, portanto, o desenvolvimento e persistência de sintomas característicos após a exposição a um ou mais eventos traumáticos. As reações emocionais ao evento traumático não fazem mais parte do critério A, já que a apresentação clínica do TEPT é variável. Por exemplo, alguns indivíduos podem reagir com temor, desespero, ou horror, havendo um predomínio dessas revivências de medo. Em outros, estados de humor anedônicos ou disfóricos e cognições negativas podem ser mais perturbadores. Determinados pacientes exibirão um quadro clínico no qual a excitação e sintomas reativos externalizantes serão proeminentes, enquanto em outros, sintomas dissociativos predominarão. Por fim, algumas pessoas exibirão combinações desses padrões de sintomas. Assim, a definição do DSM-5 ampliou o escopo do TEPT de seu foco tradicional em respostas de medo para incluir outras reações emocionais ao trauma. Por exemplo, militares treinados e profissionais que atuam em primeiros socorros a vítimas de acidentes

costumam reagir agudamente a um grande estressor sem experimentar medo como a principal resposta emocional (FRIEDMAN et al., 2011).

Com relação ao tipo de trauma sofrido, os eventos traumáticos do critério A que são experimentados diretamente incluem, mas não se limitam a, exposição a guerra como combatente ou civil, ameaça ou ocorrência real de agressão física (ataque físico, assalto, furto, abuso físico), ameaça ou ocorrência real de violência sexual, sequestro, ser mantido refém, ataque terrorista, tortura, encarceramento como prisioneiro de guerra, desastres naturais ou perpetrados pelo homem e acidentes automobilísticos graves. É importante assinalar que uma doença potencialmente fatal ou uma condição clínica debilitante não são consideradas necessariamente eventos traumáticos. Incidentes médicos que se qualificam como eventos traumáticos incluem eventos súbitos e catastróficos. Eventos testemunhados incluem, mas não se limitam a, observação de ameça de lesão ou lesão real grave, morte natural, abuso físico ou sexual de outra pessoa em virtude de agressão violenta, violência doméstica, acidente, guerra ou desastre ou catástrofe médica envolvendo um filho. Outrossim, a exposição indireta por ter conhecimento do evento está limitada a experiências que afetam parentes ou amigos próximos e experiências violentas ou acidentais (por exemplo, morte por causas naturais não se qualifica). Esses eventos incluem ataque pessoal violento, suicídio, acidente grave e lesão grave (AMERICAN PSYCHIATRIC ASSOCIATION, 2013).

O evento traumático pode ser revivenciado de diversas maneiras. É comum que a pessoa tenha lembranças recorrentes, involuntárias e intrusivas do evento (critério B1). Essas lembranças recorrentes do evento habitualmente incluem componentes comportamentais sensoriais ou fisiológicos. Um sintoma comum de revivência são sonhos angustiantes que repetem o evento em si ou são representativos ou relacionados tematicamente às ameaças principais envolvidas no evento traumático (critério B2). O sujeito pode experimentar sintomas dissociativos que duram desde alguns segundos até várias horas ou até mesmo dias, durante os quais aspectos do evento são revividos e a pessoa se comporta como se o evento estivesse ocorrendo novamente (critério B3). Por exemplo, intrusões visuais ou sensoriais breves de parte do evento traumático são conhecidos como *flashbacks*. Embora geralmente breves, esses sintomas mas altamente perturbadores, muitas vezes acompanhados de hiperatividade. Frequentemente ocorre sofrimento psicológico intenso (critério B4) ou reatividade fisiológica (critério B5) quando o indivíduo é exposto a "gatilhos" (eventos precipitadores que se assemelham a ou simbolizam algum aspecto do evento traumático), por exemplo: cheiro de fumaça depois de um incêndio; ver alguém semelhante a um criminoso que o atacou. Ainda, o fator desencadeante pode ser uma sensação física como aceleração

cardíaca ou tontura. Estímulos associados ao trauma passam a ser evitados pelo paciente de maneira persistente. Assim, é comum a evitação de lembranças, pensamentos, ou diálogos a respeito do trauma sofrido, bem como quaisquer atividades, objetos, situações ou pessoas que desencadeiem lembranças do evento (critério C2). As alterações negativas em cognições ou no humor associadas ao trauma (critério D1) podem assumir diversas formas, incluindo sintomas amnésticos tipicamente dissociativos (incapacidade de recordar algum aspecto importante do evento traumático, mas não devido a lesão craniana ou ao efeito de drogas). Outra forma são expectativas negativas exageradas e persistentes a respeito de aspectos importantes da vida (critério D2), por exemplo: "Nunca mais serei feliz"; "O mundo é um local muito perigoso"; "Nunca mais poderei confiar em ninguém". De maneira semelhante, pacientes com TEPT podem exibir cognições errôneas persistentes a respeito das causas do trauma que os levam a se culpar ou a culpar a outrem (critério D3), por exemplo: "Por que eu o deixei sair de casa naquele dia?"; "Eu deveria ter escolhido outro caminho". Ainda, um estado de humor negativo persistente (como raiva, culpa, vergonha) surge ou piora depois da exposição ao evento (critério D4). Ou então o indivíduo pode apresentar interesse ou participação notadamente menor em atividades que antes eram prazerosas (critério D5), sentindo-se alheio ou isolado de outras pessoas (critério D6), mas também pode exibir incapacidade persistente de sentir emoções positivas, tais como: felicidade, alegria, satisfação ou emoções associadas a intimidade, ternura e sexualidade (critério D7) (AMERICAN PSYCHIATRIC ASSOCIATION, 2013).

Além disso, os pacientes com TEPT exibem alterações marcantes na excitação e na reatividade, muitoas vezes irritando-se facilmente ou até mesmo adotando um comportamento agressivo mediante pouca ou nenhuma provocação (critério E1), ocasiões em que podem envolver-se em brigas ou destruir objetos. Alguns pacientes passam a comportar-se de maneira imprudente e até autodestrutiva (critério E2), como: dirigir perigosamente, abusar de álcool ou outras drogas, manifestar conduta automutilante ou suicida. O TEPT é com frequência caracterizado por hipersensibilidade a ameaças potenciais, incluindo as relacionadas à experiência traumática (critério E3). Indivíduos com TEPT podem apresentar-se bastante reativos a estímulos inesperados, exibindo uma resposta de sobressalto intensa ou nervosismo mediante ruídos elevados ou movimentos inesperados (critério E4), por exemplo: pulando de susto em resposta a um toque em seu ombro. Dificuldades de concentração, incluindo dificuldade para lembrar-se de eventos rotineiros ou participar de tarefas que exijam concentração são comumente relatadas (critério E5). Problemas para iniciar e manter o sono são comuns no TEPT e podem estar associados a pesadelos e preocupações com a segurança

ou a hiperexcitação generalizada, que interfere no sono adequado (critério E6). Alguns indivíduos também sofrem sintomas dissociativos persistentes de distanciamento do próprio corpo (despersonalização) ou do mundo ao redor (desrealização). Caso esses sintomas se façam presentes o TEPT levará o especificador "com sintomas dissociativos" (AMERICAN PSYCHIATRIC ASSOCIATION, 2013).

1.2 ASPECTOS EPIDEMIOLÓGICOS E ÔNUS DA DOENÇA

Embora a maioria dos indivíduos responda a um evento traumático de maneira resiliente, um grupo de pessoas (geralmente cerca de 7.8% dos expostos) irá desenvolver o TEPT (KESSLER et al., 1995). Trata-se, portanto, de uma patologia prevalente em termos globais, com metade de todos os casos sendo persistentes. As estimativas mundias variam entre os países, sendo influenciadas pela natureza do trauma (por exemplo, são esperadas prevalências mais elevadas durante uma guerra civil, ou em vítimas de violência sexual) e pela acurácia dos instrumentos validados utilizados em sua mensuração. Enquanto as prevalências ao longo da vida fornecem uma estimativa da proporção da população que desenvolve TEPT, prevalências atuais ou de 12 meses incluem novos casos (incidentes) e casos persistentes. A proporção de casos nos últimos 12 meses entre os casos ao longo da vida é um indicador de TEPT persistente. No entanto, as prevalências no último mês têm grande relevância para informar o ônus atribuído ao TEPT em um determinado momento (por exemplo, taxas de absenteísmo ao trabalho, necessidade de uso de serviços de saúde) (KOENEN et al., 2017).

Estudos epidemiológicos relataram taxas de prevalência do TEPT ao longo da vida de 13 a 20,4% para o sexo feminino e 6,2 a 8,2% para o sexo masculino (BRESLAU et al., 1991; KESSLER et al., 1995). A prevalência média de TEPT conforme dados publicados em uma revisão sistemática (SANTIAGO et al., 2013) foi de 28,8% (variação = 3,1 a 7,5%) em 1 mês e de 17,0% (variação = 0,6 a 43,8%) em 12 meses. Com relação ao curso clínico da doença cerca de um terço (34,8%) dos pacientes teve remissão dos sintomas após 3 meses, enquanto quase 40% das pessoas com TEPT (39,1%) apresentaram um curso crônico (SANTIAGO et al., 2013).

O TEPT tem um impacto significativo na maioria das áreas de funcionamento diário, conforme conceituado na Classificação Internacional de Funcionalidade, Incapacidade e

Saúde da OMS. Quando comparados a pacientes sem TEPT indivíduos com o diagnóstico apresentaram deficiências significativas ($p < 0,001$) com tamanhos de efeito de médio a grande ($d > 0,5$) nos domínios tarefas e demandas gerais; mobilidade; autocuidado; vida doméstica; relações interpessoais; vida comunitária, social e cívica. Deficiências significativas com tamanhos de efeito pequenos a médios nos mesmos domínios foram observados quando o TEPT foi comparado a outros transtornos mentais. Portanto, a detecção precoce e o tratamento direcionado à recuperação da funcionalidade são fundamentais nessa população de pacientes (JELLESTAD et al., 2021).

1.3 FATORES DE RISCO E PROGNÓSTICOS

Dado o fato de a maioria das pessoas expostas a eventos traumáticos não desenvolverem o TEPT, há diferenças individuais importantes na propensão em manifestar o transtorno, além dos fatores socioambientais envolvidos (BRYANT et al., 2017).

Muitos dos fatores de risco são os mesmos observados em diversos transtornos psiquiátricos, como: sexo feminino, baixo nível socioeconômico, transtorno mental prévio, histórico familiar de transtornos mentais e hitória de abuso na infância. Em termos de fatores de vulnerabilidade mais específicos para o TEPT, existem evidências de que algumas características da natureza do evento traumático têm maior probabilidade de desencadear a patologia. Assim, há maior probabilidade de ocorrência após eventos traumáticos interpessoais e trauma prolongado (BREWIN et al., 2000; TORTELLA-FELIU et al., 2019; CHRISTIANSEN e BERKE, 2020). Por exemplo, há taxas mais baixas do transtorno após desastres naturais (5 a 10%, em média) quando comparadas à agressão sexual (acima de 40%) (KESSLER et al., 1995; CREAMER et al., 2001).

A resposta subjetiva ao trauma também é preditiva, com reações dissociativas agudas (MURRAY et al., 2002; GREENE, 2018) e avaliações catastróficas sobre o resultado do evento estando associadas à maior incidência e gravidade posterior do TEPT. As condições sociofamiliares pós-trauma também estão associadas ao TEPT, com baixo suporte social e estressores continuados (por exemplo, ser vítima de violência doméstica) contribuindo para um maior risco de desenvolvimento da patologia (BREWIN et al., 2000; HOWARD et al., 2013; FARHOOD et al., 2018).

Cumpre ressaltar que após grandes catástrofes, transtornos psiquiátricos como depressão, ansiedade e transtorno de estresse pós-traumático são comuns e bio-desastres podem atuar como barreiras ao acesso a cuidados médico-psiquiátricos adequados. Nesse contexto, a doença por coronavírus 2019 (COVID-19), causada pelo coronavírus 2 da síndrome respiratória aguda grave (SARS-CoV-2), foi relatada pela primeira vez em Wuhan, província de Hubei, China em dezembro de 2019. O surto provocado pelo vírus emergente SARS-Cov-2 tem sido considerado a pandemia mais grave desde a gripe espanhola, ocasionando milhões de mortes ao redor do mundo e perdas à saúde individual, ao bem-estar social e à economia das nações. Soma-se aos fatores etiológicos psicossociais o fato de o vírus SARS-Cov-2 ter neurotropismo pelo sistema nervoso central (SNC). Ele invade as células endoteliais via receptor transmembrana da enzima conversora de angiotensina, possibilitado pela protease transmembrana serina 2. A elevação das citocinas e a ativação microglial resultam em aumento de glutamato e ácido quinolínico e disfunção neurotransmissora. A cascata de coagulação e elevação do fator de *Von Willebrand* propiciam eventos trombóticos. Assim, as alterações neurotransmissoras, incluindo a excitotoxicidade glutamatérgica, o comprometimento vascular e a hipóxia contribuem para disfunção e/ou perda neuronal pós-COVID. Em consonância com fatores socioambientais como o adoecimento agudo de entes queridos, essas alterações neurobiológicas atribuídas ao vírus resultam em um aumento na incidência de transtornos neuropsiquiátricos, incluindo o TEPT. Em uma importante coorte com 236.379 pacientes a incidência de transtornos neuropsiquiátricos nos seis meses que se seguiram ao diagnóstico de Covid-19 foi de 33,62% (IC 95% 33·17 – 34·07), sendo que nos pacientes com COVID-19 grave internados em UTI a incidência foi 46,42% (IC 95% 44·78 – 48·09) (TAQUET et al., 2021). A prevalência geral de TEPT associada a pandemia de COVID-19 foi de 24,9% (IC 95%: 11,0% - 46,8%) segundo uma metanálise cuja busca sistemática de artigos foi conduzida na literatura até maio/2020 (ZHAO et al., 2021). Em uma outra metanálise com dados extraídos até outubro/2020 foi reportada uma prevalência média de TEPT associado ao COVID-19 de 28.34% (IC 95% 23.03 - 34.32%). (QIU et al., 2021)

1.4 NEUROBIOLOGIA DO TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO

Um dos modelos neurobiológicos mais estudados no desenvolvimento do TEPT envolve o condicionamento de medo. Esse modelo postula que, no momento do trauma, a

liberação de hormônios do estresse em associação com o medo experimentado pelo indivíduo resulta em um forte aprendizado associativo entre as pistas presentes no momento do trauma e as respostas ao medo. Essas pistas associadas assumem a propriedade de antever ameaças futuras, resultando, assim, em uma revivência do medo quando o indivíduo é exposto a lembretes internos e externos do trauma. Esse modelo também postula que a recuperação das reações iniciais de estresse geralmente envolve o aprendizado da extinção, no qual a pessoa é repetidamente exposta a lembretes do trauma, mas nessas ocasiões não há consequência adversa; dessa forma há um novo aprendizado de que as pistas previamente condicionadas agora sinalizam segurança (PITMAN et al., 2012; BRYANT, 2019). Além disso, há evidências de mudanças neurobiológicas ocorridas nos pacientes com TEPT em circuitos tipicamente implicados no condicionamento do medo, como amígdala, córtex pré-frontal e hipocampo. Dados de uma metanálise indicam que o TEPT está associado a um tamanho menor do hipocampo e que esse achado pode ser observado bilateralmente (SMITH, 2005). Todavia, se a redução volumétrica hipocampal é fator de risco para TEPT ou consequência do mesmo ainda resta ser determinado em novos estudos (LOGUE et al., 2019; PATEL et al., 2012). Outras pesquisas usaram tarefas de provocação de medo para ativar a rede de respostas a ameaças em pacientes com TEPT. Um dos achados mais consistentes foi a subativação das regiões do córtex pré-frontal medial, sugerindo o comprometimento dos processos regulatórios que promovem a extinção (PATEL et al., 2012). Ademais, há evidências de desregulação noradrenérgica, a qual foi implicada nos sintomas intrusivos de revivência traumática (HENDRICKSON e RASKIND, 2016; MCGAUGH, 2000; SOUTHWICK et al., 1997).

Consistente com os modelos de condicionamento do medo também é a evidência de frequência cardíaca de repouso elevada nos dias após o trauma naqueles que subsequentemente desenvolvem o TEPT (BRYANT et al., 2000), particularmente em resposta a lembretes do trauma (O'DONNELL et al., 2007).

Embora níveis aumentados de cortisol estejam tipicamente associados ao estresse crônico, no TEPT são encontrados níveis mais baixos de cortisol peri-trauma. Além disso, os níveis reduzidos de cortisol logo após a ocorrência de um evento traumático são preditores de maior gravidade dos sintomas de TEPT nos meses subsequentes (DELAHANTY et al., 2000; DE MORAES COSTA, 2016). Fisiologicamente a ligação do cortisol aos receptores de glicocorticóides gera um ciclo de feedback negativo que promove a homeostase em resposta ao estresse (YEHUDA, 1997). O achado aparentemente paradoxal acerca dos glicocorticóides em resposta ao trauma de pacientes que posteriormente desenvolverão o TEPT pode ser

interpretado em termos de uma atividade continuamente elevada do eixo hipotálamo-hipófise-adrenal (HPA), resultando em uma resposta catecolaminérgica protraída e exagerada, gerando uma consolidação excessiva de memórias traumáticas. Esta ideia recebeu algum apoio de estudos relatando que, em modelos animais, a administração de hidrocortisona logo após a exposição ao estressor resulta em redução de reações semelhantes ao TEPT (COHEN et al., 2008). Há, também, evidências em humanos de que a administração precoce de glicocorticoides após uma trauma psíquico limitaria os sintomas subsequentes de TEPT (ZOHAR et al., 2011).

Também é importante assinalar que há evidências indiretas de um potencial papel protetor opioide na fase aguda após um trauma psíquico (HOLBROOK et al., 2010). O *locus coeruleus*, que produz noradrenalina, é inibido pela morfina e o trabalho com animais indica que injeções de morfina na amígdala prejudicam a consolidação da memória de medo. Contudo, ainda são necessários ensaios clínicos randomizados (ECRs) em humanos (BRYANT et al., 2009).

Possíveis fatores neurobiológicos associados a uma prevalência mais elevada do TEPT no sexo feminino de acorodo com a literatura incluem: maior resposta noradrenérgica a estímulos aversivos (LITHARI et al., 2010; SEGAL e CAHILL, 2009); ampliação da magnitude do sobressalto potencializado pelo contexto (GRILLON, 2008) e maior reatividade da amígdala após estímulos ameaçadores (WILLIAMS et al., 2005). Ainda, a progesterona poderia facilitar memórias emocionais por ligar-se aos receptores de glicocorticóides, afetando, assim, a sua liberação endógena (KIRSCHBAUM et al., 1999).

Por fim, há evidências indicando que fatores genéticos respondem por 30 a 72% da vulnerabilidade para desenvolver o TEPT (TRUE et al., 1993; SARTOR et al., 2011). São exemplos: o polimorfismo funcional na região promotora do gene do transportador de serotonina (SLC6A4) (LESCH et al., 1996), o alelo curto (5-HTTLPR S) que reduz a expressão serotoninérgica (HARTLEY et al., 2012) e uma variante funcional em um gene que codifica uma co-chaperona do receptor glicocorticóide (FKBP5) (BINDER et al., 2008). Contudo, os genes associados ao TEPT são também ligados a outros transtornos psiquiátricos, como o transtorno depressivo maior, o transtorno de ansiedade generalizada, o transtorno do pânico e uso de substâncias (KOENEN et al., 2008).

1.5 TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO E SONO

Alterações do sono são comumente relatadas por pacientes com TEPT (MAHER et al., 2006). Por exemplo, os estudos documentam estimativas de até 80 a 90% dos pacientes experimentando sintomas de insônia e 50 a 70% manifestando pesadelos (NEYLAN et al., 1998; LESKIN et al., 2002).

Quando comparados com controles saudáveis, indivíduos com TEPT relatam má qualidade do sono. Eles descrevem baixa eficiência do sono, maior latência do sono, insônia de manutenção; sono interrompido por maior número de despertares e ocorrência mais frequente de sono não restaurador, agravando o sofrimento e prejuízos associados durante o dia (LIPINSKA et al., 2016; SLIGHTAM et al., 2018). A estreita ligação entre trauma e sono se reflete, por exemplo, nos critérios diagnósticos da patologia, que incluem pesadelos e perturbação do sono (por exemplo: dificuldade para iniciar ou manter o sono, ou sono agitado) (AMERICAN PSYCHIATRIC ASSOCIATION, 2013).

As alterações do sono estão associadas a maior gravidade, prejuízo funcional e cronicidade do transtorno (GIOSAN et al., 2015; SHORT et al., 2018). Por exemplo, dados prospectivos de mulheres jovens vítimas de agressão sexual com TEPT versus controles sem TEPT evidenciaram uma qualidade de sono prejudicada e que o escore global do Índice de qualidade do sono de Pittsburgh (PSQI) foi um preditor significativo de melhora do TEPT. Essa melhor qualidade do sono significativamente associada à melhora do TEPT foi independente de depressão e de ansiedade (YEH et al., 2021).

Em comparação com dados mais robustos de alterações subjetivas no sono de pacientes com TEPT, a documentação de alterações objetivas (por exemplo, por meio de polissonografia ou actigrafia) produziu dados pouco consistentes (MAHER et al., 2006). Embora algumas pesquisas sugiram maior fragmentação do sono e despertares noturnos em pacientes com TEPT, outros estudos não encontraram diferenças quando comparados a indivíduos controles (HARVEY et al., 2003). Os resultados de uma metanálise que incluiu vinte estudos polissonográficos comparando o sono em pessoas com e sem TEPT mostraram que os pacientes com TEPT tiveram mais sono de estágio 1, menos sono de ondas lentas e maior densidade de movimento rápido dos olhos (REM). Essa disfunção do sono REM observada poderia refletir os padrões estereotipados de pesadelos repetitivos, bem como maiores sobressaltos. No entanto, não há um perfil de perturbações objetivas do sono que sejam específicas do TEPT, especialmente quando o comparamos a pacientes diagnosticados com outros transtornos neuropsiquiátricos. (KOBAYASHI et al., 2007).

Algumas teorias têm sido propostas para elucidar a relação entre TEPT e distúrbios do sono sugerindo alterações no funcionamento da amigdala, hipocampo e córtex pré-frontal medial durante o sono REM (EL-SOLH et al., 2018). Os achados de neuroimagem funcional em pacientes com TEPT são consistentes com modelos animais e estudos pré-clínicos de condicionamento e extinção do medo em humanos. Eles demonstram uma hiper-responsividade da amígdala a estímulos relacionados à ameaça, bem como redução da capacidade de resposta do córtex pré-frontal medial, que exerce controle inibitório sobre a amígdala. Tanto a hiperatividade amigdaliana quanto a redução da atividade do córtex pré-frontal medial afetam a regulação do sono REM e não-REM (GERMAIN et al., 2008).

1.6 ABORDAGEM FARMACOLÓGICA BASEADA EM EVIDÊNCIAS

1.6.1 Tratamento Farmacológico do TEPT

Abordagens farmacológicas e não farmacológicas têm sido usadas para aliviar sintomas nas pessoas com TEPT. Mediante o crescente reconhecimento de que o TEPT é caracterizado por disfunções neurobiológicas específicas e que os seus variados grupos de sintomas (por exemplo, intrusivos, de entorpecimento ou hiperexcitação) possam ser mediados por diferentes neurotransmissores, o uso de medicamentos ganhou maior embasamento científico (YEHUDA et al., 2015).

Os fármacos que têm sido utilizados incluem principalmente antidepressivos, antipsicóticos e anticonvulsivantes. Atualmente, dois inibidores seletivos da recaptação da serotonina (ISRS), sertralina e paroxetina, são os únicos medicamentos aprovados pelo *Food and Drug Administration* para o TEPT, sendo geralmente recomendadas em diretrizes como a primeira abordagem medicamentosa a ser implementada. Outrossim, o tratamento farmacológico do TEPT tem sido alvo de intensos debates na literatura, pois não há consenso nas principais diretrizes quanto à efetividade dos agentes farmacológicos mais comumente prescritos (APA, 2019; ALLIANCE, 2018; VA/DoD, 2017).

Portanto, além de sintetizar as pesquisas existentes, a avaliação ampla e contínua da literatura por meio de metanálises atualizadas de ECRs de farmacoterapia no TEPT pode ser útil para a elucidação de várias questões, por exemplo: como o uso de novos agentes surgidos

mais recentemente se compara às medicações mais antigas? Há alguma medicação mais tolerável para o paciente em termos de eventos adversos, quando comparada às demais? Há fármacos mais eficazes para a melhora de sintomas específicos, como qualidade do sono?

Diante de tal fato, faz-se mister empregar uma metodologia capaz de apontar a qualidade das evidências. Considerando os milhões de pessoas afetadas pelo trauma, a adequada identificação de fármacos com um perfil favorável de benefícios *versus* riscos seria capaz de nortear a prática clínica, otimizando os desfechos do tratamento e, com isso, reduzindo o ônus para a saúde e a sociedade devido à doença (BRYANT, 2019).

1.6.2 Tratamento farmacológico das alterações do sono associadas ao TEPT

O tratamento das principais alterações do sono associadas ao TEPT tem se baseado na prática no uso de medicações como indutores do sono benzodiazepínicos e não-benzodiazepínicos e antidepressivos, apesar da escassez de evidências de sua eficácia e de preocupações acerca de sua segurança nessa população (LIPINSKA et al., 2016). Tendo em vista resultados conflitantes e preocupações sobre tolerância, dependência e efeitos adversos de ordem cognitiva, o uso de indutores do sono benzodiazepínicos não é recomendado para o tratamento dos distúrbios do sono associados ao TEPT (GUINA et al., 2015). Embora os hipnóticos não benzodiazepínicos estejam associados a menor risco de dependência e não afetem de maneira proeminente a arquitetura do sono (NUTT e STAHL, 2010), as evidências disponíveis até o momento não os apoiam como tratamento de primeira linha para distúrbios do sono associados ao TEPT. Por exemplo, um ECR examinando a eficácia do zolpidem como terapia adjuvante a um ISRS demonstrou que, em comparação com a hipnoterapia, o zolpidem não foi eficaz na redução dos distúrbios do sono relacionados ao TEPT (ABRAMOWITZ et al., 2008). Por outro lado, os participantes com TEPT de um ECR de eszopiclona controlado por placebo relataram melhora da qualidade geral do sono e redução da latência do sono com a medicação. Todavia, este estudo possui limitações, incluindo um pequeno tamanho amostral (N = 24) e curta duração (3 semanas) (POLLACK et al., 2011). Assim, estudos novos e robustos, baseados na mensuração de alterações objetivas e subjetivas do sono no TEPT são altamente desejáveis a fim de estabelecer a eficácia e a segurança dos indutores do sono em pacientes portadores do transtorno (LIPINSKA et al., 2016).

Com relação aos pesadelos no TEPT, metanálises de ensaios clínicos randomizados comprovaram a eficácia da prazosina para esse sintoma em particular, havendo a necessidade de maiores estudos para avaliar os seus efeitos noutras queixas relacionadas ao sono, como a insônia (GEORGE et al., 2016; ZHANG et al., 2020).

Outrossim, os antidepressivos são os psicofármacos mais comumente utilizados no TEPT. Além de serem a única classe farmacológica com duas medicações aprovadas pelo FDA para o transtorno, eles foram estudados mais amplamente e também são prescritos para o tratamento do transtorno depressivo maior, que é uma patologia frequentemente comórbida com o TEPT. Todavia, para o tratamento dos sintomas relacionados ao sono e melhora da qualidade geral de sono no TEPT os dados são escassos e não há consenso quanto ao seu uso. Ademais, mesmo os antidepressivos que foram considerados primeira linha de tratamento por diretrizes do manejo farmacológico do TEPT (como o ISRS sertralina e o ISRSN venlafaxina) (APA, 2019; ALLIANCE, 2018; VA/DoD, 2017) parecem exibir efeitos modestos ou até mesmo adversos no sono (COLVONEN et al., 2018). A trazodona, por exemplo, é um antidepressivo comumente prescrito para pacientes com insônia inicial devido às suas propriedades farmacológicas (NUTT e STAHL, 2010), mas o seu uso para a melhora da qualidade do sono no TEPT é apoiado por relatos de caso e ensaios abertos. Assim, resta inequívoca a importância de operacionalizar a busca e a interpretação de evidências de maior nível que dêem suporte à prática clínica.

2 OBJETIVOS

2.1 OBJETIVO GERAL

- Avaliar eficácia e aceitabilidade comparada dos psicofármacos para o tratamento do TEPT em adultos.
- Avaliar eficácia, aceitabilidade e tolerabilidade comparada dos antidepressivos para tratar problemas de sono associados ao TEPT em adultos.

2.2 OBJETIVOS ESPECÍFICOS

- Investigar quais psicofármacos são mais eficazes do que o placebo para a redução dos sintomas de TEPT em adultos.
- Investigar quais psicofármacos são mais bem aceitos do que o placebo para a redução dos sintomas de TEPT em adultos.
- Investigar quais antidepressivos são mais eficazes do que o placebo para a melhora da qualidade do sono em pacientes adultos com TEPT.
- Investigar quais antidepressivos são mais bem aceitos do que o placebo para a melhora da qualidade do sono em pacientes adultos com TEPT.
- Investigar quais antidepressivos são mais bem tolerados do que o placebo para a melhora da qualidade do sono em pacientes adultos com TEPT.

- Determinar qual é o melhor antidepressivo para o aprimoramento da qualidade do sono em pacientes adultos com TEPT, com base na eficácia, aceitabilidade e tolerabilidade.

3 METODOLOGIA, RESULTADOS E DISCUSSÃO

As seções “Métodos”, “Resultados” e “Discussão” estão apresentados nesta tese na forma de dois artigos científicos, um deles publicado na revista *Journal of Psychiatric Research* e o outro manuscrito submetido ao periódico *European Neuropsychopharmacology*.

Pharmacological Treatments for Adults with Post-Traumatic Stress Disorder: A Network Meta-Analysis of Comparative Efficacy and Acceptability

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HIGHLIGHTS

- The network meta-analysis (NMA) strengthens the evidence base for the utilization of topiramate, risperidone, quetiapine, paroxetine, venlafaxine, fluoxetine, and sertraline as possible first-line alternatives for reducing symptoms of post-traumatic stress disorder (PTSD).
- Fluoxetine, lamotrigine, and phenelzine outperformed placebo in terms of acceptability.
- When a balance has to be made between efficacy and acceptability, this NMA supports fluoxetine as a first-line pharmacological choice for PTSD.
- To the best of our knowledge, this is the largest contemporary NMA on the subject and the addition of new medications is an important extension of previous meta-analyses, enabling a larger number of drug comparisons.
- The present NMA provides the most up-to date body of information to health practitioners about the pharmacological treatment options for PTSD supported by statistically significant evidence and highlights several noteworthy aspects relevant to day-to-day practice.

ABSTRACT

Background: The purpose of this study was to compare efficacy and acceptability among drug treatments for adults with post-traumatic stress disorder (PTSD) through a systematic review, random-effects pairwise and network meta-analyses. **Methods:** Double-blind randomized controlled trials comparing pharmacological interventions for adults with PTSD were searched from database inception through Aug. 28, 2018, on Cochrane (Central), Embase, LILACS, PILOTS, PsycINFO, PubMed, and Web of Science. Clinical trial registries and the websites of pharmaceutical companies were also searched. The GRADE system was used to assess the quality of the evidence. **Results**: The systematic review included 58 studies comprising 6766 patients randomized to 26 different interventions. Regarding efficacy, topiramate (SMD=-0.57;95%CrI: -1.07,-0.10), risperidone (SMD=-0.53;95%CrI: -0.93,-0.15), quetiapine (SMD=-0.59;95%CrI: -1.06,-0.11), paroxetine (SMD=-0.35;95%CrI: -0.48,-0.21), venlafaxine (SMD=-0.25;95%CrI: -0.44,-0.05), fluoxetine (SMD=-0.28;95%CrI: -0.46,-0.08), and sertraline (SMD=-0.21;95%CrI: -0.33,-0.09) outperformed placebo. Moreover, phenelzine (RR=3.39;95%CrI: 1.43,11.09), lamotrigine (RR=4.39;95%CrI: 1.18,26.38), and fluoxetine (RR=1.28%CrI: 1.01,1.59) outperformed placebo in terms of acceptability. **Conclusions**: The NMA supports topiramate, risperidone, quetiapine, paroxetine, venlafaxine, fluoxetine and sertraline as effective pharmacological choices for the treatment of PTSD. Quetiapine and topiramate have the shortcoming of relying on a few small studies, but the clinically meaningful change in symptoms is noteworthy and merits further investigation. Among the pharmacological treatments with evidence of efficacy compared to placebo, fluoxetine achieved a relatively high rank regarding acceptability. To the best of our knowledge, this is the largest contemporary NMA on the subject and the addition of new medications is an important extension of previous meta-analyses, enabling a larger number of drug comparisons.

Keywords: Stress Disorders, Post-Traumatic; Network Meta-Analysis; Multiple Treatment Comparison Meta-Analysis; Psychopharmacology.

1. INTRODUCTION

Exposure to a traumatic life event has been associated with substantial long-term consequences, including an increased risk for suicide and post-traumatic stress disorder (PTSD) (Bryant, 2019; Shalev et al., 2019; Yehuda et al., 2015; Wilks et al., 2019). The lasting severe psychological effects of PTSD contribute to disability and premature mortality and require the considerable utilization of healthcare services (Bryant, 2019; Pacella et al., 2013).

Drug therapy for PTSD may assist by correcting dysfunctions of the neurotransmitter and neuroendocrine systems as well as functional neuroanatomical abnormalities thought to play a role in causing and/or maintaining the symptoms (Yehuda et al., 2015; Uniyal et al., 2019). Although the specific role of neurotransmitter systems in the psychopathology of PTSD awaits further elucidation, a few serotonergic drugs have been reported to promote neuroendocrine changes and increase hippocampal volume (a smaller hippocampus has been observed in individuals with PTSD) (Pitman et al., 2012; Vermetten et al., 2003). Serotonergic and noradrenergic drugs also contribute to the treatment of PTSD, diminishing the re-experiencing of the traumatic event and engendering potential clinical benefits (Bryant et al., 2019; Costa, 2016). Moreover, evidence of glutamatergic abnormalities found in studies on PTSD in humans implies that glutamate-modulating agents may be useful pharmacologic treatments for PTSD (Averill et al., 2017).

However, the optimal pharmacological strategy is challenging due to the high prevalence of psychiatric and substance use comorbidities (Bryant, 2019; Krystal et al., 2017; NICE, 2018; APA, 2017). Nearly half of PTSD patients do not experience remission after a period of more than three years, which underscores a significant unmet need for pharmacotherapy that is scientifically sound and supported by clinical practice (Krystal et al., 2017; Morina et al., 2014). Furthermore, the substantial comorbidity rates underscore the need to identify effective, well-accepted drugs that can be used for individuals with PTSD who struggle with another psychiatric disorder or clinical condition (Nichter et al., 2020; Bryant, 2019; Krystal et al., 2017; APA, 2013).

Drug recommendations differ across PTSD treatment guidelines (NICE, 2018; APA, 2017; VA/DoD, 2017). Since the last publication of a multiple-treatments meta-

analysis (Cipriani et al., 2018), the number of studies and medications has increased, enabling more and new drug comparisons. Thus, it remains unclear what currently available pharmacological strategy is the most effective for PTSD. In the present systematic review and network meta-analysis (NMA), we use a unique set of eligibility criteria, update and extend cumulative evidence, adding new drugs as well as novel published and unpublished randomized controlled trials (RCTs) not included in previous meta-analyses (Cipriani et al., 2018; Watts et al., 2013; Hoskins et al., 2015) to contribute knowledge to the field. The decision to use unpublished RCTs was based on the fact that meta-analyses involving only published studies may overestimate effect sizes and lead to improper conclusions (Siddaway et al., 2019). Furthermore, we synthesize and critique the existing literature, pointing out where evidence is missing and where its quality is low.

2. METHODS

This study followed the PRISMA for Network Meta-Analyses extension statement (the checklist is presented in Appendix S1 in the data supplement) and Cochrane's standards for the conduct of new Cochrane Intervention Reviews (Hutton et al., 2015; Higgins et al., 2016a; Higgins et al., 2016b). We also used the GRADE system to estimate de certainty of evidence (Puhan et al., 2014). The protocol for this study was registered with PROSPERO (CRD42017055620).

2.1 Selection criteria

We employed a methodical, comprehensive, replicable and systematic search process in order to synthesize evidence from Randomized controlled trials (RCTs) of pharmacotherapy in adult patients with PTSD.

What questions does this systematic review and network meta-analysis aimed to answer?

(a) Is pharmacotherapy an effective form of treatment for PTSD in adults?

(b) What is the best pharmacological treatment for adult patients with a PTSD diagnose, based on efficacy?

(c) Is medication well accepted for patients in terms of all-cause discontinuation during the pharmacological treatment?

(d) What is the best pharmacological treatment for adult patients with a PTSD diagnose, based on acceptability?

The selection of double-blind randomized controlled trials (RCT) was based on the following eligibility criteria:

Participants: Studies including adults diagnosed with PTSD provided by a validated measure of diagnosis. We placed no restrictions on the basis of gender of patients, type of trauma suffered (e.g. combat trauma, sexual trauma, interpersonal violence, natural disaster), duration of PTSD symptoms, treatment setting (inpatients or outpatients), or comorbidities (e.g. major depression, alcohol use disorder). With respect to severity of PTSD, studies in which all included participants were deemed to be treatment-resistant were excluded, since our focus was not patients suffering from

treatment-refractory PTSD who previously failed to respond to established treatments (Hamner et al., 2014; Koek et al., 2016; Sippel et al., 2018).

Intervention: Utilization of any active drug, used combined or as monotherapy, for at least 8 weeks, allocated by a parallel assignment (non-crossover trial). Trials of treatment-resistant or treatment-refractory PTSD (definition according to the trial authors') were excluded, as we believe this could interfere with the transitivity assumption of NMA and because our target was not strategies for augmenting antidepressants in treatment-resistant PTSD (Hamner et al., 2014; Koek et al., 2016; Sippel et al., 2018). The studies assessing medication prophylaxis for PTSD or medication administered exclusively or primarily for the treatment of comorbidities in PTSD (e.g., disulfiram or naltrexone for alcohol dependence) were not eligible for inclusion in this review.

Comparator: Use of placebo or another active drug (head-to-head trial). We also included trials with multiple medication arms. RCTs using an intervention and its comparison in patients with ongoing psychiatric pharmacotherapy regimens typical for PTSD (the last not randomly assigned), though limiting the ability to explore the interactive effects of pharmacotherapies, were not excluded from the systematic review.

Outcomes: Our outcomes were PTSD treatment efficacy and acceptability. We defined efficacy as mean change scores (from baseline to endpoint) on continuous measures of symptom severity (continuous outcome) accordingly to the Clinician Administered PTSD Scale (Blake et al., 1995) or related measure (Brewin et al., 2005). We defined acceptability as the number of patients who left the study early for any reason (treatment discontinuation/any cause dropouts) during the pharmacological treatment of the total number of patients randomly assigned to each treatment group.

2.2 Search strategy

An extensive literature search was performed to reduce the risk of skewed data and identify as much relevant evidence as possible (Higgins et al., 2016b). We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, LILACS, PILOTS, PsycINFO, PubMed (MEDLINE), and Web of Science databases for articles published up to August 28th, 2018 (Appendix S2 in the data supplement.). Hand searches were also performed of the reference lists of retrieved papers and previous

systematic reviews. Complementary searches were performed in clinical trial registries as well as the websites of pharmaceutical companies for drugs of interest.

Two reviewers (G.M.C. and A.J.S.B.) independently screened papers to identify eligible studies. Duplicates were removed with the aid of the Mendeley® Reference Manager (Elsevier, Oxford, UK). Titles and abstracts were analyzed for the preselection of relevant articles to be submitted to full-text analysis. Studies without abstracts but with titles suggesting relevance to the objectives of this review were also submitted to full-text analysis.

2.3 Data collection

The articles were scrutinized carefully and the following characteristics were extracted from each trial: sample size; drug class, dose range of interventions, and comparisons; treatment duration; type of trauma; age and sex of participants; diagnosis of PTSD and severity measures; and funding sources. Authors were contacted by e-mail to obtain missing information when necessary. Divergences of opinion between the two reviewers were discussed and if a consensus was not reached, a third senior researcher (C.M.) made the final judgment regarding inclusion or exclusion.

2.4 Data analysis

Efficacy analysis was performed to compare the reduction in symptoms of PTSD using continuous measures of symptom severity (continuous outcome). We extracted mean and standard deviation (SD) values of the change in symptoms from baseline in both treatment and control groups provided by each study. If not available, the change from baseline in each treatment arm was calculated based on baseline and follow-up mean and SD values considering no correlation between these values (conservative approach for estimating SD for the change from baseline). For one trial (Padala et al., 2006), the missing SDs were imputed by calculating pooled SDs from all the other studies in the same meta-analysis that used the clinician-administered PTSD scale (Blake et al., 1995) to measure symptoms in patients treated with risperidone. One trial (Batki et al., 2014) was excluded from the efficacy analysis (both pairwise and network) due to incomplete outcome data. Standardized mean differences (SMDs) constituted the effect size measure since different PTSD rating scales were used (Higgins et al., 2016a;

Higgins et al., 2016b). Acceptability (dichotomous outcome) was analyzed by calculating relative risk (RR). It was not possible to obtain all-cause dropouts per treatment group in three published (Baker et al., 1995; Becker et al., 2007; Davidson et al., 2006) and one unpublished trial (SKB627) which were consequently excluded from both pairwise and network analysis. When multiple arms with fixed doses of the same drug were used within a trial (Martenyi et al., 2007; Marshall et al., 2001), the arm with the largest change in symptoms was analyzed for efficacy, while the number of randomized and withdrawn subjects was summed across groups for the analysis of acceptability, as performed elsewhere (Slee et al., 2019).

Direct evidence was computed for all pairwise comparisons with available head-to-head data. For those comparisons with more than one study, traditional meta-analysis using random-effects model with DerSimonian and Laird (1986) variance estimator were applied. Heterogeneity was evaluated using the inconsistency test proposed by Higgins et al. (2003). As performed in a previous study (Hayasaka et al., 2015), each three-arm trial was analyzed as three two-arm trials and the sample size of each arm was divided by half, when necessary, to avoid double-counting the same subjects. Results are presented as point estimates with 95% confidence intervals (CI).

The mixed treatment comparison (MTC) methodology (Lu and Ades, 2004) was chosen to carry out the NMA. The model uses a Bayesian hierarchical framework to simultaneously compare multiple treatments via a common comparator. Inference was performed using Markov Chain Monte Carlo (MCMC) technique. Goodness of fit of the models was evaluated by means of residual deviance and the deviance information criteria (DIC) to compare model adjustment between random and fixed models. Consistency assumption was assessed through the Bayesian P-values produced by the node-splitting method (Dias et al., 2010). Significance level was set at 0.05/k (k=number of comparisons) to adjust for multiple comparisons. Results are presented as point estimates (the median values) and their respective 95% credible intervals (CrI). CrI are the Bayesian analogous to the frequentist confidence intervals. We also estimated the surface under the cumulative ranking curve (SUCRA) probabilities (the probability of being the best treatment based on efficacy or acceptability).

Data were analyzed using the meta, coda, rjags and gemtc packages of the R statistical software (version 3.4.4) and WinBUGS software version 1.4 (Medical Research Council Biostatistics Unit, Cambridge, UK).

2.5 Publication bias

Publication bias was assessed visually using funnel plots and Egger's test was used for the statistical assessment of asymmetry (Egger et al., 1997). To complement the assessment of publication bias, the "trim-and-fill" method was performed to make strong assumptions regarding funnel plot asymmetry (Duval and Tweedie, 2000).

2.6 Risk of bias and quality assessment

The reviewers independently assessed the risk of bias for each trial included in the review (Higgins et al., 2016b). Also, the GRADE criteria was used to rate the quality of the evidence (Puhan et al., 2014) with the aid of the GRADEpro Guideline Development Tool Software (GRADEpro GDT, 2015) to assess the certainty of direct evidence. GRADE is used to rate the certainty of evidence for a treatment efficacy from high to very low. If pairwise and indirect estimates were coherent, then the higher of their ratings was attributed to the network meta-analysis estimates, as described by Khera et al. (2016).

3. RESULTS

The search strategy led to the retrieval of 15073 records from the databases and 73 additional records through other sources (six from the reference lists of relevant retrieved papers and previous systematic reviews). After the removal of duplicates (N=2708), exclusion based on titles and abstracts (N=12333), and exclusion following the full-text analyses (N=120), 58 RCTs with a total of 6766 participants randomized to 26 different interventions were included in the present systematic review based on the eligibility criteria (Figure 1). The characteristics of these 58 trials are displayed in Table S1 in the data supplement.

3.1 Outcome measures

The network of available comparisons is shown in Figure 2. This network geometry shows which drugs have been compared directly in RCTs, and which were informed indirectly. The direct and indirect evidence was used to inform the network of eligible comparisons, although it relied mostly on comparisons of active drugs versus placebo, as few drugs have been directly compared. The study comparing fluvoxamine and reboxetine (Spivak et al., 2006) was excluded since this comparison was not connected in the network.

The league table (Figure 3) displays the NMA results for efficacy and acceptability. In the league table, the treatments are ranked according to their surface under the cumulative ranking curve (SUCRA) values of efficacy.

3.1.1 Efficacy

Based on the NMA results, the following medications proved significantly superior to placebo with respect to efficacy: topiramate (SMD=-0.57; 95%CrI: -1.07,-0.10; moderate certainty of evidence [CE]), risperidone SMD=-0.53; 95%CrI: -0.93,-0.15; low CE), quetiapine (SMD=-0.59; 95%CrI: -1.06,-0.11; high CE), paroxetine (SMD=-0.35; 95%CrI: -0.48,-0.21; low CE), venlafaxine (SMD=-0.25; 95%CrI: -0.44,-0.05; moderate CE), fluoxetine (SMD=-0.28; 95%CrI: -0.46,-0.08; moderate CE), and sertraline (SMD=-0.21; 95%CrI: -0.33,-0.09; moderate CE).

In the comparisons between active drugs, topiramate outperformed prazosin (SMD=- 0.60; 95%CrI: -1.11,-0.07; low CE), citalopram (SMD=-0.76; 95%CrI: -1.44,-0.06; low CE), and divalproex (SMD=-0.76; 95%CrI: -1.40,-0.15; low CE); risperidone was associated with significantly greater improvement in symptom severity from baseline compared to prazosin (SMD=-0.55; 95%CrI: -0.99,-0.12; low CE), tiagabine (SMD=-0.52; 95%CrI: -1.03,-1.49; low CE), citalopram (SMD=-0.72; 95%CrI: -1.32,-0.07; very low CE), and divalproex (SMD=-0.73; 95%CrI: -1.28,-0.18; low CE); quetiapine was significantly better than prazosin (SMD=-0.60; 95%CrI: -1.11,-0.10; moderate CE), citalopram (SMD=-0.77; 95%CrI: -1.45,-0.08; low CE), and divalproex (SMD=-0.78; 95%CrI: -1.38,-0.16; low CE); paroxetine outperformed prazosin (SMD=-0.37; 95%CrI: -0.59,-0.13; low CE), citalopram (SMD=-0.53; 95%CrI: -1.03,-0.02; very low CE), and divalproex (SMD=-0.54; 95%CrI: -0.95,-0.12; low CE); venlafaxine was superior to divalproex (SMD=-0.44; 95%CrI: -0.88,-0.01); low CE); and fluoxetine was associated with significantly greater efficacy compared to prazosin (SMD=-0.29; 95%CrI: -0.55,-0.02; low CE) and divalproex (SMD=-0.46; 95%CrI: -0.90,-0.02; low CE). These results were supported by head-to-head meta-analysis (exhibited in Figure S1 in the data supplement). Heterogeneity was moderate for the comparisons of paroxetine versus placebo (I^2=37%) and sertraline versus placebo (I^2=39%) and low for all the other direct comparisons of efficacy (I^2=0% for most comparisons).

According to the NMA hierarchy of competing interventions topiramate was positioned first, presenting the highest probability of being the best treatment regarding the efficacy outcome, followed in decreasing order by risperidone, olanzapine, and quetiapine and the other treatments displayed in Figure S3 and Table S2 in the data supplement.

3.1.2 Acceptability

The data extracted from 53 trials enabled analyses of acceptability for 25 out of 26 medications. The head-to-head meta-analysis results for all-cause discontinuation from medication during pharmacological treatment are shown in detail in Figure S2 in the data supplement. Heterogeneity was high for the comparison of NK1RA versus placebo (I^2=84%) and low for all the other comparisons of acceptability (I^2=0% for most comparisons).

Examining the network results for all-cause dropouts (Figure 3), we found that phenelzine (RR=3.39; 95%CrI: 1.43,11.09; moderate CE), lamotrigine (RR=4.39; 95%CrI: 1.18,26.38; low CE), and fluoxetine (RR=1.28; 95%CrI: 1.01,1.59; moderate CE) proved to be significantly superior to placebo. Moreover, quetiapine outperformed olanzapine (RR=2.78; 95%CrI: 1.01,9.66; moderate CE) and fluoxetine was better than sertraline (RR=1.47; 95%CrI: 1.07,2.00; low CE) in terms of dropouts. Also, phenelzine and lamotrigine were significantly superior to most drugs, as demonstrated in Figure 3. Phenelzine was ranked first in acceptability, followed in decreasing order by lamotrigine, vilazodone, quetiapine and all the other treatments exhibited in Figure S3 and Table S2 in the data supplement. Guanfacine was ranked last among all twenty-five treatments analyzed.

Figure 4 displays the relative treatment effects of active treatment versus placebo for the two outcomes in the NMA. The effect sizes are reported in the SUCRA order of efficacy (a) and acceptability (b).

3.2 Model Adequacy

Models were fitted based on three chains with 40,000 burn-ins and 250,000 iterations for inference and using noninformative priors. Following the DIC results, the two networks were better fitted using the random effects model with homogeneous variance. The number of pairwise comparisons in closed loops was 5 for both the efficacy and acceptability networks. No evidence of inconsistence was found for the two networks (the smallest Bayesian p-values was 0.47).

3.3 Risk of bias

Twenty-four percent of the information derived from studies with a high risk of bias (14 out of 58 trials). Overall and study-level risk of bias assessments are summarized in Figures S4 and S5 in the supplementary material.

3.4 Publication bias

Funnel plots including all studies that have compared an active treatment versus placebo for the outcomes efficacy and acceptability are illustrated in the Figure S6 in the data supplement. There was no evidence of publication bias for either outcome

based on visual and statistical assessments (P-values=0.84 for efficacy and 0.37 for acceptability; Egger's test). Following the imputation of "missing" studies using a trim-and-fill analysis, the overall treatment effects from the random-effects model were similar for efficacy (SMD=0.27; 95% CI: -0.39 to -0.15; P <0.0001). However, the risk ratio decreased for acceptability, altering the direction of the results (RR=0.92; 95% CI: 0.84 to 1.00; P=0.05) and indicating possible publication bias.

4. DISCUSSION

To the best of our knowledge, this is the largest contemporary NMA on pharmacological therapy for PTSD. The present data expand upon previous meta-analyses (Cipriani et al., 2018; Hoskins et al., 2015; Watts et al., 2013) by including trials with quetiapine, ziprasidone, and vilazodone.

This NMA highlights several effective treatment choices for the reduction of PTSD-related symptoms across different classes of medications, leading to the conclusion that there is a lack of a "class effect" in PTSD (Watts et al., 2013). The following treatments were associated with significantly greater efficacy when compared directly and indirectly with placebo: topiramate, risperidone, quetiapine, paroxetine, venlafaxine, fluoxetine, and sertraline. Overall, these results are consistent with a previous meta-analysis (Watts et al., 2013). Moreover, fluoxetine, lamotrigine, and phenelzine performed significantly better than placebo in terms of discontinuation for any reason in both the pairwise and network meta-analyses.

Phenelzine was also favored over many other active treatments in terms of dropout rates, which is in agreement with data reported in the work of Cipriani et al. (2018). Although phenelzine had the highest observed effect versus placebo regarding efficacy, this was a non-significant effect, resulting in a low SUCRA. Importantly, evidence from our NMA for phenelzine relates to the available direct evidence, which was based on a single study (Kosten et al., 1991). We obtained the effect measures by subtracting the change-from-baseline scores. Such an analysis rather than a comparison of final values gives more precise, less biased estimates of treatment effects (Higgins et al., 2019).

Although evidence-based information supports the use of pharmacotherapy for PTSD, clinical information is often imperfect and significant treatment needs remain unmet for the disorder. Although PTSD is a highly complex, heterogeneous condition, only two medications have been approved by the Food and Drug Administration (FDA) to encompass its myriad of symptoms (Yehuda et al., 2015; Bryant, 2019, APA, 2013): sertraline and paroxetine. According to the most recent guidelines (VA/DOD, 2017; APA, 2017; NICE, 2018), these selective serotonin reuptake inhibitors are usually the first pharmacological intervention for PTSD, but many patients fail to respond or have either a partial or inadequate response to these "first-line" treatments (Hendriksen et al., 2014). Our NMA findings strengthen evidence for the use of sertraline and paroxetine

in PTSD. The antidepressants fluoxetine and venlafaxine also significantly decreased symptoms of PTSD, which is consistent with previous meta-analyses and guidelines (Watts et al., 2013; Cipriani et al., 2018; VA/DOD 2017; APA 2017; NICE 2018). Furthermore, the efficacy results suggest that there is no significant difference between fluoxetine and venlafaxine or between fluoxetine and the medications approved by the FDA for PTSD (paroxetine and sertraline). Regarding acceptability, fluoxetine outperformed sertraline and was the only antidepressant among these drugs to outperform placebo regarding both outcomes, which is a major finding. Nonetheless, it was not presumably the best drug in the overall ranking for efficacy or acceptability. For adults with PTSD, fluoxetine exhibited both relative benefits and harms, with a better risk-benefit ratio against placebo when both outcomes are weighed together (better improvement in PTSD symptoms with fewer withdrawal symptoms from medication due to any cause).

PTSD is widely recognized as a disorder that typically runs a chronic, fluctuating course and is prone to recurrence. Thus, medications are generally needed for a prolonged period. Moreover, individuals with the condition are 80% more likely than those without PTSD to have symptoms that meet diagnostic criteria for at least one other mental disorder (Yehuda et al., 2015; Bryant, 2019; APA, 2013). It is therefore not surprising that "off label" medications play a crucial role in real-world treatment for PTSD, but the use of these medications should be supported by statistically significant evidence from meta-analyses (Krystal et al., 2017). Patients with PTSD and comorbid bipolar disorder appear to be a high-risk population that requires monitoring for suicide, for whom antidepressants should be used with caution due to risk of mood destabilization (Otto et al., 2004). Conversely, such patients could benefit from atypical antipsychotics, such as quetiapine or risperidone, which could also help improve sleep, aggressiveness and comorbid psychotic symptoms (Villarreal et al., 2018). However, one must bear in mind that the poor acceptability, alongside the risk of metabolic effects may limit their utilization in clinical practice.

The present NMA offers the strongest evidence to date suggesting the efficacy of quetiapine for the treatment of PTSD. The symptoms often found in this population that make PTSD particularly challenging (e.g., anxiety, insomnia, irritability, and comorbid unipolar or bipolar depression) could be managed with quetiapine (Villarreal et al., 2016; Villarreal et al., 2018). In the trial conducted by Villarreal et al. (Villarreal et al., 2016) quetiapine was used as monotherapy for PTSD with an average dose of 258

mg/day and no patients dropped out of the medication group due to a lack of efficacy. Adverse events were generally mild and the safety scales administered by the authors revealed no significant differences between quetiapine and placebo. In the network comparisons, we found quetiapine to be superior to olanzapine and neither better nor worse than placebo, lamotrigine, or phenelzine in terms of acceptability. However, the efficacy of quetiapine for PTSD has the shortcoming of relying on a single trial (Villarreal et al., 2016) predominantly involving males, including solely combat-associated PTSD, which limits the generalizability of the results. As previous studies (Watts et al., 2013; Friedman et al., 2007) have shown that effect sizes for drugs are smaller in males and especially veterans in comparison to civilians, the clinically meaningful change in symptoms found with quetiapine is noteworthy and merits further investigation.

Topiramate showed greater efficacy over placebo and outranked other active drugs in the NMA results. Patients with PTSD who struggle with obesity or another metabolic disorder could benefit from topiramate due to its effect on weight loss and the lack of potential for abuse (Lopresti et al., 2013; Khera et al., 2016). However, the results regarding topiramate were based on only two trials (Tucker et al., 2007, Yeh et al., 2011) with small sample sizes of nonveterans, exhibiting a moderate CE. Thus, cautious interpretation is required, as these factors could affect its applicability. Given our more stringent eligibility criteria, some trials evaluating the effect of topiramate for PTSD were excluded from the meta-analysis (Batki et al., 2014; Akuchekian et al., 2004; Lindley et al., 2007).

The issue of prior treatment response was addressed in a previous meta-analysis (Watts et al., 2013), suggesting that this could bias the results and more research was needed regarding the ideal sequence of pharmacotherapy in PTSD. Therefore, unlike a previous NMA on this subject (Cipriani et al., 2018), we did not include strategies for augmenting antidepressants in treatment-refractory PTSD, since our focus was not on treatment-resistant PTSD and we believed our approach would reduce heterogeneity (Hamer et al., 2004; Koek et al., 2016; Sippel et al., 2018). As stated by Stein and Norman (2019), distinguishing prior responses to treatment is crucial to interpreting and contextualizing data from individual trials. Moreover, trials differ in other characteristics that could affect efficacy and acceptability estimates (e.g., the proportion of women, proportion of veterans, and duration of treatment). In the present NMA, differences were examined on the individual RCT level rather than the individual

participant level, which is common in meta-analyses. Therefore, one should be cautious when drawing conclusions and other relevant outcomes, such as drug availability, the physician's familiarity with the treatment, side effects/tolerability, and drug costs, should be considered when choosing the best treatment (Mbuagbaw et al., 2017).

4.1 Limitations and implications for future work

Although the funnel plots did not indicate publication bias, the trim-and-fill method indicated this possibility in terms of drug acceptability (Duval and Tweedie, 2000). Moreover, our team may have overlooked some unpublished trials, which should be considered when assessing the results.

Rankings with regards to efficacy and acceptability may exaggerate small differences in relative effects, as the magnitude of differences and uncertainty around the effect estimate between treatments are not considered in these hierarchies. Therefore, the magnitude of absolute effects should be taken into consideration to minimize potential biases and support a particular recommendation of the "best drug" or "drug of choice". Ultimately, we deemed that the difference in outcomes between drugs according to rankings was not likely to be of major clinical importance.

Although the outcome results were based on evidence extracted from a large body of trials and numerous drugs, these studies were predominantly derived from direct evidence of low quality (Puhan et al., 2014).

Due to the strict eligibility criteria, our conclusions may not apply to short-term treatments, subthreshold PTSD, or treatment-resistant PTSD (Koek et al., 2016; McLaughlin et al., 2015).

Despite these limitations, the present NMA highlights several noteworthy aspects relevant to day-to-day practice.

5. CONCLUSIONS

This NMA is not intended to set a standard of care, but rather facilitate decision making in clinical practice. It does so by offering important evidence to provide more conclusive information for health professionals who need to select a pharmacotherapy among multiple intervention options (Higgins et al., 2019). When a balance has to be made between efficacy and acceptability, this NMA supports fluoxetine as a first-line pharmacological choice for PTSD.

Additionally, it strengthens the evidence base for the utilization of topiramate, risperidone, quetiapine, paroxetine, venlafaxine, and sertraline as possible first-line alternatives for reducing symptoms of PTSD. Moreover, fluoxetine, lamotrigine, and phenelzine outperformed placebo in terms of acceptability.

Although the agreement between pairwise and network meta-analyses increases confidence in the results, the analysis relied mainly on comparisons of active drugs versus placebo with limited CE. These shortcomings underscore the need for well-designed, rigorous, large RCTs with mostly head-to-head comparison that could have the potential to improve the available body of information and provide more conclusive evidence.

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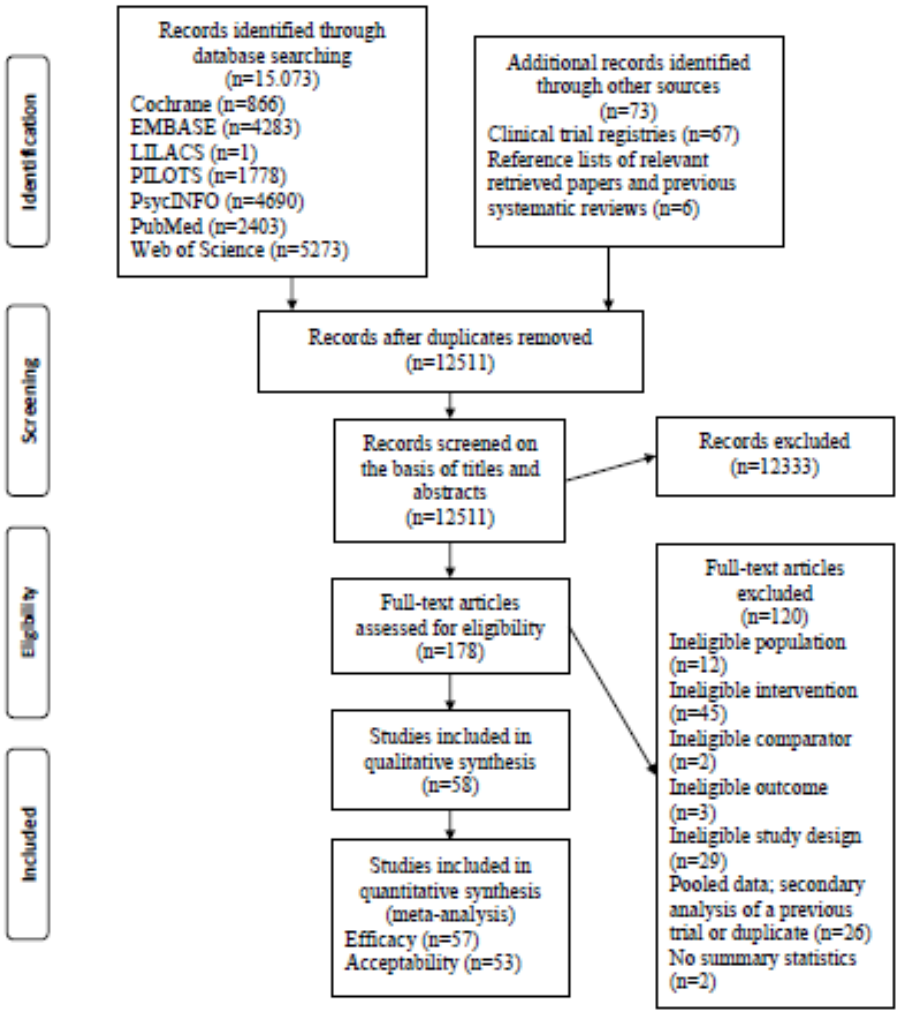
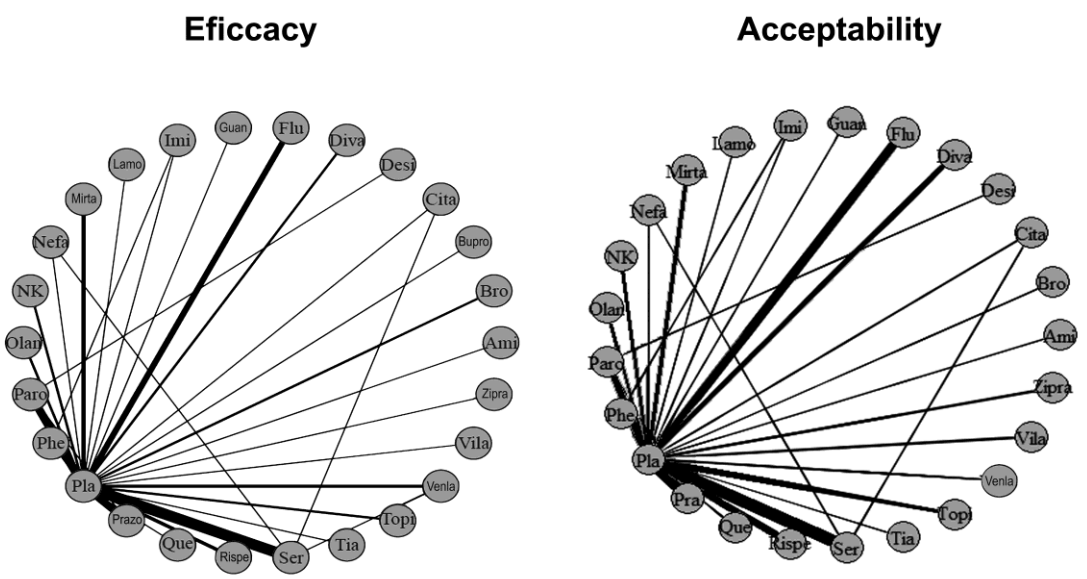
Figure 1. Flow Diagram of Study Selection



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Figure 2. Network of Eligible Comparisons for Efficacy and Acceptability



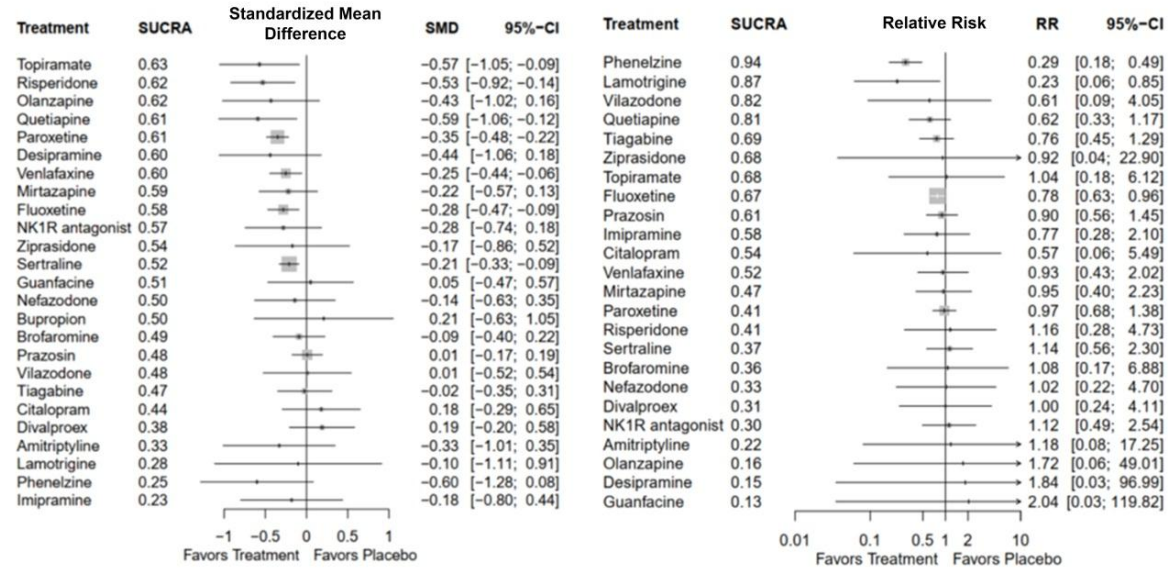
The width of the lines indicates the number of trials comparing every pair of treatments. Ami=amitriptyline. Bro=brofaromide. Bupro=bupropion. Cita=citalopram. Desi=desipramine. Diva=divalproex. Flu=fluoxetine. Gran=guanfacine. Imi=imipramine. Lamo=lamotrigine. Mirta=mirtazapine. Nefa=nefazodone. NK=NK1RA. Olan=olanzapine. Paro=paroxetine. Phe=phenelzine. Pla= placebo. Prazo=prazosin. Que=quetiapine. Rispe=risperidone. Ser=sertraline. Tia=tiagabine. Topi=topiramate. Venla=venlafaxine. Vila=vilazodone. Zipra=ziprasidone.

Figure 3. League Table Showing Network Meta-analysis Results for Efficacy and Acceptability

	Topi	Rispe	Olan	Que	Paro	Desi	Venla	Mirta	Flu	NK	Pla	Zipra	Ser	Guan	Nefa	Bupro	Bro	Prazo	Vila	Tia	Cita	Diva	Ami	Lamo	Phe	Imi
Topi	**Topi**	0.90	0.61	1.69	1.08	0.56	1.12	1.10	1.34	0.94	1.04	1.14	0.91	0.51	1.03		0.96	1.16	1.71	1.37	1.80	1.04	0.88	**4.58**	**3.58**	1.36
		(0.38, 2.06)	(0.17, 1.87)	(0.71, 4.24)	(0.52, 2.16)	(0.14, 1.91)	(0.52, 2.46)	(0.49, 2.34)	(0.64, 2.77)	(0.44, 1.97)	(0.52, 2.09)	(0.25, 5.12)	(0.44, 1.86)	(0.12, 1.96)	(0.41, 2.39)		(0.35, 2.57)	(0.55, 2.40)	(0.49, 6.34)	(0.63, 3.02)	(0.43, 7.40)	(0.42, 2.52)	(0.26, 2.89)	**(1.04, 29.87)**	**1.16, 13.79**	(0.54, 3.17)
Rispe	-0.41	**Rispe**	0.68	1.90	1.19	0.63	1.25	1.23	1.49	1.04	1.16	1.29	1.02	0.57	1.14		1.08	1.29	1.90	1.54	2.03	1.17	0.99	**5.17**	**3.95**	1.51
	(-0.67, 0.56)		(0.21, 1.87)	(0.94, 4.08)	(0.76, 2.04)	(0.16, 1.98)	(0.71, 2.35)	(0.71, 2.25)	(0.93, 2.58)	(0.64, 1.87)	(0.76, 1.91)	(0.30, 5.43)	(0.64, 1.74)	(0.14, 2.02)	(0.55, 2.41)		(0.47, 2.44)	(0.79, 2.24)	(0.64, 6.84)	(0.88, 2.82)	(0.52, 7.07)	(0.57, 2.43)	(0.34, 2.82)	**(1.27, 32.27)**	**1.51, 14.34**	(0.76, 3.17)
Olan	-0.14	-0.10	**Olan**	**2.78**	1.77	0.92	1.87	1.82	2.21	1.56	1.72	1.93	1.51	0.85	1.7		1.6	1.92	2.88	2.25	3.06	1.71	1.46	**7.83**	**6.07**	2.22
	(-0.91, 0.61)	(-0.82, 0.61)		**(1.01, 9.66)**	(0.73, 5.28)	(0.2, 4.14)	(0.72, 5.78)	(0.69, 5.84)	(0.9, 6.59)	(0.61, 4.88)	(0.72, 5.08)	(0.38, 10.3)	(0.62, 4.55)	(0.18, 3.98)	(0.57, 5.68)		(0.52, 5.66)	(0.78, 5.73)	(0.72, 13.41)	(0.87, 7.09)	(0.64, 14.13)	(0.62, 5.77)	(0.4, 6.2)	**(1.58, 58.54)**	**1.68, 28.09**	(0.8, 7.57)
Que	0.10	0.06	0.16	**Que**	0.63	0.33	0.66	0.65	0.79	0.55	0.62	0.67	0.54	0.3	0.6		0.57	0.68	1	0.81	1.08	0.61	0.52	2.73	2.1	0.79
	(-0.66, 0.68)	(-0.55, 0.66)	(-0.59, 0.90)		(0.34, 1.13)	(0.08, 1.07)	(0.33, 1.3)	(0.32, 1.27)	(0.41, 1.46)	(0.29, 1.05)	(0.34, 1.05)	(0.15, 2.81)	(0.28, 0.97)	(0.07, 1.06)	(0.26, 1.36)		(0.22, 1.35)	(0.36, 1.27)	(0.31, 3.56)	(0.4, 1.59)	(0.27, 3.82)	(0.27, 1.34)	(0.17, 1.54)	(0.64, 17.01)	(0.72, 7.86)	(0.36, 1.76)
Paro	-0.22	-0.18	-0.08	-0.23	**Paro**	0.53	1.05	1.03	1.25	0.87	0.97	1.07	0.86	0.48	0.96		0.90	1.08	1.58	1.28	1.69	0.97	0.82	**4.25**	**3.31**	1.26
	(-0.74, 0.27)	(-0.59, 0.22)	(-0.68, 0.53)	(-0.72, 0.25)		(0.15, 1.46)	(0.70, 1.56)	(0.67, 1.52)	(0.92, 1.64)	(0.65, 1.23)	(0.82, 1.14)	(0.27, 4.18)	(0.65, 1.10)	(0.13, 1.51)	(0.51, 1.76)		(0.43, 1.78)	(0.81, 1.46)	(0.56, 4.90)	(0.85, 1.94)	(0.47, 5.42)	(0.53, 1.73)	(0.29, 2.13)	**(1.12, 25.93)**	**1.37, 10.99**	(0.70, 2.26)
Desi	-0.13	-0.1	0.005	-0.14	0.1	**Desi**	2.00	1.96	2.37	1.66	1.84	2.02	1.61	0.92	1.82		1.73	2.08	3.05	2.42	3.26	1.85	1.58	8.21	**6.50**	2.42
	(-0.92, 0.65)	(-0.84, 0.62)	(-0.86, 0.87)	(-0.94, 0.63)	(-0.50, 0.7)		(0.67, 7.58)	(0.65, 7.55)	(0.82, 8.74)	(0.56, 6.33)	(0.66, 6.80)	(0.37, 13.59)	(0.56, 5.85)	(0.17, 4.96)	(0.56, 7.99)		(0.48, 7.13)	(0.71, 7.58)	(0.72, 16.50)	(0.82, 9.50)	(0.65, 18.34)	(0.59, 7.49)	(0.36, 7.70)	(0.50, 69.37)	**1.61, 35.19**	(0.74, 10.04)
Venla	-0.32	-0.29	-0.18	-0.33	-0.10	-0.19	**Venla**	0.98	1.19	0.83	0.93	1.01	0.82	0.45	0.91		0.86	1.03	1.49	1.22	1.62	0.92	0.78	**4.08**	**3.15**	1.21
	(-0.86, 0.18)	(-.72, 0.13)	(-0.8, 0.45)	(-0.84, 0.17)	(-0.33, 0.12)	(-0.83, 0.46)		(0.58, 1.64)	(0.76, 1.8)	(0.53, 1.35)	(0.65, 1.33)	(0.25, 4.19)	(0.53, 1.23)	(0.12, 1.52)	(0.44, 1.81)		(0.39, 1.83)	(0.66, 1.61)	(0.51, 4.93)	(0.72, 2.13)	(0.44, 5.43)	(0.48, 1.79)	(0.27, 2.13)	**(1.03, 25.59)**	**1.23, 10.83**	(0.61, 2.33)
Mirta	-0.35	-0.32	-0.20	-0.37	-0.13	-0.21	-0.02	**Mirta**	1.21	0.85	0.95	1.03	0.83	0.46	0.93		0.87	1.05	1.55	1.25	1.64	0.95	0.8	**4.19**	**3.21**	1.23
	(-0.95, 0.25)	(-0.84, 0.22)	(-0.89, 0.49)	(-0.94, 0.22)	(-0.5, 0.25)	(-0.91, 0.50)	(-0.41, 0.38)		(0.79, 1.9)	(0.55, 1.41)	(0.66, 1.39)	**0.47, 2.11**	(0.55, 1.29)	(0.12, 1.55)	(0.47, 1.86)		(0.39, 1.9)	(0.67, 1.67)	(0.52, 5.21)	(0.74, 2.16)	(0.45, 5.79)	(0.47, 1.86)	(0.28, 2.17)	**(1.08, 24.83)**	**1.24, 11.44**	(0.63, 2.4)
Flu	-0.3	-0.26	-0.16	-0.31	-0.07	-0.16	0.02	0.06	**Flu**	0.7	**0.78**	0.85	**0.68**	0.38	0.76		0.73	0.86	1.27	1.02	1.35	0.66	0.66	3.42	**2.64**	1.01
	(-0.83, 0.20)	(-0.7, 0.18)	(-0.77, 0.47)	(-0.82, 0.18)	(-0.31, 0.15)	(-0.80, 0.50)	(-0.24, 0.3)	(-0.36, 0.44)		(0.5, 1.05)	**(0.63, 0.99)**	(0.22, 3.39)	**(0.50, 0.93)**	(0.1, 1.24)	(0.4, 1.44)		(0.34, 1.46)	(0.61, 1.24)	(0.45, 4.03)	(0.67, 1.65)	(0.38, 4.52)	(0.24, 1.72)	(0.24, 1.72)	(0.88, 21.47)	**(1.09, 8.73)**	(0.55, 1.86)
NK	-0.3	-0.25	-0.16	-0.30	-0.07	-0.16	0.03	0.06	0.01	**NK**	1.12	1.21	0.98	0.55	1.1		1.03	1.24	1.8	1.47	1.92	1.11	0.95	**4.85**	**3.77**	1.44
	(-0.97, 0.38)	(-0.86, 0.37)	(-0.91, 0.62)	(-0.98, 0.36)	(-0.55, 0.40)	(-0.91, 0.61)	(-0.48, 0.53)	(-0.52, 0.63)	(-0.50, 0.51)		(0.81, 1.44)	(0.3, 4.91)	(0.66, 1.35)	(0.15, 1.79)	(0.56, 2.05)		(0.47, 2.11)	(0.83, 1.77)	(0.62, 5.9)	(0.89, 2.33)	(0.52, 6.47)	(0.57, 2.01)	(0.32, 2.44)	**(1.24, 29.57)**	**1.52, 12.75**	(0.74, 2.68)
Pla	**-0.57**	**-0.53**	-0.43	**-0.59**	**-0.35**	-0.44	**-0.25**	-0.22	**-0.28**	-0.28	**Pla**	1.09	0.88	0.49	0.98		0.93	1.11	1.63	1.31	1.74	1.00	0.85	**4.39**	**3.39**	1.3
	(-1.07, -0.10)	**(-0.93, -0.15)**	(-1.01, 0.17)	**(-1.06, -0.11)**	**-0.48, -0.21**	(-1.06, 0.18)	**-0.44, -0.05**	(-0.59, 0.12)	**-0.46, -0.08**	(-0.75, 0.18)		(0.28, 4.24)	(0.71, 1.07)	(0.14, 1.55)	(0.53, 1.76)		(0.45, 1.79)	(0.86, 1.44)	(0.58, 5.14)	(0.91, 1.96)	(0.49, 5.56)	(0.56, 1.74)	(0.31, 2.18)	**(1.18, 26.38)**	**1.43, 11.09**	(0.74, 2.29)
Zipra	-0.40	-0.37	-0.26	-0.41	-0.18	-0.28	-0.08	-0.06	-0.10	-0.11	0.17	**Zipra**	0.8	0.44	0.89		0.85	1.01	1.5	1.2	1.61	0.91	0.77	4.08	3.16	1.19
	(-1.26, 0.43)	(-1.16, 0.44)	(-1.18, 0.7)	(-1.27, 0.42)	(-0.9, 0.53)	(-1.19, 0.65)	(-0.79, 0.64)	(-0.81, 0.74)	(-0.83, 0.62)	(-0.94, 0.70)	(-0.52, 0.87)		(0.2, 3.21)	(0.07, 2.6)	(0.21, 3.87)		(0.19, 3.81)	(0.26, 4.06)	(0.29, 8.13)	(0.29, 5.02)	(0.25, 9.23)	(0.21, 3.86)	(0.15, 4.05)	(0.63, 34.58)	(0.67, 18.23)	(0.28, 5.27)
Ser	-0.37	-0.33	-0.22	-0.38	-0.14	-0.23	-0.04	-0.01	-0.07	-0.08	**0.21**	0.04	**Ser**	0.56	1.12		1.06	1.27	1.85	1.49	1.97	1.14	0.97	**5**	**3.87**	1.48
	(-0.88, 0.13)	(-0.73, 0.09)	(-0.83, 0.4)	(-0.87, 0.10)	(-0.32, 0.04)	(-0.86, 0.40)	(-0.24, 0.16)	(-0.40, 0.35)	(-0.30, 0.16)	(-0.56, 0.40)	**(0.09, 0.33)**	(-0.66, 0.74)		(0.15, 1.77)	(0.61, 2.04)		(0.5, 2.13)	(0.92, 1.78)	(0.65, 6.02)	(0.99, 2.33)	(0.54, 6.54)	(0.62, 2.07)	(0.35, 2.48)	**(1.3, 30.52)**	**1.61, 12.81**	(0.83, 2.68)
Guan	-0.63	-0.59	-0.49	-0.64	-0.40	-0.50	-0.30	-0.27	-0.33	-0.34	-0.05	-0.22	-0.26	**Guan**	2.01		1.92	2.27	3.38	2.68	3.58	2.05	1.76	**9.25**	**7.15**	2.69
	(-1.36, 0.06)	(-1.25, 0.04)	(-1.28, 0.29)	(-1.35, 0.05)	(-0.94, 0.12)	(-1.3, 0.30)	(-0.88, 0.24)	(-0.90, 0.33)	(-0.90, 0.22)	(-1.02, 0.34)	(-0.58, 0.46)	(-1.09, 0.64)	(-0.8, 0.27)		(0.57, 8.03)		(0.48, 8.31)	(0.69, 8.32)	(0.73, 18.29)	(0.82, 10.32)	(0.67, 20.95)	(0.57, 8.32)	(0.38, 8.2)	**(1.53, 78.73)**	**1.65, 40.54**	(0.74, 10.45)
Nefa	-0.43	-0.4	-0.28	-0.44	-0.20	-0.30	-0.11	-0.08	-0.14	-0.14	0.14	-0.02	-0.07	0.2	**Nefa**		0.94	1.12	1.66	1.34	1.76	1.01	0.86	**4.5**	**3.48**	1.32
	(-1.16, 0.22)	(-1.02, 0.23)	(-1.07, 0.47)	(-1.13, 0.24)	(-0.72, 0.3)	(-1.1, 0.5)	(-0.62, 0.40)	(-0.70, 0.50)	(-0.66, 0.40)	(-0.82, 0.55)	(-0.35, 0.63)	(-0.90, 0.84)	(-0.56, 0.42)	(-0.55, 0.89)			(0.37, 2.33)	(0.6, 2.23)	(0.51, 5.93)	(0.68, 2.76)	(0.44, 6.78)	(0.45, 2.28)	(0.28, 2.6)	**(1.05, 29.48)**	**1.19, 13.01**	(0.60, 3.00)
Bupro	-0.78	-0.75	-0.64	-0.80	-0.56	-0.67	-0.46	-0.43	-0.50	-0.50	-0.21	-0.37	-0.42	-0.16	-0.36	**Bupro**										
	(-1.8, 0.16)	(-1.7, 0.16)	(-1.7, 0.38)	(-1.79, 0.16)	(-1.45, 0.27)	(-1.72, 0.38)	(-1.33, 0.40)	(-1.38, 0.45)	(-1.36, 0.38)	(-1.49, 0.44)	(-1.08, 0.61)	(-1.51, 0.70)	(-1.3, 0.41)	(-1.15, 0.81)	(-1.33, 0.60)											
Bro	-0.48	-0.44	-0.34	-0.5	-0.25	-0.35	-0.15	-0.12	-0.18	-0.20	0.09	-0.07	-0.11	-0.04	-0.05	0.3	**Bro**	1.2	1.76	1.42	1.9	1.08	0.93	**4.83**	**3.73**	1.39
	(-1.06, 0.1)	(-0.94, 0.07)	(-1.00, 0.33)	(-1.04, 0.10)	(-0.6, 0.10)	(-1.02, 0.35)	(-0.52, 0.23)	(-0.60, 0.33)	(-0.55, 0.21)	(-0.76, 0.38)	(-0.21, 0.42)	(-0.83, 0.70)	(-0.45, 0.23)	(-0.64, 0.55)	(-0.64, 0.55)	(-0.56, 1.25)		(0.59, 2.57)	(0.52, 6.87)	(0.65, 3.22)	(0.44, 7.63)	(0.46, 2.75)	(0.27, 2.96)	**(1.05, 31.41)**	**(1.2, 14.58)**	(0.62, 3.47)
Prazo	**-0.60**	**-0.55**	-0.44	**-0.60**	**-0.37**	-0.45	-0.26	-0.23	**-0.29**	-0.30	-0.01	-0.17	-0.22	0.03	-0.16	0.2	-0.11	**Prazo**	1.46	1.18	1.57	0.9	0.76	**3.94**	**3.07**	1.17
	(-1.11, -0.07)	**(-0.99, -0.12)**	(-1.07, 0.18)	**(-1.11, -0.10)**	**-0.59, -0.13**	(-1.1, 0.18)	(-0.53, 0.01)	(-0.64, 0.15)	**-0.55, -0.02**	(-0.79, 0.21)	(-0.20, 0.17)	(-0.90, 0.54)	(-0.44, 0.01)	(-0.52, 0.6)	(-0.67, 0.38)	(-0.64, 1.1)	(-0.49, 0.26)		(0.5, 4.6)	(0.75, 1.89)	(0.43, 5.11)	(0.47, 1.65)	(0.28, 2.01)	**(1.04, 24.42)**	**1.24, 10.48**	(0.63, 2.15)
Vila	-0.58	-0.55	-0.44	-0.60	-0.36	-0.45	-0.25	-0.23	-0.29	-0.30	-0.01	-0.17	-0.22	0.04	-0.15	0.2	-0,1	0.01	**Vila**	0.81	1.05	0.61	0.51	2.69	2.12	0.8
	(-1.3, 0.16)	(-1.2, 0.1)	(-1.23, 0.34)	(-1.32, 0.11)	(-0.91, 0.20)	(-1.27, 0.38)	(-0.83, 0.31)	(-0.86, 0.40)	(-0.84, 0.29)	(-1.01, 0.41)	(-0.54, 0.53)	(-1.06, 0.70)	(-0.76, 0.34)	(-0.68, 0.82)	(-0.87, 0.57)	-(0.77, 1.24)	(-0.74, 0.53)	(-0.55, 0.57)		(0.24, 2.35)	(0.2, 5.22)	(0.17, 1.93)	(0.12, 2.16)	(0.46, 20.98)	(0.48, 10.14)	(0.22, 2.54)
Tia	-0.56	**-0.52**	-0.42	-0.57	-0.32	-0.42	-0.22	-0.20	-0.25	-0.27	0.02	-0.14	-0.19	0.07	-0.12	0.24	-0.08	0.04	0.02	**Tia**	1.33	0.76	0.64	3.35	**2.6**	0.99
	(-1.15, 0.02)	**(-1.03, -0.01)**	(-1.08, 0.28)	(-1.14, 0.02)	(-0.7, 0.03)	(-1.12, 0.3)	(-0.61, 0.16)	(-0.70, 0.27)	(-0.63, 0.12)	(-0.82, 0.31)	(-0.31, 0.35)	(-0.90, 0.60)	(-0.54, 0.17)	(-0.53, 0.7)	(-0.70, 0.47)	(-0.65, 1.17)	(-0.53, 0.37)	(-0.35, 0.42)	(-0.61, 0.66)		(0.36, 4.46)	(0.38, 1.47)	(0.22, 1.75)	(0.85, 20.6)	**(1.02, 8.88)**	(0.51, 1.95)
Cita	**-0.76**	**-0.72**	-0.61	**-0.77**	**-0.53**	-0.62	-0.43	-0.40	-0.45	-0.46	-0.18	-0.35	-0.39	-0.13	-0.32	0.04	-0.27	-0.17	-0.17	-0.2	**Cita**	0.57	0.49	2.57	2.00	0.74
	(-1.44, -0.06)	**(-1.32, -0.07)**	(-1.38, 0.18)	**(-1.45, -0.08)**	**-1.03, -0.02**	(-1.40, 0.18)	(-0.93, 0.09)	(-1.01, 0.20)	(-0.10, 0.07)	(-1.12, 0.22)	(-0.65, 0.30)	(-1.22, 0.51)	(-0.86, 0.1)	(-0.82, 0.62)	(-1.00, 0.37)	(-0.91, 1.05)	(-0.88, 0.31)	(-0.68, 0.37)	(-0.91, 0.55)	(-0.80, 0.40)		(0.15, 2.24)	(0.1, 2.28)	(0.43, 22.63)	(0.44, 11.55)	(0.2, 3.03)
Diva	**-0.76**	**-0.73**	-0.62	**-0.78**	**-0.54**	-0.63	**-0.44**	-0.41	**-0.46**	-0.47	-0.19	-0.35	-0.4	-0.14	-0.33	0.03	-0.29	-0.18	-0.18	-0.21	-0.01	**Diva**	0.85	**4.45**	**3.45**	1.29
	(-1.40, -0.15)	**(-1.28, -0.18)**	(-1.33, 0.08)	**(-1.38, -0.16)**	**-0.95, -0.12**	(-1.35, 0.1)	**-0.88, -0.01**	(-0.94, 0.10)	**-0.90, -0.02**	(-1.10, 0.12)	(-0.59, 0.20)	(-1.16, 0.44)	(-0.81, 0.14)	(-0.79, 0.51)	(-0.96, 0.30)	(-0.91, 0.96)	(-0.80, 0.22)	(-0.62, 0.26)	(-0.84, 0.47)	(-0.72, 0.31)	(-0.63, 0.62)		(0.22, 2.32)	**(1.04, 28.40)**	**1.24, 12.88**	(0.59, 2.89)
Ami	-0.25	-0.21	-0.10	-0.26	-0.02	-0.12	0.08	0.10	0.05	0.04	0.33	0.15	0.12	0.38	0.2	0.54	0.23	0.34	0.33	0.31	0.51	0.5	**Ami**	**5.20**	**4.08**	1.54
	(-1.1, 0.57)	(-0.99, 0.58)	(-1.01, 0.79)	(-1.11, 0.57)	(-0.71, 0.69)	(-1.04, 0.80)	(-0.63, 0.80)	(-0.68, 0.86)	(-0.66, 0.76)	(-0.81, 0.87)	(-0.35, 1.01)	(-0.82, 1.17)	(-0.57, 0.80)	(-0.47, 1.25)	(-0.67, 1.03)	(-0.55, 1.65)	(-0.54, 0.99)	(-0.37, 1.06)	(-0.53, 1.2)	(-0.47, 1. 5)	(-0.35, 1.35)	(-0.27, 1.31)		**(1.04, 38.38)**	**1.11, 18.93**	(0.51, 4.7)
Lamo	-0.47	-0.44	-0.33	-0.49	-0.25	-0.34	-0.15	-0.12	-0.17	-0.18	0.1	-0.05	-0.1	0.15	-0.04	0.33	0.01	0.11	0.13	0.08	0.29	0.28	-0.23	**Lamo**	0.78	0.3
	(-1.58, 0.64)	(-1.51, 0.65)	(-1.47, 0.84)	(-1.60, 0.61)	(-1.26, 0.78)	(-1.53, 0.85)	(-1.16, 0.90)	(-1.20, 0.95)	(-1.2, 0.85)	(-1.34, 0.93)	(-0.91, 1.12)	(-1.31, 1.17)	(-1.12, 0.91)	(-1.01, 1.3)	(-1.17, 1.12)	(-1.03, 1.66)	(-1.07, 1.08)	(-0.9, 1.16)	(-1.05, 1.27)	(-0.97, 1.13)	(-0.84, 1.41)	(-0.8, 1.42)	(-1.41, 1.03)		(0.11, 4.74)	(0.04, 1.28)
Phe	0.03	0.07	0.17	0.01	0.25	0.15	0.34	0.36	0.32	0.31	0.60	0.43	0.4	0.65	0.45	0.83	0.5	0.62	0.61	0.59	0.78	0.8	0.28	0.49	**Phe**	**0.38**
	(-0.84, 0.84)	(-0.7, 0.84)	(-0.74, 1.08)	(-0.82, 0.83)	(-0.42, 0.94)	(-0.72, 1.10)	(-0.34, 1.08)	(-0.36, 1.15)	(-0.36, 1.03)	(-0.50, 1.14)	(-0.07, 1.30)	(-0.53, 1.40)	(-0.29, 1.1)	(-0.17, 1.5)	(-0.35, 1.27)	(-0.27, 1.91)	(-0.24, 1.25)	(-0.09, 1.33)	(-0.25, 1.48)	(-0.19, 1.31)	(-0.04, 1.6)	(-0.01, 1.55)	(-0.67, 1.21)	(-0.73, 1.75)		**(0.12, 0.93)**
Imi	-0.39	-0.36	-0.26	-0.41	-0.17	-0.26	-0.07	-0.05	-0.10	-0.11	0.18	0.01	-0.03	0.23	0.04	0.4	0.08	0.19	0.18	0.16	0.36	0.37	-0.15	0.07	-0.43	**Imi**
	(-1.21, 0.34)	(-1.09, 0.36)	(-1.1, 0.62)	(-1.19, 0.35)	(-0.81, 0.43)	(-1.10, 0.60)	(-0.71, 0.55)	(-0.75, 0.63)	(-0.75, 0.52)	(-0.89, 0.65)	(-0.45, 0.79)	(-0.93, 0.92)	(-0.66, 0.58)	(-0.59, 1.04)	(-0.74, 0.8)	(-0.63, 1.43)	(-0.62, 0.76)	(-0.47, 0.82)	(-0.63, 1.02)	(-0.58, 0.85)	(-0.42, 1.14)	(-0.36, 1.07)	(-1.09, 0.76)	(-1.15, 1.28)	(-1.01, 0.16)	

Drugs are reported in SUCRA order of efficacy. Data are RR (95% CrI) for acceptability (upper triangle) and SMD (95% CrI) for efficacy (lower triangle, blue). For efficacy, SMD values lower than 0 favor the column –defining treatment and SMD values higher than 0 favor the row-defining treatment. For acceptability, RR lower than 1 favor the row-defining treatment and RR higher than 1 favor the column –defining treatment (indicating that the favored medicament had fewer all-cause discontinuations during the pharmacological treatment). Statistically significant results are in bold.
CrI=credible interval. SMD= standardized mean difference. RR=relative risk. Ami=amitriptyline. Bro=brofaromide. Bupro=bupropion. Cita=citalopram. Desi=desipramine. Diva=divalproex. Flu=fluoxetine. Gran=guanfacine. Imi=imipramine. Lamo=lamotrigine. Mirta=mirtazapine. Nefa=nefazodone. NK=NK1RA. Olan=olanzapine. Paro=paroxetine. Phe=phenelzine. Pla= placebo. Prazo=prazosin. Que=quetiapine. Rispe=risperidone. Ser=sertraline. Tia=tiagabine. Topi=topiramate. Venla=venlafaxine. Vila=vilazodone. Zipra=ziprasidone.

Figure 4. Network Meta-analysis Results for the Comparison of Active Treatment Versus Placebo.



Effect sizes are reported in SUCRA order of efficacy (a) and acceptability (b). CrI=credible interval. SMD= standardized mean difference. RR=relative risk. SUCRA= surface under the cumulative ranking curve.

CONFLICT OF INTEREST AND ROLE OF FUNDING SOURCE

Declarations of interest: none.

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AUTHORS' STATEMENT

The present study is a network meta-analysis, and all analyses were based on existing data. We declared that no competing interests exist.

Authors' contributions: GMC and FBZ provided substantial contributions to the conception of the work, for the acquisition, analysis, and interpretation of data and revised it critically for important intellectual content. GMC and AJSB selected the articles and extracted the data. PKZ analyzed the data, provided substantial contributions to the interpretation of the data and the writing of the final version. CFM helped drafting the work and revising it critically. All authors revised and approved the final version to be published.

SUPPLEMENTARY DATA

Appendix S1. PRISMA Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-Analysis (NMA)

Appendix S2. Search Strategy in Cochane (Central), Embase, LILACS, PILOTS, PsycINFO, PubMed, and Web of Science

Figure S1. Results of Pairwise Meta-analysis for Efficacy

Figure S2. Results of Pairwise Meta-analysis for Acceptability

Figure S3. Probabilities Estimated for Each Treatment in the Network of Achieving a Particular Placement in a Ranking of Efficacy and Acceptability from Best to Worst

Figure S4. Risk of Bias Graph for All Eligible Studies

Figure S5. Risk of Bias Summary for All Eligible Studies

Figure S6. Funnel Plots for the Outcomes Efficacy and Acceptability

Table S1. Characteristics of the Randomized Controlled Trials Included in the Systematic Review

Table S2. Hierarchy of Competing Interventions of the Network Meta-Analysis in Terms of Treatment Rankings for Efficacy and Acceptability

References. List of Randomized Controlled Trials Included in the Systematic Review

Appendix S1. PRISMA Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-Analysis (NMA)

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
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.	3,4
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*.	5,6
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7,8,9
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.	7
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).*	7,8,9
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.	9,10
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix S2

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).	Figure 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.	9, 10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10, 11; Table S1
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.	10,11
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.	12
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.*	10,11,12
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.*	10,11,12
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.	11
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).	12
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).*	
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at	14; Figure 1

		each stage, 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.	Figure 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.	15,16,17
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.	Table S1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	17; Figure S4; Figure 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 networks.*	14,15,16,17; Figure S1; Figure S2
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.	Figure 3; Figure 4; Table S2; Figure S1; Figure S2; Figure S3
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.	17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	
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).	
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).	19,20,21,22,23
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).*	23,24
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	25

FUNDING			
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.	Table S1

Appendix S2. Search Strategy in the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, LILACS, PILOTS, PsycINFO, PubMed (MEDLINE), and Web of Science Databases

Cochane (Central):

#1MeSH descriptor: [Stress Disorders, Post-Traumatic] explode all trees
#2 PTSD
#3 #1 OR #2
#4 MeSH descriptor: [Anticonvulsants] explode all trees
#5 MeSH descriptor: [Antidepressive Agents] explode all trees
#6 MeSH descriptor: [Antipsychotic Agents] explode all trees
#7 MeSH descriptor: [Anti-Anxiety Agents] explode all trees
#8 MeSH descriptor: [Benzodiazepines] explode all trees
#9 dopamin*
#10 MeSH descriptor: [Drug Therapy] explode all trees
#11 MeSH descriptor: [Monoamine Oxidase Inhibitors] explode all trees
#12 MeSH descriptor: [Neurotransmitter Agents] explode all trees
#13 noradrenerg*
#14 MeSH descriptor: [Norepinephrine] explode all trees
#15 MeSH descriptor: [Psychotropic Drugs] explode all trees
#16 MeSH descriptor: [Neurotransmitter Uptake Inhibitors] explode all trees
#17 seroto*
#18 alprazolam OR amitriptyline OR amoxapine OR aripiprazole OR asenapine OR baclofen OR brofaromine OR bupropion OR cannabinoids OR carbamazepine OR citalopram OR clomipramine OR clonazepam OR clonidine OR cortisol OR cyproheptadine OR d-cycloserine OR desipramine OR desvenlafaxine OR diazepam OR divalproex OR doxepin OR duloxetine OR escitalopram OR eszopiclone OR fenfluramine OR flumazenil OR fludocortisone OR fluoxetine OR fluphenazine OR fluvoxamine OR flurazepam OR gabapentine OR guanfacine OR haloperidol OR hydrocortizone OR hypnotics OR imipramine OR inositol OR iproniazid OR isocarboxazid OR lamotrigine OR levomilnacipran OR lithium OR lurasidone OR maprotiline OR melatonin OR methadone OR mianserin OR milnacipran OR

mirtazapine OR moclobemide OR molindone OR morphine OR naloxone OR naltrexone OR nefazodone OR nitrazepam OR nomifensine OR norfenfluramine OR nortriptyline OR noxiptiline OR olanzapine OR oxcarbazepine OR oxytocin OR paliperidone OR paroxetine OR pregabalin OR propranolol OR phenelzine OR pheniprazine OR prazosin OR procaine OR propanolol OR prosulpride OR protriptyline OR quetiapine OR ramelteon OR reboxetine OR risperidone OR ritanserin OR rivastigmine OR selegiline OR sertraline OR sulpiride OR tiagabine OR tianeptine OR atomoxetine OR topiramate OR tranylcypromine OR trazodone OR trimipramine OR tryptophan OR venlafaxine OR vilazodone OR vortioxetine OR yohimbine OR zimeldine OR ziprasidone OR zolpidem OR zopiclone

#19 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18

#20 #3 AND #19

EMBASE:

((('anticonvulsive agent'/exp OR 'anticonvulsive agent') OR ('antidepressant agent'/exp OR 'antidepressant agent') OR ('neuroleptic agent'/exp OR 'neuroleptic agent') OR ('anxiolytic agent'/exp OR 'anxiolytic agent') OR benzodiazepine* OR dopamin* OR ('drug therapy'/exp OR 'drug therapy') OR ('monoamine oxidase inhibitor'/exp OR 'monoamine oxidase inhibitor') OR ('agents interacting with transmitter, hormone or drug receptors'/exp OR 'agents interacting with transmitter, hormone or drug receptors') OR noradrenerg* OR ('noradrenalin'/exp OR 'noradrenalin') OR ('psychotropic agent'/exp OR 'psychotropic agent') OR (uptake OR reuptake OR 're uptake') OR seroto* OR ('serotonin noradrenalin reuptake inhibitor'/exp OR 'serotonin noradrenalin reuptake inhibitor') OR ('serotonin uptake inhibitor'/exp OR 'serotonin uptake inhibitor') OR ('tricyclic antidepressant agent'/exp OR 'tricyclic antidepressant agent') OR ('alprazolam'/exp OR alprazolam OR 'amitriptyline'/exp OR amitriptyline OR 'aripiprazole'/exp OR aripiprazole OR 'asenapine'/exp OR asenapine OR 'atomoxetine'/exp OR atomoxetine OR 'baclofen'/exp OR baclofen OR benzodiazepine* OR 'brofaromine'/exp OR brofaromine OR 'bupropion'/exp OR bupropion OR 'cannabinoids'/exp OR cannabinoids OR 'carbamazepine'/exp OR carbamazepine OR 'citalopram'/exp OR citalopram OR 'clomipramine'/exp OR clomipramine OR

'clonazepam'/exp OR clonazepam OR 'clonidine'/exp OR clonidine OR 'cortisol'/exp OR cortisol OR 'cyproheptadine'/exp OR cyproheptadine OR 'd cycloserine'/exp OR 'd cycloserine' OR 'desipramine'/exp OR desipramine OR 'desvenlafaxine'/exp OR desvenlafaxine OR 'diazepam'/exp OR diazepam OR 'divalproex'/exp OR divalproex OR 'doxepin'/exp OR doxepin OR 'duloxetine'/exp OR duloxetine OR 'escitalopram'/exp OR escitalopram OR 'eszopiclone'/exp OR eszopiclone OR 'fenfluramine'/exp OR fenfluramine OR 'flumazenil'/exp OR flumazenil OR fludocortisone OR 'fluoxetine'/exp OR fluoxetine OR 'fluphenazine'/exp OR fluphenazine OR 'fluvoxamine'/exp OR fluvoxamine OR 'flurazepam'/exp OR flurazepam OR gabapentine OR 'guanfacine'/exp OR guanfacine OR 'haloperidol'/exp OR haloperidol OR 'hypnotics'/exp OR hypnotics OR 'hydrocortisone'/exp OR hydrocortisone OR 'imipramine'/exp OR imipramine OR 'inositol'/exp OR inositol OR 'iproniazid'/exp OR iproniazid OR 'lamotrigine'/exp OR lamotrigine OR 'levomilnacipran'/exp OR levomilnacipran OR 'lithium'/exp OR lithium OR 'lurasidone'/exp OR lurasidone OR 'maprotiline'/exp OR maprotiline OR 'melatonin'/exp OR melatonin OR 'methadone'/exp OR methadone OR 'mianserin'/exp OR mianserin OR 'milnacipran'/exp OR milnacipran OR 'mirtazapine'/exp OR mirtazapine OR 'moclobemide'/exp OR moclobemide OR 'molindone'/exp OR molindone OR 'morphine'/exp OR morphine OR 'naloxone'/exp OR naloxone OR 'naltrexone'/exp OR naltrexone OR 'nefazodone'/exp OR nefazodone OR 'nitrazepam'/exp OR nitrazepam OR 'nomifensine'/exp OR nomifensine OR 'norfenfluramine'/exp OR norfenfluramine OR 'nortriptyline'/exp OR nortriptyline OR 'noxiptiline'/exp OR noxiptiline OR 'olanzapine'/exp OR olanzapine OR 'oxcarbazepine'/exp OR oxcarbazepine OR 'oxytocin'/exp OR oxytocin OR 'paliperidone'/exp OR paliperidone OR 'paroxetine'/exp OR paroxetine OR 'pregabalin'/exp OR pregabalin OR 'propranolol'/exp OR propranolol OR 'phenelzine'/exp OR phenelzine OR 'prazosin'/exp OR prazosin OR 'procaine'/exp OR procaine OR propanolol OR 'quetiapine'/exp OR quetiapine OR 'ramelteon'/exp OR ramelteon OR 'reboxetine'/exp OR reboxetine OR 'risperidone'/exp OR risperidone OR 'ritanserin'/exp OR ritanserin OR 'rivastigmine'/exp OR rivastigmine OR 'selegiline'/exp OR selegiline OR 'sertraline'/exp OR sertraline OR 'sulpiride'/exp OR sulpiride OR 'tiagabine'/exp OR tiagabine OR 'tianeptine'/exp OR tianeptine OR 'topiramate'/exp OR topiramate OR 'tranylcypromine'/exp OR tranylcypromine OR 'trazodone'/exp OR trazodone OR 'tryptophan'/exp OR tryptophan OR 'venlafaxine'/exp OR venlafaxine OR 'vilazodone'/exp OR vilazodone OR 'vortioxetine'/exp OR vortioxetine OR

'yohimbine'/exp OR yohimbine OR 'ziprasidone'/exp OR ziprasidone OR 'zolpidem'/exp OR zolpidem OR zopiclon)) AND (('posttraumatic stress disorder'/exp OR 'posttraumatic stress disorder') OR ((('post traumatic' OR post) AND traumatic OR posttraumatic) AND disorder*) OR ('ptsd'/exp OR ptsd) OR ('psychotrauma'/exp OR 'psychotrauma'))) AND 'human'/de AND ('article'/it OR 'article in press'/it)

LILACS:

(ptsd) or "PTSD" [Descritor de assunto] or (war trauma) or "transtornos pos-traumaticos de ESTRESSE" [Descritor de assunto] and ("PSYCHOPHARMACOLOGY") or "tratamento farmacologico" or (psicotrópicos) or "psicotropicos" [Descritor de assunto]

PILOTS:

((posttraumatic stress disorder*) OR su(posttraumatic stress disorder*) OR su(post traumatic stress) OR (posttraumatic stress) OR su(posttraumatic stress) OR su(post-traumatic stress) OR (combat disorder) OR (psychological trauma) OR (war neuros*s) OR PTSD) AND (seroton* OR norepinephrine OR noradrenaline OR dopamin* OR neurotransmitter OR 5-hydroxytrypotophan OR anticonvulsant* OR antidepress* OR antipsychotic* OR anxiolytic* OR benzodiazepine* OR hypnotics OR medicat* OR monoamine oxidase inhibitor* OR noradrenerg* OR pharmacother* OR psychotropic* OR snri* OR ssri* OR tricyclic* OR uptake OR reuptake OR re-uptake OR alprazolam OR amitriptyline OR aripiprazole OR asenapine OR atomoxetine OR baclofen OR brofaromine OR bupropion OR cannabinoids OR carbamazepine OR citalopram OR clomipramine OR clonazepam OR clonidine OR cortisol OR cyproheptadine OR d-cycloserine OR desipramine OR desvenlafaxine OR diazepam OR divalproex OR doxepin OR duloxetine OR escitalopram OR eszopiclone OR fenfluramine OR flumazenil OR fludocortisone OR fluoxetine OR fluphenazine OR fluvoxamine OR flurazepam OR gabapentine OR guanfacine OR haloperidol OR hydrocortisone OR imipramine OR inositol OR iproniazid OR lamotrigine OR levomilnacipran OR lithium OR lurasidone OR maprotiline OR melatonin OR

methadone OR mianserin OR milnacipran OR mirtazapine OR moclobemide OR molindone OR morphine OR naloxone OR naltrexone OR nefazodone OR nitrazepam OR nomifensine OR norfenfluramine OR nortriptyline OR noxiptiline OR olanzapine OR oxcarbazepine OR oxytocin OR paliperidone OR paroxetine OR pregabalin OR propranolol OR phenelzine OR prazosin OR procaine OR propanolol OR quetiapine OR ramelteon OR reboxetine OR risperidone OR ritanserin OR rivastigmine OR selegiline OR sertraline OR sulpiride OR tiagabine OR tianeptine OR topiramate OR tranylcypromine OR trazodone OR tryptophan OR venlafaxine OR vilazodone OR vortioxetine OR yohimbine OR ziprasidone OR zolpidem OR zopiclon)

PsycINFO:

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Web of Science:

#1 TÓPICO: (posttraumatic) AND TÓPICO: (stress) AND TÓPICO: (disorder)
#2 TÓPICO: (post-traumatic) AND TÓPICO: (disorder)
#3 TÓPICO: (post) AND TÓPICO: (traumatic) AND TÓPICO: (disorder)
#4 TÓPICO: (posttraumatic) AND TÓPICO: (disorder *)
#5 TÓPICO: (PTSD)
#6 TÓPICO: (combat) AND TÓPICO: (disorder *)
#7 TÓPICO: (psychological) AND TÓPICO: (trauma)
#8 TÓPICO: (war) AND TÓPICO: (injuries)
#9 #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

#10 TÓPICO: (seroton*) OR TÓPICO: (noradrenerg*) OR TÓPICO: (noradrenaline) OR TÓPICO: (dopamin*) ORTÓPICO: (neurotransmitter) OR TÓPICO: (5-hydroxytrypotophan) OR TÓPICO: (anticonvulsant*) OR TÓPICO:(antidepress*) OR TÓPICO: (antipsychotic*) OR TÓPICO: (anxiolytic*) OR TÓPICO: (benzodiazepine*) ORTÓPICO: (hypnotics) OR TÓPICO: (medicat*) OR TÓPICO: (pharmacother*) OR TÓPICO: (psychotropic*) ORTÓPICO: (snri*) OR TÓPICO: (ssri*) OR TÓPICO: (tricyclic*) OR TÓPICO: (uptake) OR TÓPICO: (reuptake) ORTÓPICO: (re-uptake)

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#15 #14 OR #13 OR #12 OR #11 OR #10

#16 #15 AND #9

Figure S1. Pairwise Meta-analysis Results for Efficacy

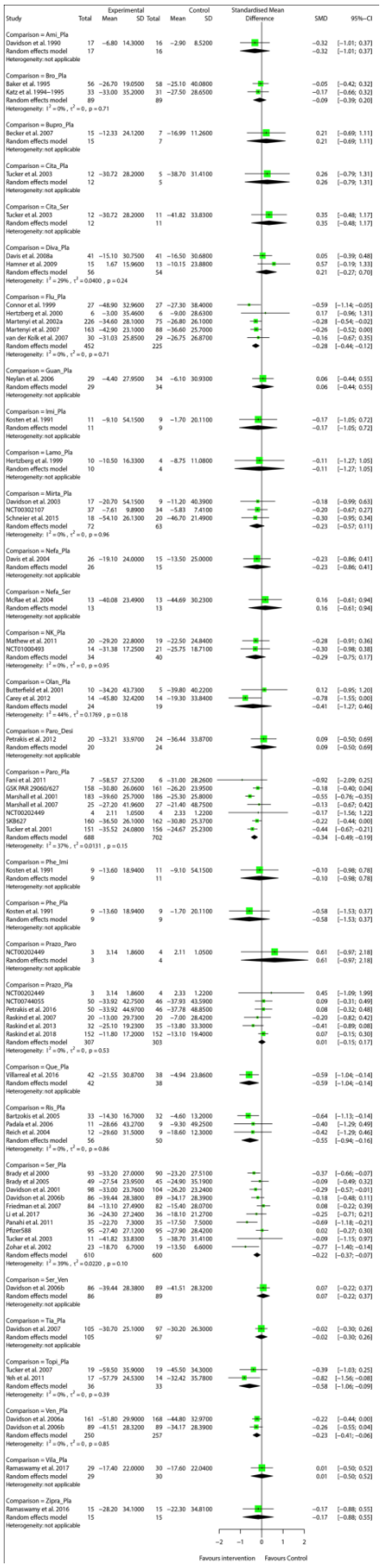


Figure S2. Pairwise Meta-analysis Results for Acceptability

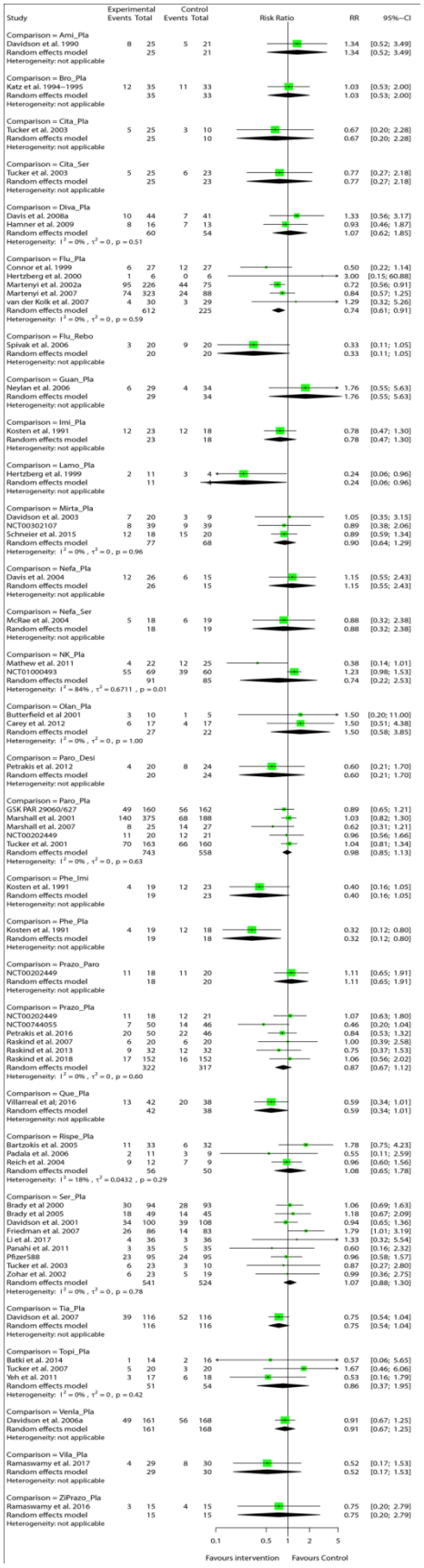
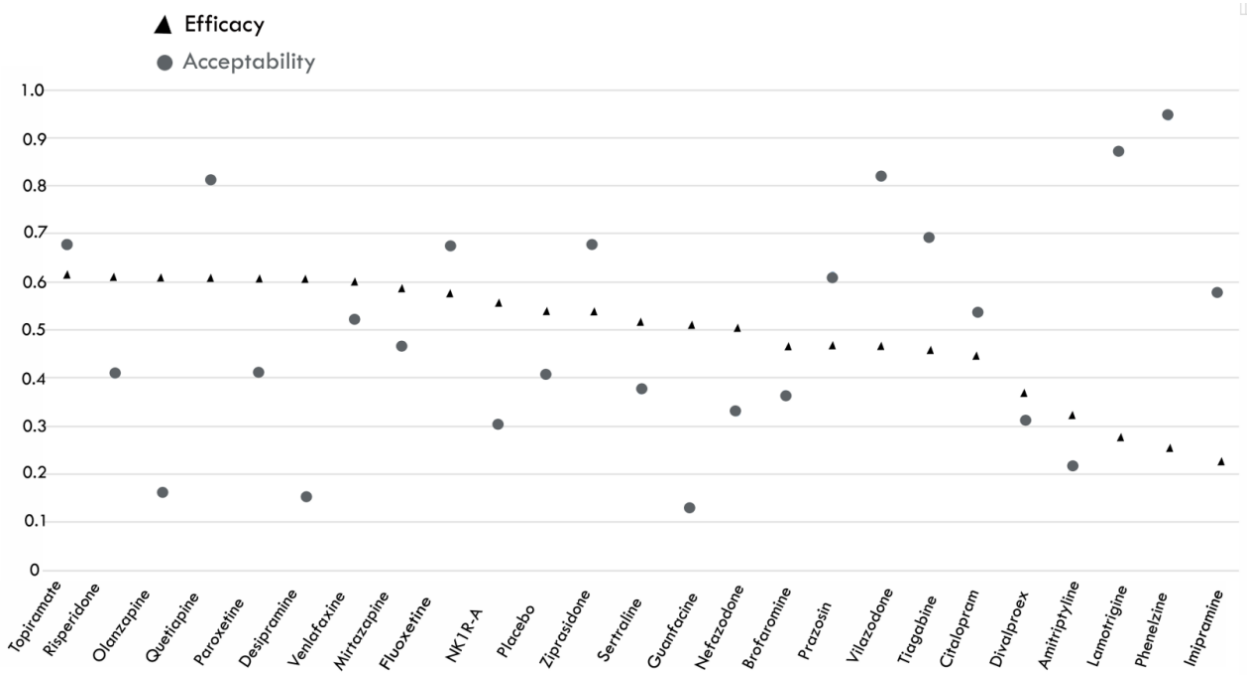
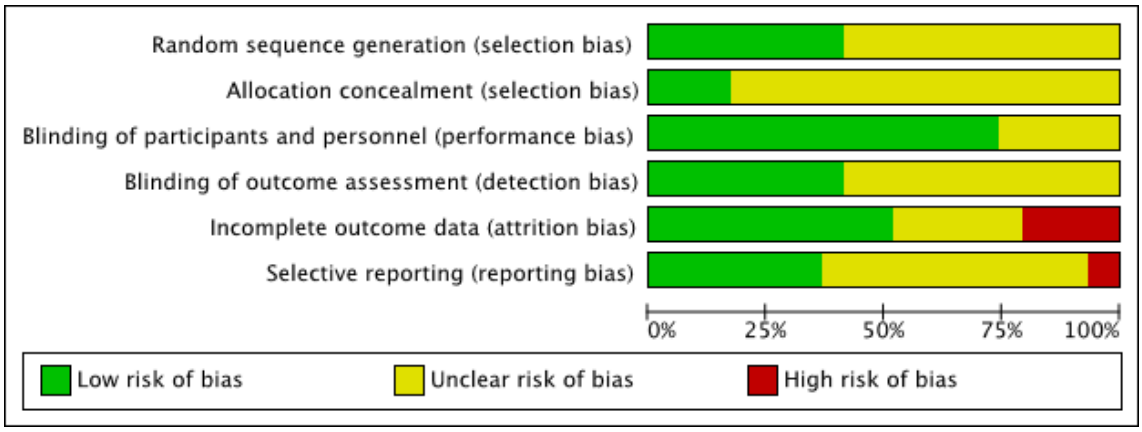


Figure S3. Probabilities Estimated for Each Treatment in the Network of Achieving a Particular Placement in a Ranking of Efficacy and Acceptability from Best to Worst



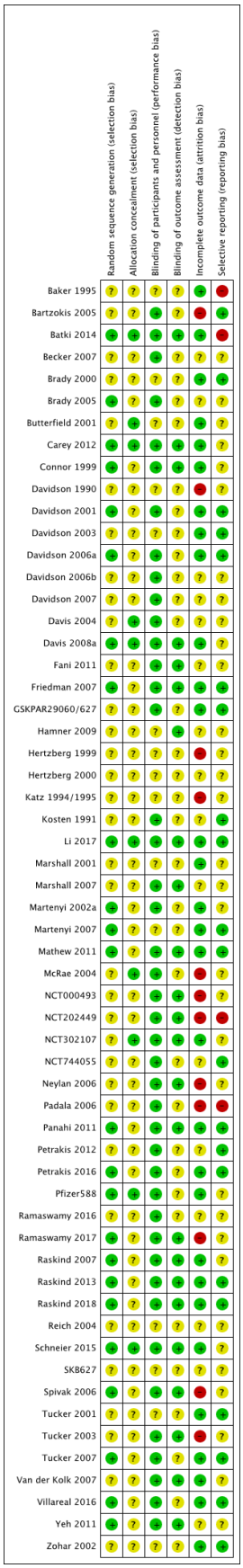
The probabilities estimated for each treatment between 0 and 1 represent the probability of being ranked highest. For the efficacy outcome, higher scores reflect higher probability of improvement in symptom severity with a particular drug. For the acceptability outcome, higher scores correspond to lower probability of all-cause discontinuation from medication during pharmacological treatment.

Figure S4. Risk of Bias Graph



Review authors' judgements about each risk of bias item presented as percentages across all included studies, using Cochrane's risk of bias assessment tool.

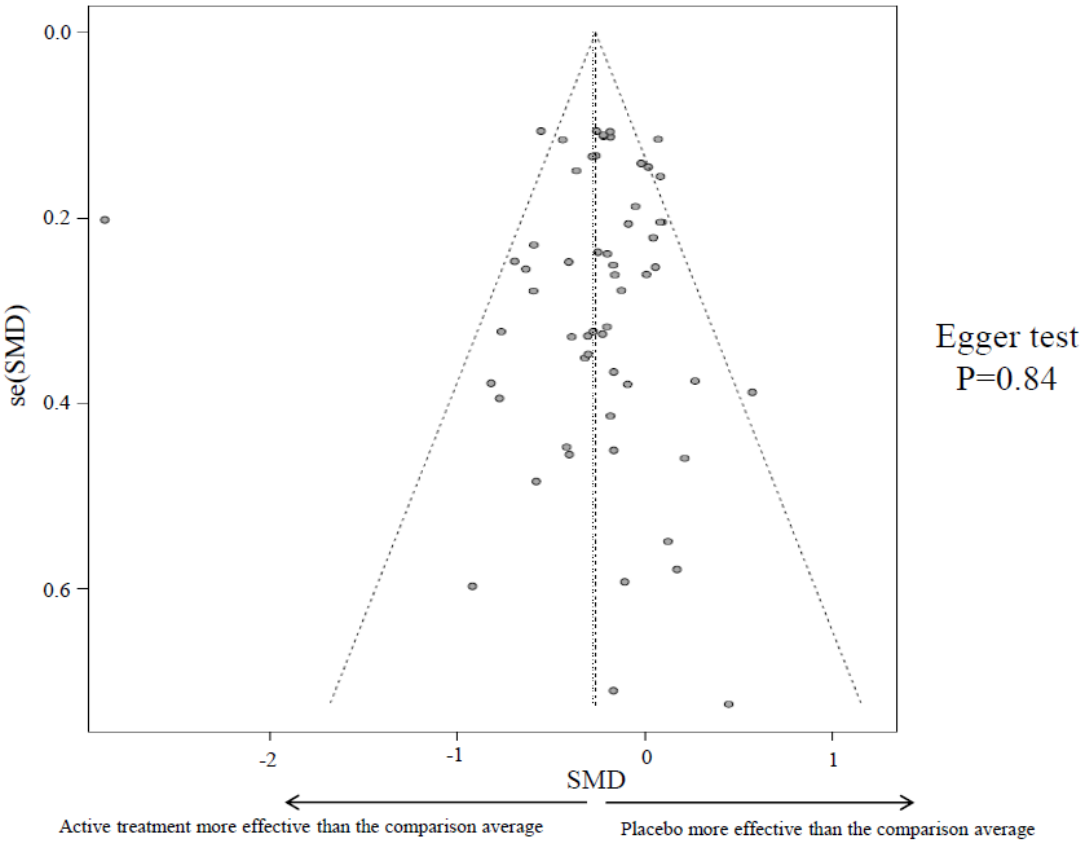
Figure S5. Risk of Bias Summary



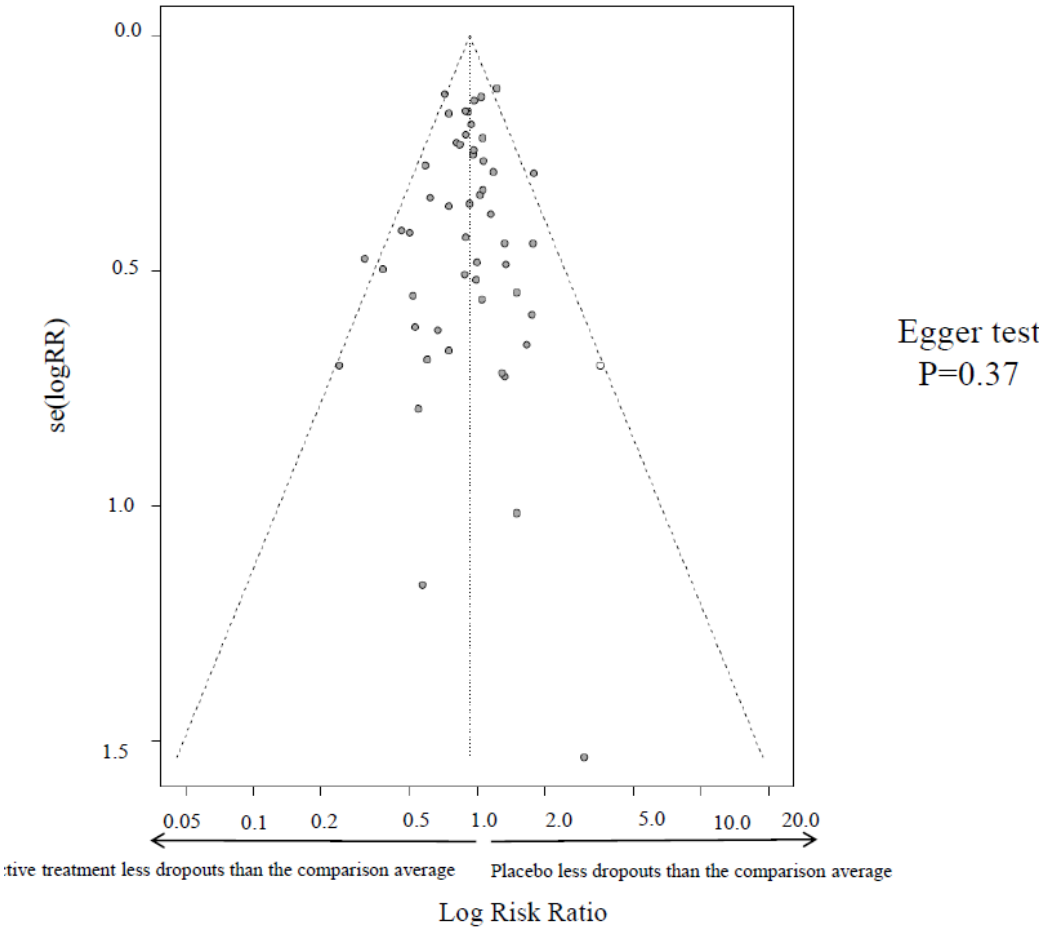
Review authors' judgements about each risk of bias item for each included study, using Cochrane's risk of bias assessment tool.

Figure S6. Funnel Plots for the Outcomes Efficacy and Acceptability

A: Funnel plot including all the comparisons of an active drug vs. placebo for the outcome change in symptoms (efficacy)



B: Funnel plot including all the comparisons of an active drug vs. placebo for the outcome any cause dropouts (acceptability), as well as “trim-and-fill” imputed studies



C: Forest plot including all the comparisons of an active drug vs. placebo for the outcome any cause dropouts (acceptability), as well as "trim-and-fill" imputed studies.

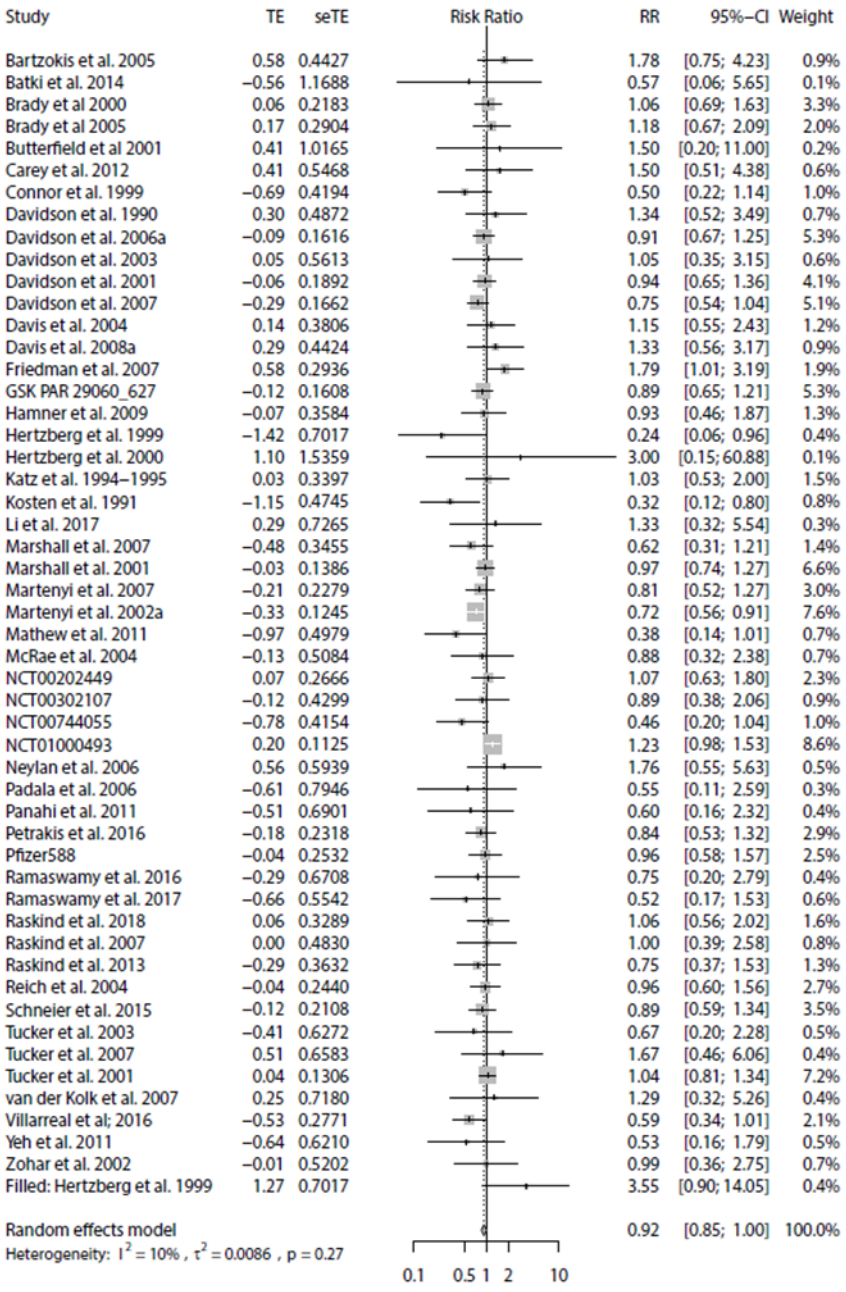


Table S1. Characteristics of the Randomized Controlled Trials Included in the Systematic Review

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
Baker et al, 1995 (1)	118 A: 56 C: 58	A: Brofaromine up to 150 mg/d C: Placebo	A: Antidepressant (Monoamine oxidase inhibitor)	12	Mixed (combat-related)	A: 45.5 C: 43	A: 12 (21.4) C: 10 (17.3)	DSM-III-R	CAPS	A: 81.6 (19.4) C: 79.7 (20.9)	NR
Bartzokis et al, 2005 (2)	65 A: 33 C: 32	A: Risperidone 1 to 3 mg/d C: Placebo	A: Atypical or Second generation antipsychotic)	16	Veterans (combat-related)	51.6 overall A: NR C: NR	A: 0 C: 0	DSM-IV	CAPS	A:102.2 (11.9) C:98.6 (15.8)	Janssen Research Foundation Marie Wilson Howells Endowment, and the Department of Veterans Affairs.
Batki et al, 2014 (3)	30 A: 14 C: 16	A: Topiramate 25 to 300 mg/d C: Placebo	A: Anticonvulsant/ mood stabilizer	12	Veterans (combat-related)	A: 49.5 C: 50.4	A: 1 (7.2) C: 1 (6.25)	DSM-IV-TR	CAPS	A: 72.8 (4.3) C: 83.1 (17.3)	Grants from the Department of Defense,

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
											National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health and with resources of the Veterans Affairs Medical Center, San Francisco, California.
Becker et al, 2007 (4)	30 A: 20 C: 10	A: Bupropion SR 100 to 300 mg/d C:	A: Antidepressant (dopamine reuptake	8	Mixed (combat-related)	50.39 overall A: NR C: NR	21 overall A: NR C: NR	DSM-IV	CAPS	A: NR C: NR	Pharmaceutical industry; Veterans Affai

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
		Placebo	inhibitor)								rs Merit Awards
Brady et al, 2000 (5)	187 A: 94 C: 93	A: Sertraline 25 to 200 mg/d C: Placebo	A: Antidepressant (Selective serotonin reuptake inhibitor)	12	Mixed (physical or sexual assault)	A: 40.2 C: 39.5	A: 71 (75.5) C: 66 (71)	DSM-III-R	CAPS-2	A: 76.6 (17.5) B:75.1 (17.7)	Pharmaceutical industry
Brady et al, 2005 (6)	94 A: 49 C: 45	A: Sertraline up to 150 mg/d C: Placebo	A: Antidepressant (Selective serotonin reuptake inhibitor)	12	Civilian (physical assault)	A: 36.7 C: 36.6	A: 21 (43) C: 22 (49)	DSM-IV	CAPS	A: 60.1 (18.1) C: 57.6 (20.3)	Pharmaceutical industry
Butterfield et al, 2001 (7)	15 A: 10 C: 5	A: Olanzapine 5 to 20mg/d C: Placebo	A: Atypical or Second generation antipsychotic)	10	Mixed (rape)	A:44.6 C: 40.4	A: 9 (90) C: 5 (100)	DSM-IV	DTS	A: 91.6 (25.4) C: 95.8 (16.7)	Pharmaceutical industry
Carey et al, 2012 (8)	34 A: 17 C:17	A: Olanzapine 5 to 10 mg/d C: Placebo	A: Atypical or Second generation antipsychotic)	8	Civilians (NR)	40.75 overall A: NR C: NR	60.7 overall A: NR C: NR	DSM-IV	CAPS	A: 79.4 (16) C:81.6 (11.3)	Pharmaceutical industry
Connor et al, 1999	54 A:27 C: 27	A: Fluoxetine 10 to 60	A: Antidepressant	12	Civilians (sexual	A: 36 C: 38	A: 24 (89) C: 25 (93)	DSM-III-R	DTS	A: 73.7 (20.4) C:79.4	Pharmaceutical indus

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
(9)		mg/d C: Placebo	(Selective serotonin reuptake inhibitor)		trauma)					(22.8)	try
Davidson et al, 1990 (10)	46 A: 25 C: 21	A: Amitriptyline 50 to 300 mg/d C: Placebo	A: Antidepressant (tricyiclic)	8	Veterans (combat-related)	49 A: NR C: NR	NR A: NR C: NR	DSM-III	IES	A: 31.8 (8.5) C: 36.6 (5.4)	Supported in part by a Veterans Administration grant
Davidson et al, 2006a (11)	329 A: 161 C: 168	A: Venlafaxine ER 37.5 to 300 mg/d C: Placebo	Antidepressant (Serotonin - noradrenaline reuptake inhibitor)	24	Mixed (nonsexual abuse)	A: 42.2 C: 40.5	A: 89 (55.3) C: 89 (53)	DSM-IV	CAPS-SX17	A: 81.0 (14.62) C: 82.9 (15.50)	Pharmaceutical industry
Davidson et al, 2006b (12)	538 A: 179 B: 173 C: 179	A: Venlafaxine ER 37.5 to 300 mg/d B: Sertraline 25 to 200 mg/d C: Placebo	A: Antidepresssant (serotonin - noradrenaline reuptake inhibitor) B: Antidepresssant (selective serotonin	12	Mixed (abuse)	32 overall A: NR B: NR C: NR	65 overall A: NR B: NR C: NR	DSM-IV	CAPS-SX17		Pharmaceutical industry

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
			reuptake inhibitor)								
Davidson et al, 2001 (13)	208 A: 100 C: 108	A: Sertraline 25 to 200 mg/d C: Placebo	A: Antidepressant (Selective serotonin reuptake inhibitor)	12	Mixed (physical or sexual assault)	A: 37.6 C: 36.6	A: 84 (84) C: 78 (72)	DSM-III-R	CAPS-2	A: 73.9 (16.2) C: 73.5 (16.1)	Pharmaceutical industry
Davidson et al, 2003 (14)	29 A: 20 C: 9	A: Mirtazapine 15 to 45 mg/d C: Placebo	A: Antidepressant (second-generation tetracyclic antidepressant)	8	Mixed (unexpected death of a significant other)	A: 48.4 C: 42.9	81 overall A: NR C: NR	DSM-IV	DTS	A: 74.8 (36.5) C: 93.8 (29.4)	Pharmaceutical industry
Davidson et al, 2007 (15)	232 A: 116 C: 116	A: Tiagabine 4 to 16 mg/d C: Placebo	A: Anticonvulsant/ mood stabilizer	12	Mixed (physical and sexual assault)	42.6 overall A: NR C: NR	66 overall A: NR C: NR	DSM-IV	CAPS	A: 82.4 (15.8) C: 82.7 (14.4)	Pharmaceutical industry
Davis et al, 2004 (16)	42 A:27 C: 15	A: Nefazodone 200 to 600 mg/d C: Placebo	A: Antidepresssant (second-generation antidepressant)	12	Mixed - though only one civilian (combat-related)	A: 53.8 C: 53.8	2.4 A: NR C: NR	DSM-IV	CAPS	A: 81.0 (20) C: 83.2 (17)	Partial funding from pharmaceutical company

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
Davis et al, 2008a (17)	85 A: 44 C: 41	A: Divalproex 1000 to 3000 mg/d C: Placebo	A: Anticonvulsant/ mood stabilizer	8	Mixed (combat-related)	55.2 A: NR C: NR	2 overall A: NR C: NR	DSM-IV	CAPS	A: 75.2 (19.1) C: 77.3 (15.3)	Drugs supplied by pharmaceutical industry
Fani et al, 2011 (18)	13 A: 7 C: 6	A: Paroxetine CR 12.5 to 62.5 mg/d C: Placebo	A: Antidepressant (Selective serotonin reuptake inhibitor)	12	Mixed (childhood sexual abuse)	A: 37.4 C: 42.5	A: 4 (57) C: 3 (50)	DSM-IV	CAPS	A: 84.86 (8.15) C:51.17 (19.8)	Pharmaceutical industry
Friedman et al, 2007 (19)	169 A: 86 C: 83	A: Sertraline 25 to 200 mg/d C: Placebo	A: Antidepresssant (Selective serotonin reuptake inhibitor)	12	Mixed (combat-related)	A: 45 C: 46	A: 18 (20.93) C: 16 (19.27)	DSM-III-R	CAPS-2	A: 72.1 (19.1) C: 73.8 (19.8)	Pharmaceutical industry
GSK PAR 29060/627[b]	322 A: 160 C: 162	A: Paroxetine 20 to 50mg/d C: Placebo	A: Antidepressant (Selective serotonin reuptake inhibitor)	12	Mixed (NR)	A: 39.5 C: 38.9	A: 85 (53) C: 88 (54.3)	DSM-IV	CAPS- 2	77.4 (18.97) C: 78.4 (16.54)	Pharmaceutical industry
Hamner et al, 2009 (20)	29 A: 16 C: 13	A: Divalproex 750 to 1500mg/d	A: Anticonvulsant/ mood stabili	10	Veterans (combat-related)	A: 52.6 C: 52.1	A: 1 (6.25) C: 0	DSM-IV	CAPS	A: 76.67 (23.80) C:77.62 (21.91)	Pharmaceutical industry

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
		C: Placebo	zer								
Hertzberg et al, 1999 (21)	15 A: 11 C: 4	A: Lamotrigine 25 to 500 mg/d C: Placebo	A: Anticonvulsant/ mood stabilizer	12	Mixed (combat-related)	43.4 overall A: NR C: NR	A: 4 (36.6) C: 1 (25)	DSM-IV	SIP	A: 44.8 (5.92) C: 43 (8.08)	Pharmaceutical industry
Hertzberg et al, 2000 (22)	12 A: 6 C: 6	A: Fluoxetine 10 to 60 mg/d C: Placebo	A: Antidepressant (Selective serotonin reuptake inhibitor)	12	War trauma (combat-related)	46 overall A: NR C: NR	A: 0 C: 0	DSM-IV	DTS	A: 106 (27) C: 111 (12)	Medication provided by pharmaceutical company; supported in part by an NIMH Grant
Katz et al, 1994-1995 (23)	68 A: 35 C:33	A: Brofaromine 50 to 150 mg/d C: Placebo	A: Antidepressant (Monoamine oxidase inhibitor)	14 (8 for efficacy analysis)	Mixed (physical assault)	A: 37 C: 37	A: 5 (37.2) C: 6 (36.4)	DSM-III-R	CAPS	A:79.3 (18.9) C: 84.6 (16.1)	Pharmaceutical industry
Kosten et al, 1991 (24)	60 A: 19 B: 23 C: 18	A: Phenelzine 15 to 75 mg/d B: Imipramine 50 to 300 mg/d B:	A: Antidepressant (monoamine oxidase inhibitor) B:	8	Vietnam veterans (combat-related)	A: 39 B: 39 C: 38	A: 0 B: 0 C: 0	DSM-III	IES	A: 30.6 (15.2) B: 36.5 (16.7) C: 33.0 (13.4)	Medication provided by pharmaceutical industry

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
		C: Placebo	Antidepressant (tricyclic)								
Li et al, 2017 (25)	72 A: 36 C: 36	A: Sertraline up to 135 mg/d C: Placebo	Antidepressant (Selective serotonin reuptake inhibitor)	12	Mixed (combat-related)	A: 47.1 C: 44.9 p=0.12	A: 5 (13.9) C: 4 (11.1)	DSM-IV	IES-R	A: 64.8 (4.1) C: 63.9 (3.7)	Science and Technology Talents Program of Harbin and Heilongjiang Natural Science Foundation
Marshall et al, 2001 (26)	563 A: 188 B: 187 C: 188	A: Paroxetine 20mg B: Paroxetine 40mg C: Placebo	A: Antidepressant (Selective serotonin reuptake inhibitor) B: Antidepressant (Selective serotonin reuptake inhibitor)	12	Mixed (assault)	A: 41.5 B: 42.4 C: 41.6	A: 126 (67) B: 127 (68) C: 124 (66)	DSM-IV	CAPS-2	A: 75.3 (16.1) B: 74.3 (15.6) C:74.4 (15.9)	Pharmaceutical industry
Mars	63	A:	A:	10	Civilia	39.8	67	DSM-	CAP	A:	Phar

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
hall et al, 2007 (27)	A: 25 C: 27	Paroxetine 10 to 60 mg/d C: Placebo	Antidepressant (Selective serotonin reuptake inhibitor)		ns (physical assault or abuse)	overall A: NR C: NR	overall A: NR C: NR	IV	S	82.8 (25.4) C:84.2 (26.7)	maceutical industry
Martenyi et al, 2002 a/b (28)	301 A: 226 C: 75	A: Fluoxetine 20 to 80 mg/d C: Placebo	A: Antidepresssant (Selective serotonin reuptake inhibitor)	12	Mixed (combat-related)	A: 38 C: 37	A: 46 (20) C: 11 (15)	DSM-IV	CAPS	A: 80.5 (NR) C: 81.3 (NR)	Pharmaceutical company
Marteny et al, 2007 (29)	411 A: 163 B: 160 C: 88	A: Fluoxetine 20 mg/d B: Fluoxetine 40 mg/d C: Placebo	A: Antidepresssant (Selective serotonin reuptake inhibitor) B: Antidepresssant (Selective serotonin reuptake inhibitor)	12	Mixed (sexual assault)	A: 41.03 B: 39.96 C: 41.47	A: 71.2 (116) B: 71.9 (115) C: 71.6 (63)	DSM-IV	CAPS	A: 78.93 (15.92) B: 78.20 (15.39) C: 75.44 (16.75)	Pharmaceutical industry
Mathew et al, 2011 (30)	47 A: 22 C: 25	A: NK-1 RA GR205171	A: New drug (Neurokinin-	8	Mixed (abuse)	A: 38.7 C: 43.0	A: 12 (54.5) C: 11 (44)	DSM-IV	CAPS	A: 72.7 (12.1) C: 73.6 (15.6)	Pharmaceutical industry

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
		5mg/d C:Placebo	1 Receptor Antagonist/ NK-1RA)								and NIMH Grant
McRae et al, 2004 (31)	37 A: 18 C:19	A: Nefazodone 100 to 600 mg/d C: Sertraline 50 to 200 mg/d	A: Second-generation antidepressant C: Antidepressant (selective serotonin reuptake inhibitor)	12	Mixed (sexual assault)	A: 41.85 C: 38.69	A: 10 (77) B: 10 (77)	DSM-IV	CAPS-2	A:68.805 (7.70) B: 73.77 (16.40)	Pharmaceutical industry
NCT00202449[c]	59 A: 18 B: 20 C: 21	A: Prazosin 1 to 30 mg/d B: Paroxetine 20 mg/d C: Placebo	A: Anti-hypertensive (Alpha-1 adrenal receptor antagonist) B: Antidepressant (Selective Serotonin Reuptake Inhibitor)	12	Veterans (combat-related)	A: 29 B: 28 C: 32	A: 1 (5.6) B: 1 (5.0) C: 1 (4.8)	DSM-IV	CGI-C	A: NR B: NR C: NR	Seattle Institute for Biomedical and Clinical Research
NCT	78	A:	A:	8	Vetera	A:	A:2 (	DSM-	SIP	A: NR	US

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
00302107[d]	A: 39 C: 39	Mirtazapine 15 to 45 mg/d C: Placebo	Antidepressant (second-generation tetracyclic antidepressant)		n (combat-related)	37.7 C: 38.1	5.1) C: 3 (7.7)	IV		C: NR	Department of Veterans Affairs
NCT00744055[e]	96 A: 50 C: 46	A: Prazosin 16mg/d C: Placebo	A: Alpha blocker (alpha-1 adrenergic receptor antagonist that blocks the actions of NE on alpha-1 receptors)	12	Veterans (combat related)	A: 44.5 C: 43.4	A: 4(8) C: 2 (4.3)	DSM-IV	CAPS	A: 71.86 (20.32) C: 75.86 (14.44)	Yale University
NCT01000493[f]	129 A: 69 C: 60	A: Orvepitant (GW823296) 60 mg/d C: Placebo	A: New drug (Neurokinin-1 Receptor Antagonist/ NK-1RA)	12	Civilians (NR)	A: 37 C: 36.3	A: 52 (75.4) C: 47 (78.3)	DSM-IV	CAPS	A: NR C: NR	Pharmaceutical industry
Neylan et al, 2006 (32)	63 A: 29 C: 34	A: Guanfacine 0.5 to 3 mg/d	A: Anti-hypertensive (alpha	8	Veterans (combat-related	A: NR C: NR	A: NR C: NR	DSM-IV	CAPS	A: 67.1 (20.6) C: 69.4 (20.8)	VA Sierra Pacific

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
		C: Placebo	2A adrenergic receptor agonist)		)						Mental Illness Research, Education, Clinical Center
Padala et al, 2006 (33)	20 A: 11 C: 9	A: Risperidone 1 to 6 mg/d C: Placebo	A: Antipsychotic (Atypical or Second generation antipsychotic)	12 (10 for primary outcomes)	Civilians (domestic violence and sexual assault)	A: 39.2 C: 43.8	A: 11 (100) C: 9 (100)	M.I.N.I.	CAPS	A: 79.3 (NR) C: 80.6 (NR)	Pharmaceutical industry
Panahi et al, 2011 (34)	70 A: 35 C: 35	A: Sertraline 50 to 200 mg/d C: Placebo	A: Antidepressant (Selective serotonin reuptake inhibitor)	10	Veterans (combat-related)	A: 46.5 C: 44.6	A: 0 C: 0	DSM-IV-TR	IES-R	A: 65.30 (3.80) C: 65.10 (4.80)	Baqiyatallah University of Medical Sciences
Petrakis et al, 2012 (35)	88 A: 20 C: 24	A: Paroxetine 10 to 40 mg/d C: Desipramine 25 to 200 mg/d	A: Antidepressant (Selective serotonin reuptake inhibitor C: Antidepressant	12	Mixed (combat-related)	A: 49.15 C: 47.04	A: 1 (5) C: 3 (12.5)	DSM-IV	CAPS	A: 69.81 (23.10) C: 77.83 (23.67)	VISN I Mental Illness Research Education and Clinical Center; VA

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
			(Tricyclic)								Alcohol Center and Clinical Neuroscience Division of the VA National Center for PTSD
Petrakis et al, 2016 (36)	96 A: 50 C: 46	A: Prazosin 2 to 16 mg/d C: Placebo	A: Alpha blocker (alpha-1 adrenergic receptor antagonist that blocks the actions of NE on alpha-1 receptors)	13 (12 for efficacy assessment)	Veterans (combat-related)	A: 44.5 C: 43.4	A: 4 (8) C: 2 (4.44)	DSM-IV	CAPS	A:71.86 (20.32) C:75.86 (14.44)	Department of Defense USA
Pfizer 588[g]	190 A: 95 C: 95	A: Sertraline 50 to 200 mg/d C: Placebo	A: Antidepressant (Selective serotonin reuptake inhibit	10	Civilians (physical/sexual assault)	37 overall A: NR C: NR	75 overall A: NR C: NR	DSM-III-R	CAPS-2	A: NR C: NR	Pharmaceutical industry

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
			or)								
Ramaswamy et al, 2016 (37)	30 A:15 C:15	A: Ziprasidone 40 to 80 mg/d C: Placebo	A: Atypical or Second generation antipsychotic	9	Mixed (sexual or physical assault)	A:39.5 C: 38.3	A: 12 (80) C: 14 (93.3)	DSM-IV	CAPS	A: 79.90 (17.82) C: 75.40 (17.82)	Pharmaceutical industry
Ramaswamy et al, 2017 (38)	59 A: 29 C: 30	A: Vilazodone 10 to 40 mg/d	Antidepressant (serotonin partial agonist and reuptake inhibitor)	12	Veterans (combat-related)	A: 33.6 C: 31.8	A: 2 (3) C: 1 (3)	DSM-IV	CAPS	75.3 (14) C: 75.6 (12.92)	Pharmaceutical industry
Raskind et al, 2007 (39)	40 A: 20 C: 20	A: Prazosin 1 to 15 mg/d C: Placebo	A: Alpha blocker (alpha-1 adrenergic receptor antagonist that blocks the actions of NE on alpha-1 receptors)	8	Veterans (combat-related)	56 overall A: NR C: NR	5 overall A: NR C: NR	DSM-IV	CAPS	A: 76 (22.00) C: 78 (18.00)	Department of Veterans Affairs; NIH grant
Raskind et al, 2013 (40)	67 A: 32 C: 35	A: Prazosin 1 to 10mg/d/women and 20	Anti-hypertensive (Alpha-1 adrenal	15	Veterans (combat-related)	A: 30.0 C: 30.8	A: 6 (18.8) C: 4 (11.5)	DSM-IV	CAPS	A: 77.30 (23.66) C: 85.7 (23.09)	Department of Veterans Affairs;

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
		mg/d/men C: Placebo	receptor antagonist)								NIH grant
Raskind et al, 2018 (41)	304 A: 152 C: 152	A: Prazosin 1 to 20 mg/d C: Placebo	A: Alpha blocker (alpha-1 adrenergic receptor antagonist that blocks the actions of NE on alpha-1 receptors)	10	Veterans (combat-related)	A: 52.3 C: 51.4	A: 6 (3.9) C: 2 (6.7)	DSM-IV	CAPS	A: 80.70 (15.50) C: 81.90 (17.10)	Department of Veterans Affairs Cooperative Studies Program
Reich et al, 2004 (42)	21 A: 12 C: 9	A: Risperidone 0.5 to 8 mg/d C: Placebo	A: Antipsychotic (Atypical or Second generation antipsychotic)	8	Civilians (female childhood abuse)	A: 30.6 C: 24.2	A: 12 (100) B: 9 (100)	DSM-III-R	CAPS-2	A: 63.5 (17.4) C: 65.6 (13.8)	Pharmaceutical industry
Schneie et al, 2015 (43)	38 A: 18 C: 20	A: Mirtazapine 30 to 45 mg/d C: Placebo	A: Antidepressant (second-generation tetracyclic	24	Civilians (assault)	A: 37.6 C: 42.4	A: 12 (66.7) C: 11 (61.1)	DSM-IV	CAPS	A: 77.90 (19.50) C: 81.30 (12.20)	Research Foundation for Mental Hygiene, Incor

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
			antidepressant)								porated.
SKB 627[h]	322 A: 160 C: 162	A: Paroxetine 20 to 50 mg/d C: Placebo	A: Antidepressant (Selective serotonin reuptake inhibitor)	12	NR	18-75 (mean NR) A:NR C:NR	53.7 overall A:NR C: NR	DSM-IV	CAPS-2	NR	Pharmaceutical industry
Spivak et al, 2006 (44)	40 A: 20 B: 20	A: Reboxetine 8 mg/d C: Fluvoxamine 150 mg/d	A: Antidepressant (Selective norepinephrine reuptake inhibitor) C: Antidepressant (Selective serotonine reuptake inhibitor)	8	Civilian (motor vehicle accidents)	A: 39.7 B: 42.7	A: 9 (46) B: 9 (47)	DSM-IV	CAPS-2	A: 74.9 (14.9) C: 81.8 (11.0)	Grant from the Medical Corps of the Israel Defense Force and the Pharmaceutical industry
Tucker et al, 2001 (45)	323 A: 163 C: 160	A: Paroxetine 20 to 50 mg/d C: Placebo	A: Antidepressant (Selective serotonin reuptake inhibitor)	12	Mixed (interpersonal violence, non-combat related)	A: 41.9 C: 39.8	A: 108 (66.2) C: 105 (65.4)	DSM-IV	CAPS-2	A: 74.32 (17.75) C: 73.24 (15.81)	Pharmaceutical industry
Tuck	59	A:	A:	10	Mixed	A:	A:17	DSM-	CAP	A:	Phar

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
er et al, 2003 (46)	A: 25 B: 23 C: 10	Citalopram 20 to 50 mg/d B: Sertraline 50 to 200 mg/d C: Placebo	Antidepressant (Selective serotonin reuptake inhibitor) B: Antidepressant (Selective serotonin reuptake inhibitor)		(Physical abuse, assault)	39.2 B: 39.1 C: 36.8	(68) B: 18 (78.3) C: 8 (80)	IV	S	91.0 (10.58) B: 83.91 (17.28) C: 94.20 (11.9)	maceutical industry
Tucker et al, 2007 (47)	40 A: 20 C: 20	A: Topiramate 25 to 400 mg/d C: Placebo	A: Anticonvulsant/ mood stabilizer	8	Civilians (childhood sexual abuse)	A: 42 C: 41	A: 16 (79) C: 16 (79)	DSM-IV	CAPS	A: 88.3 (13.8) C: 91.1 (13.7)	Ortho-McNeil Neurologics Incorporated
Van der Kolk et al, 2007 (48)	59 A: 30 C: 29	A: Fluoxetine 10 to 60 mg/d C: Placebo	A: Antidepressant (Selective serotonin reuptake inhibitor)	8	Mixed (interpersonal victimization)	A: 34.1 C: 35.7	A: 26 (86.7) B: 25 (86.2)	DSM-IV	CAPS	A: 73.7 (13.4) B: 70.3 (13.0)	Grant from NIMH
Villarreal et al, 2016 (49)	80 A: 42 C: 38	A: Quetiapine 25 to 400 mg/d C:	A: Atypical or Second generation	12	Veterans (combat-related)	52	A: 4 (10) C: 1 (3)	DSM-IV	CAPS	A: 75.40 (16.00) C: 70.60 (11.70)	Investigator-initiated grant from

Source/ Period	Sample Size, No. per Group[a]	Interventions: Drug, Dose Range, mg/d	Drug class of interventions	Treatment Duration, weeks	Type of Trauma (predominant)	Age, Mean, y	Female Sex, No. (%)	Diagnosis of PTSD	Severity Measure of PTSD	Severity of PTSD at Baseline, Mean (SD)	Funding Sources
		Placebo	antipsychotic								pharmaceutical industry
Yeh et al, 2011 (50)	35 A: 17 C:18	A: Topiramate 25 to 200 mg/d C: Placebo	A: Anticonvulsant/ mood stabilizer	12	Civilians (urban violence)	A: 43.7 C: 36.5	A: 12 (70.58) C: 9 (64.28)	DSM-IV	CAPS	A: 79.64 (12.03) C: 64.33 (22.00)	Federal University of São Paulo
Zohar et al, 2002 (51)	42 A: 23 C: 19	A: Sertraline 50 to 200 mg/d C: Placebo	A: Antidepresssant (Selective serotonin reuptake inhibitor)	10	Veterans (combat-related)	A: 41 C: 38	A: 4 (17) C: 1 (5)	DSM-III-R	CAPS-2	A: 91.20 (13.30) C: 93.30 (11.70)	Pharmaceutical industry

[a]No.of patients randomly allocated to each treatment.
[b] A 12-Week, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Efficacy and Tolerability of Paroxetine in Patients Suffering from Post-traumatic Stress Disorder (PTSD). GlaxoSmithKline.
[c] Prazosin vs Paroxetine in Combat Stress-Related Post-Traumatic Stress Disorder (PTSD) Nightmares & Sleep Disturbance. ClinicalTrials.gov Identifier: NCT00202449.
[d] A Placebo-Controlled Study of Mirtazapine for PTSD. ClinicalTrials.gov Identifier: NCT00302107.
[e] Prazosin for Treatment of Patients With Alcohol Dependence (AD) and Post Traumatic Stress Disorder (PTSD). ClinicalTrials.gov Identifier: NCT00744055.
[f] Orvepitant (GW823296) in Adult Post Traumatic Stress Disorder. ClinicalTrials.gov Identifier: NCT01000493.
CAPS=Clinician-Administered PTSD Scale
[g]A placebo-controlled, double-blind, flexible dose study of sertraline in the treatment of post-traumatic stress disorder. Final study report: Protocol 96 CE21-0682 (unpublished data). Information provided by the pharmaceutical company.
[h]A 12 week, double-blind, placebo-controlled, parallel group study to assess the efficacy and tolerability of paroxetine in patients suffering from Posttraumatic Stress Disorder (PTSD). Unpublished. SmithKline Beecham
CAPS-2=one-week symptom status version of the Clinician-Administered PTSD Scale. CAPS-SX17=17-item Clinician-administered PTSD Scale, 1-week symptom status version.
CBT=Cognitive behavioural therapy.
CGI=The Clinical Global Impression – Severity scale (CGI-S) or Improvement scale (CGI-I).
CR=controlled-release.

DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders, 3th Edition, Text Revision.
DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.
DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision.
DTS=Davidson Trauma Scale.
ECT=Electroconvulsive therapy.
EMDR=Eye movement desensitization and reprocessing.
HAMD=Hamilton Depression Rating Scale.
M.I.N.I. =Mini-International Neuropsychiatric Interview .
MADRS=Montgomery–Åsberg Depression Rating Scale.
NIH= National Institutes of Health.
NR=not reported.
PTSD=Posttraumatic stress disorder.
SCID=Structured Clinical Interview for DSM-IV Axis I Disorders.
SIP =Structured Interview for PTSD.
SNRIs=Serotonin and norepinephrine reuptake inhibitors.
SR=Sustained release.
SSRIs= Selective serotonin reuptake inhibitors.
US=United States.
VA=Veterans Administration.

Table S2. Hierarchy of Competing Interventions of the Network Meta-analysis in Terms of Treatment Rankings for Efficacy and Acceptability

Efficacy			Acceptability		
Ranking	Treatment	Ranking Probabilites	Ranking	Treatment	Ranking Probabilites
1	Topiramate	0.6281	1	Phenelzine	0.9447
2	Risperidone	0.6197	2	Lamotrigine	0.8722
3	Olanzapine	0.6167	3	Vilazodone	0.8178
4	Quetiapine	0.6158	4	Quetiapine	0.8113
5	Paroxetine	0.6087	5	Tiagabine	0.6937
6	Desipramine	0.6027	6	Ziprasidone	0.6792
7	Venlafaxine	0.6001	7	Topiramate	0.6752
8	Mirtazapine	0.5946	8	Fluoxetine	0.6728
9	Fluoxetine	0.5822	9	Prazosin	0.6129
10	NK1R-A	0.5665	10	Imipramine	0.5783
11	Placebo	0.5494	11	Citalopram	0.5369
12	Ziprasidone	0.5449	12	Venlafaxine	0.5223
13	Sertraline	0.5238	13	Mirtazapine	0.4670
14	Guanfacine	0.5123	14	Paroxetine	0.4122
15	Nefazodone	0.5042	15	Risperidone	0.4081
16	Bupropione	0.4969	16	Placebo	0.4063
17	Brofaromine	0.4864	17	Sertraline	0.3743
18	Prazosin	0.4846	18	Brofaromine	0.3654
19	Vilazodone	0.4808	19	Nefazodone	0.3294
20	Tiagabine	0.4718	20	Divalproex	0.3113
21	Citalopram	0.44	21	NK1R-A	0.3048
22	Divalproex	0.3768	22	Amitriptyline	0.2168
23	Amitriptyline	0.3297	23	Olanzapine	0.1617
24	Lamotrigine	0.2841	24	Desipramine	0.1537
25	Phenelzine	0.2514	25	Guanfacine	0.1314
26	Imipramine	0.228			

The figure shows the probabilities estimated for each treatment in the network of achieving a particular placement in a ranking of treatment effects from best to worst.

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Efficacy, Acceptability, and Tolerability of Antidepressants for Sleep Disturbance in Post-Traumatic Stress Disorder: a Systematic Review and Network Meta-Analysis

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HIGHLIGHTS

- Although rarely measured in the primary trials of Post-traumatic Stress Disorder (PTSD) pharmacotherapy, sleep disturbance is frequently observed over the course of PTSD. However, considerable uncertainty remains regarding the balance of benefits and risks in the use of antidepressants for sleep disturbances in PTSD.
- To our knowledge, the present network meta-analysis is the most comprehensive synthesis of data on currently available antidepressants for sleep disturbance in adults with PTSD.
- Patients with PTSD do not seem to experience sufficient relief from sleep-related symptoms with antidepressants. According to the present network meta-analysis, mirtazapine, paroxetine, nefazodone, and bupropion were not more beneficial than placebo for improving overall sleep quality in PTSD.
- According to the NMA results, sertraline seems to alleviate many of the sleep complaints associated with PTSD. However, due to the low certainty of evidence according to the GRADE approach, these estimates are not robust enough to guide clinical decisions.

ABSTRACT

Sleep complaints are a common occurrence in post-traumatic stress disorder (PTSD) and may remain after evidence-based treatment for PTSD has been implemented. If left untreated, sleep disturbance can perpetuate or aggravate the disorder. A systematic review and network meta-analysis (NMA) of randomized controlled trials (RCTs) was conducted comparing efficacy, acceptability, and tolerability among antidepressants for sleep disturbance in adults with PTSD, using Cochane's RoB2.0 and GRADE approach for NMA. The Cochrane Library, LILACS, PsycINFO, PTSDpubs, and PubMed Central databases were searched from inception to November 29, 2020, leading to the retrieval of 3,733 reports. After the selection process, seven RCTs were included in the review (N=600). We found low certainty of evidence (LCE) that sertraline may improve sleep quality (measured by PSQI) in patients with PTSD (MD –0.48, 95% CrI –0.63 to –0.32). Sertraline was as well accepted (RR 1.12, 95% CrI –0.83 to 1.52, very low certainty [VLCE]) and as well tolerated as placebo (RR 0.58, 95% CrI 0.28 to 1.14, LCE). Mirtazapine (MD –3.35, 95% CrI –9.06 to 2.39, LCE), paroxetine (MD –3.13, 95% CrI –7.47 to 1.26, VLCE), nefazodone (MD –0.25, 95% CrI –5.95 to 5.38, VLCE), and bupropion (MD –2.28, 95% CrI –4.75 to 0.21, VLCE) were similar to placebo for improving sleep quality. These antidepressants resulted in little or no benefit for sleep disturbances in PTSD. Although the NMA suggested that sertraline may improve sleep in PTSD compared to placebo, due to the low certainty, these estimates are not robust enough to guide clinical decisions.

Keywords: Stress Disorders, Post-Traumatic; Network Meta-Analysis; Multiple Treatment Comparison Meta-Analysis; Sleep.

INTRODUCTION

Sleep disturbance is a primary complaint of a substantial number of patients suffering from post-traumatic stress disorder (PTSD), which is a chronic, debilitating psychiatric disorder. In a national sample of 2,647 American adults who met the DSM-5 criteria for PTSD (American Psychiatric Association, 2013), more than 92% reported at least one sleep disturbance (Milanak et al., 2019). Specifically, 70 to 92% of veterans and civilians with PTSD have difficulty initiating or maintaining sleep and 19 to 71% report having distressing dreams (Maher et al., 2006; Pruiksma et al., 2016).

In addition to restoring social and occupational functioning, optimal medication for PTSD should provide sustained relief from the associated sleep problems. Such problems include the core symptoms of difficulty initiating or maintaining sleep as well as restless sleep and nightmares, the latter two of which are associated with the re-experience of the traumatic event, while insomnia is an expression of the heightened arousal and reactivity associated with the disorder (American Psychiatric Association, 2013; Akinnusi et al., 2019; Davidson et al., 2001). Research has demonstrated more positive PTSD treatment outcomes among individuals for whom an improvement in sleep is achieved (Zalta et al., 2020) . However, managing sleep disturbances in PTSD is quite challenging, as such disturbances are prevalent, persistent, and distressing. Moreover, residual insomnia and distressing dreams often remain even after evidence-based treatment for PTSD is implemented. If left untreated, these symptoms can perpetuate or aggravate the disorder (Biggs et al., 2020).

Although a growing body of evidence shows that sleep quality is an important aspect to consider in clinical decision making with regards to interventions for individuals with PTSD, the underlying pathogenesis of sleep disturbance remains unclear. No distinct profile has been identified regarding objective sleep disturbances or specific sleep-related biomarkers associated with PTSD (Koffel et al., 2016). Moreover, there is no current evidence to guide decisions on the management of sleep complaints in individuals suffering from PTSD (American Psychological Association, 2017; National Institute for Health and Care Excellence, 2018; van Liempt et al., 2006; U.S. Department of Veterans Affairs, 2017). With the exception of prazosin, which reduces the occurrence of nightmares associated with the disorder, there is no specific

pharmacotherapy for sleep disturbances in PTSD (Zhang et al., 2020). The use of antidepressants is widespread in PTSD, but none is approved for sleep disorders and evidence of the effectiveness of these medications in this regard remains unclear. Health care providers should exercise caution and weigh the potential benefit against the potential harm when making judgements about commonly prescribed drugs, such as antidepressants.

To assist clinicians in daily practice and identify future research needs, we compared the efficacy, acceptability, and tolerability of antidepressants with regards to improving overall sleep quality by reducing sleep disturbances in adult patients with a diagnosis of PTSD. For such, a network meta-analysis (NMA) was performed and the GRADE approach was used for the interpretation of the results.

EXPERIMENTAL PROCEDURES

Protocol and registration

The protocol for the study was registered with PROSPERO (CRD42021234399). This paper was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA checklist) incorporating network meta-analysis (Hutton et al., 2015).

Eligibility criteria

The research question for the present systematic review was formulated using the PICOS characteristics, as follows:

- P (population) = Adults with a primary diagnosis of PTSD according to standardized diagnostic criteria, such as the Diagnostic and Statistical Manual (DSM) (American Psychiatric Association, 2013) or International Classification of Diseases (ICD) (World Health Organization, 1992);
- I (intervention) = Antidepressants of various pharmacological classes administered in the therapeutic dose range: selective serotonin reuptake inhibitors/SSRIs (e.g., fluoxetine, paroxetine, sertraline, citalopram, escitalopram); serotonin and norepinephrine reuptake inhibitors/SNRIs (e.g., venlafaxine, desvenlafaxine); tricyclic antidepressants/TCAs (e.g., amitriptyline, imipramine); monoamine oxidase inhibitors/MAOIs: (e.g., brofaromine, phenelzine); dopamine reuptake inhibitor (e.g., bupropion); serotonin partial agonist and reuptake inhibitor (e.g., vilazodone); other antidepressant drugs/second-generation antidepressants (e.g., mirtazapine, nefazodone, trazodone);
- C (comparison) = Placebo or another active antidepressant;
- O (outcomes) = Efficacy, acceptability, and tolerability;
- S (study design) = Only randomized controlled trials (RCTs).

No restrictions were imposed with regards to age, gender, PTSD duration or severity, duration or severity of sleep complaints, patient setting (inpatient or community), or type of trauma (combat versus noncombat). No restrictions were imposed on interventions with regards to drug preparation, administration route, timing of delivery, frequency, or dose (e.g., smaller doses [subtherapeutic for depression] may

be suitable for sleep complaints) (Everitt et al., 2018). We included trials in which the same supplementary intervention (e.g., additional behavioral or psychological co-intervention intended to improve sleep) was delivered to all study arms. This decision was made because it more closely resembles feasible treatment strategies used to improve sleep outcomes for patients in real-world practice. For instance, the most recent guidelines for the management of chronic insomnia recommend that all patients receive cognitive behavioral therapy for insomnia (CBT-I) as a primary intervention, adding pharmacological therapy for those in whom CBT-I alone was unsuccessful (Qaseem et al., 2016; Riemann et al., 2017; Sateia et al., 2017). Conversely, pharmacotherapy offers an alternative treatment modality for patients with PTSD who fail or decline CBT-I (Akinnusi et al., 2019).

Exclusion criteria: studies involving patients with obstructive sleep apnea syndrome, which is managed primarily as a respiratory disorder (McCleery and Sharpley, 2020), individuals with PTSD and a comorbid substance use disorder, and studies in which the intervention was a single dose.

Information sources and search strategies

The following electronic databases were systematically searched from database inception up to November 29, 2020: Cochrane Library, LILACS, PsycINFO, PTSDpubs, and PubMed Central. Grey literature was searched in clinical trials registers, such as Clinical Trials (U.S. National Library of Medicine) and clinical study reports (Clinical Study Data Request). We also hand searched the reference lists of the studies selected. Relevant individuals and organizations were contacted for information on incomplete, unpublished, or ongoing studies (e.g., pharmaceutical industry; sponsors; regulatory agency sources). The full search strategies for all databases, including the filters and limits used, are presented in the supplementary material (Appendix S2).

Study selection

Two independent reviewers (GMC and PMC) screened titles and abstracts to ensure that the eligibility criteria were applied consistently. Multiple reports of the same study were identified and associated with each other manually. Full texts of potentially eligible studies were screened by the same independent reviewers. All disagreements

were solved by discussion and consensus. When a disagreement persisted, a third reviewer was consulted (CFM). No automated tools were used during this process.

Data collection process

For each eligible trial, data extraction was conducted by one reviewer (GMC) and cross-checked by another two (FBZ and PKZ). Authors were contacted to provide further data when necessary. The data were extracted using a table built in a Word file. When reported, intention-to-treat data were also extracted.

Data items

To enable the syntheses and the risk-of-bias appraisal, we collected as many details as possible on the methods, participants, setting, context, interventions, outcomes, results, publications, and investigators of each report included in the review. The following data were sought (Higgins et al., 2020):

- Recruitment and sampling procedures; follow-up period; details on random sequence generation, allocation concealment, and blinding; source(s) of funding; statistical methods used, including methods used to prevent and address missing data;
- Setting; study eligibility criteria (e.g., diagnostic criteria; age, gender, type of trauma; comorbidities of participants at baseline);
- Drug components, dose administered, timing, and frequency of intervention(s) and comparison(s);
- Instrument(s) used to assess the efficacy outcome (name of scale, upper and lower limits, and whether a high or low score was more favorable); timing of outcome measurements of efficacy, acceptability (measured as discontinuation for any reason), and tolerability (withdrawal from medication due to adverse events); number of participants randomly assigned and included in the analysis for each outcome.

The primary outcome was efficacy at reducing sleep disturbances. Sleep problems included any well-defined disturbances in the sleep process, such as difficulty initiating or maintaining sleep, restless sleep, and nightmares. These disturbances were identified on the basis of subjective or objective measures using validated scales, such as the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) or Items 2 and/or 13 of the

Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995). The PSQI is a self-rated assessment of sleep quality and its components. The respondent is asked to report on his or her sleep habits and quality of sleep in the past month. The clinical features appraised are subjective sleep quality, sleep latency (i.e., how long it takes to fall asleep), sleep duration, habitual sleep efficiency (i.e., the percentage of time in bed that one is asleep), sleep disturbances, use of sleeping medication, and daytime dysfunction. Seven component scores are derived, each ranging from 0 (no difficulty) to 3 (severe difficulty). The component scores are summed to produce a global score ranging from 0 to 21, with lower scores denoting better sleep quality (Buysse et al., 1989). A meta-analysis concluded that the PSQI is a reliable, valid screening tool for sleep dysfunction in both clinical and non-clinical samples (Mollayeva et al., 2016). Item B-2 "recurrent distressing dreams of the event" is a single item from the CAPS instrument. The rating consists of two parts (frequency and intensity, both scored 0 to 4). The total score is derived from the frequency plus intensity ratings and ranges from 0 to 8, with higher scores denoting a worse state. Item 13 of the CAPS instrument measures sleep disturbance (e.g., difficulty initiating or maintaining sleep, restless sleep) (Blake et al., 1995).

Regarding the primary outcome, we extracted the mean change (and standard deviation) in symptoms from baseline to endpoint. When not reported, the differences were calculated by subtracting the final mean from the baseline mean and the standard deviation of the changes was calculated using the formula SD delta= $\sqrt{}$ [$(SD1)^2$ + $(SD2)^2$ – (2*r*SD1*SD2)], in which SD is the standard deviation of the mean baseline value and SD2 is the standard deviation of the mean endpoint value. To be conservative, a correlation r equal to 0 was assumed (Higgins et al., 2020). Data on the acceptability outcome included the number of participants who withdrew from treatment for any reason and the total number of patients randomly assigned to that treatment group. The number of subjects who left the study early due to adverse events and the total number randomly assigned to each treatment group were extracted to measure tolerability. We also investigated whether adverse events were collected systematically (in the same manner for each participant using defined methods, such as a questionnaire or laboratory test) or non-systematically (e.g., voluntary report).

We performed all analyses using intention-to-treat data, when available. Whenever possible, e-mail contact with the original investigators was made to request missing data.

Risk of bias within individual studies

Two independent reviewers (GMC and PMC) assessed the risk of bias using Version 2 of the Cochrane Risk-of-Bias Tool for randomized trials (RoB 2.0) (Sterne et al., 2019). Each study was rated as "low risk of bias", "some concerns", or "high risk of bias" across the following domains: bias arising from the randomization process; bias due to deviations from the intended intervention; bias from missing outcome data; bias in measurement of outcomes, and bias in selection of the reported results, including deviations from the registered protocol. We rated trials as having an overall high risk of bias if one or more domains were rated "high risk of bias" and as having an overall low risk of bias if all domains were rated "low risk of bias".

Summary measures

To compare interventions, results were pooled using mean differences (MD) for efficacy, as this outcome was measured using the same scale (PSQI) (Buysse et al., 1989) in all studies. Acceptability and tolerability were compared using relative risk (RR) (Higgins et al., 2020).

Planned methods of analysis

One multi-arm trial fulfilled the eligibility criteria and was included in the systematic review. However, this three-arm trial (NCT00202449) was analyzed as a two-arm trial because one of the groups was not an eligible intervention (prazosin). Traditional pairwise meta-analyses with random-effects models were performed using the DerSimonian and Laird estimator for between-study variability (DerSimonian and Laird, 1986). Statistical heterogeneity was assessed in each pairwise comparison using the I^2 statistic and Cochran test. Forest plots were created for all direct comparisons and the results were presented as mean and 95% confidence intervals (CI).

To compare all treatments in a single model, network meta-analyses using a Bayesian framework were performed for each outcome. Treatments were grouped into common nodes based on each drug independently of class or protocol used (e.g., dose, duration). We used node splitting models to assess local incoherence and obtain indirect estimates. Both fixed- and random-effects models with homogeneity of variances were adjusted using minimally informative priors for all parameters. All models included four Markov chains with 24,000 interactions after an initial burn-in of 4000 and a

thinning of 10. The deviance information criterion (DIC) was used to choose the best fit. The assessment of inconsistency (incoherence) was not required due to the star shape of the networks. Results were presented in league tables as MD = (efficacy) or RR (acceptability and tolerability) with respective 95% credible intervals (CrI). The ranking probabilities estimated for each treatment in the network of achieving a particular placement in an ordering of treatment effects from best to worst were reported as surface under the cumulative ranking curve (SUCRA) (Hutton et al., 2015). All analyses were performed using the R statistical software, version 4.0.4 (*meta*, *gemtc*, and *rjags* packages) (Schwarzer, 2015).

We planned on conducting sensitivity analyses to assess whether study quality would affect the results by excluding RCTs with a high risk of bias and excluding studies with fewer than 10 subjects per arm. For trials in which an additional behavioral or psychological co-intervention was delivered to both arms, we planned to investigate whether the intervention effect was modified by the addition of the supplementary intervention through subgroup analysis.

Certainty of evidence

The certainty of evidence was assessed for each comparison using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for NMA (Bonner et al., 2018; Brignardello-Petersen et al., 2018; Puhan et al., 2014). As only randomized controlled trials (RCTs) were eligible, NMA treatment effects were initially assigned a high confidence rating. Risk of bias, inconsistency, indirectness, and publication bias would downgrade the rating one or two levels for each pairwise comparison. We then identified the two closest direct comparisons that contributed to each indirect comparison and the one with the lowest certainty was adopted. The final step integrated all the intermediate judgements to assign a confidence rating to each NMA treatment effect. As no pair of comparisons had both direct and indirect evidence, we found no reason to downgrade for incoherence (Veroniki et al., 2013). Finally, we could downgrade one or two levels due to imprecision for the NMA estimate.

RESULTS

Article selection and study characteristics

The search conducted on November 29, 2020 led to the retrieval of 3733 records (3697 identified through database searching and 36 additional records identified through other sources), as shown in the article selection flowchart (Figure 1). Seven RCTs (N = 600) were eligible for inclusion in the systematic review. The characteristics of the trials included are shown in Figure S1 of the supplementary material. RCTs addressing the effect of antidepressants in individuals with PTSD that met many but not all inclusion criteria ('near-misses') (Page et al., 2021) are presented in References S2 of the supplementary material.

Presentation of network structure and summary of network geometry

The graphical representations of the networks for all available comparisons are displayed in Figure 2. All geometries had incomplete connections (loose ends rather than closed loops) because most treatments were not compared directly to each other.

Risk of bias

Four studies had a high risk of bias according to the RoB 2.0 appraisal, whereas three had a low risk (Sterne et al., 2019; McGuinness and Higgins, 2021). The risk of bias domains for all eligible trials and the graph of the overall risk of bias are shown in Supplementary Figure S5.

Publication bias

The small number of studies included in the present review impeded the assessment of the likelihood of publication bias through funnel plots. Moreover, Egger's test was not used to determine whether the risk of publication bias was significant because less than ten studies were included in the quantitative meta-analysis. Therefore, the certainty of evidence for all comparisons of the network was downgraded due to serious concern regarding publication bias when pharmaceutical company funding was associated with a positive outcome favoring the sponsored treatment and/or selective publication of the trial was based on the direction and magnitude of its results.

Synthesis of results

One trial (Ramaswamy et al., 2017) was excluded from the quantitative meta-analyses because it was the only one not to use the PSQI to evaluate efficacy. The outcome measure reported in this trial was a change in mean sleep scores on CAPS Items 2 and 13 rather than overall sleep quality measured using the PSQI. However, according to Ramaswamy et al. (2017), the analysis of the core PTSD sleep symptoms (CAPS Items 2 and 13) revealed no significant difference in sleep measures between groups from baseline to the endpoint of the trial ($P > 0.1$). Regarding efficacy, the pairwise meta-analyses showed that bupropion (MD = -2.28, 95% CI: -4.77 to 0.21), sertraline (MD = -0.03, 95% CI: -1.18 to 1.12), paroxetine (MD = -3.11, 95% CI: -7.49 to 1.27), and mirtazapine (MD = -3.40, 95% CI: -9.14 to 2.34) resulted in no improvement in overall sleep quality in individuals with PTSD compared to placebo (Figure S1 of supplementary material). Significant evidence of heterogeneity was found among trials with sertraline versus placebo ($I^2 = 77\%$, $P = 0.04$) regarding treatment efficacy. The results of the network meta-analyses for the efficacy and acceptability outcomes are presented as a league table in Figure 3. Regarding efficacy in reducing sleep disturbances during the course of PTSD in adult patients, only sertraline outperformed placebo (MD = -0.48, 95% CrI: -0.63 to -0.32), with a low certainty of evidence according to the GRADE framework (Appendix S3). We found low-certainty evidence that mirtazapine is no better than placebo (MD = -3.35, 95% CrI: -9.06 to 2.39) for an overall improvement in sleep quality in individuals with PTSD. Paroxetine (MD = -3.13, 95% CrI: -7.47 to 1.26), nefazodone (MD = -0.25, 95% CrI: -5.95 to 5.38), and bupropion (MD = -2.28, 95% CrI: -4.75 to 0.21) were also similar to placebo regarding efficacy (Appendix S3). We considered the evidence supporting these comparisons of efficacy to be of very low certainty, downgraded due to risk of bias (Figure S5), publication bias, and/or imprecision (small studies, wide 95% CrI, and CrI including zero, reflecting uncertainty with regards to the direction of the effect).

The direct pairwise comparisons of acceptability are displayed in Supplementary Figure S2. The trial by Becker et al. (2007) did not report data for all-cause discontinuation and was therefore excluded from these analyses. According to the results of the pairwise meta-analysis, acceptability was similar between placebo and the antidepressants sertraline (RR = 1.25, 95% CI: 0.67 to 2.35), paroxetine (RR = 0.96, 95% CI: 0.56 to 1.66), and mirtazapine (RR = 0.89, 95% CI: 0.59 to 1.34). Nefazodone

had similar acceptability compared to sertraline (RR = 0.88, 95% CI: 0.32 to 2.38). As shown in the upper triangle of the league table (Figure 3), all treatments had similar acceptability according to the NMA estimates. We found low certainty of evidence that mirtazapine is no better than placebo regarding acceptability. We also found low certainty that mirtazapine is similar to sertraline in measures of all-cause dropouts. We found very low certainty of evidence for all other network comparisons of acceptability (Appendix S3).

The unpublished trial NCT00202449 was excluded from the analyses of tolerability because the number of dropouts due to adverse events reported in both arms was zero. The results of the pairwise meta-analysis revealed no difference between placebo and the following antidepressants: bupropion (RR = 1.54, 95% CI: 0.07 to 34.55), sertraline (RR = 2.04, 95% CI: 0.98 to 4.23), vilazodone (RR = 3.10, 95% CI: 0.13 to 73.13), and mirtazapine (RR = 0.74, 95% CI: 0.25 to 2.21). Tolerability was also similar in the comparison of sertraline and nefazodone (RR = 1.06, 95% CI: 0.17 to 6.72). The forest plot is shown in Supplementary Figure S3. Figure 4 shows the league table with NMA estimates for tolerability. All treatments had similar tolerability according to the network meta-analysis, with very low certainty of evidence (Appendix S3), except the comparisons sertraline versus placebo, mirtazapine versus placebo, and mirtazapine versus sertraline, for which low certainty of evidence was found.

The ranking of treatments based on cumulative probability plots and SUCRAs is presented in the supplementary material (Figure S4).

We were unable to conduct the planned sensitivity analyses to assess whether study quality would affect the results (e.g., exclusion of RCTs at high risk of bias; exclusion of studies with fewer than 10 subjects per arm) because there were not enough studies in the systematic review and the number of subjects within each trial was too small to perform these subgroup analyses.

DISCUSSION

The present network meta-analysis is the most comprehensive synthesis of data on currently available antidepressants for sleep disturbance in adults with PTSD. Based on the results, patients with PTSD do not seem to experience sufficient relief from sleep-related symptoms with antidepressants. However, there are significant gaps in the evidence needed to guide clinical decisions, as we considered the evidence supporting the results to be of low and very low certainty (Puhan et al., 2014; Salanti et al., 2014).

PTSD is a maladaptive response following exposure to actual or threatened death, serious injury, or sexual violence. This disorder is characterized by intrusion symptoms associated with the traumatic event initiating or persisting one month after the event occurred (including recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event); persistent avoidance of stimuli associated with the traumatic event; negative changes in cognition and mood associated with the traumatic event, beginning or worsening after the event occurred; and marked changes in arousal and reactivity associated with the traumatic event (including sleep disturbance, such as difficulty initiating or maintaining sleep and restless sleep) (American Psychiatric Association, 2013). As mentioned, two types of sleep dysfunction are considered symptoms of PTSD. Moreover, sleep complaints are a prevalent, highly distressing feature of PTSD (Milanak et al., 2019; Maher et al., 2006; Pruiksma et al., 2016).

There is currently no commonly accepted profile of objective sleep disturbances specific to PTSD (Koffel et al., 2016). Studies have not been consistent about the type of REM sleep dysfunction or its role in the disorder. A meta-analysis of polysomnographic studies found that sleep continuity and sleep architecture are altered in PTSD. However, additional research involving polysomnography is needed to determine the potential clinical implications (Zhang et al., 2019). The variability in clinical presentations may reflect a multifaceted neurobiological mechanism that contributes to the difficulties in defining a targeted sleep treatment for individuals with PTSD (Koffel et al., 2016). Given the clinical heterogeneity of the disorder, a pharmacological agent can exhibit different efficacy for distinct symptom clusters (Freeman et al., 2020; McRae et al., 2004).

Thus, there is a need to explore the effectiveness of commonly used pharmacotherapies for PTSD at improving the quality of sleep of individuals affected by the disorder. It has been estimated that antidepressants (Everitt et al., 2018) and benzodiazepines are the most widely used medications for the symptomatic treatment of associated sleep complaints in PTSD (Davidson et al., 2001). However, GABAergic hypnotics have several side effects that caution against their use, such as rebound insomnia, cognitive deficits, physical and psychological dependence, as well as risk of interference with the normal hypothalamic–pituitary–adrenal stress response (Matar et al., 2009). Indeed, a previous meta-analysis concluded that health providers should use considerable caution when maintaining benzodiazepine prescriptions and it would be safer to avoid initiating the use of these drugs altogether in individuals with PTSD (Guina et al., 2015). Thus, antidepressants with sleep-promoting properties (e.g., trazodone, mirtazapine) or serotoninergic antidepressants have been used to manage sleep problems in patients with PTSD either as sole drugs or adjunctive medications. However, some are considered to carry risks, such as the aggravation of insomnia and/or worsening of sleep quality (Freeman et al., 2020). It has been proposed that antidepressants (e.g., nefazodone and trazodone) could be beneficial as a modality of treatment in individuals with PTSD with predominant sleep disturbances (Singareddy and Balon, 2002). However, RCTs addressing pharmacotherapy for PTSD have generally found little benefit for sleep complaints such as insomnia (Schneier et al., 2015) and meta-analyses on pharmacotherapy for PTSD-related sleep disturbance are lacking (van Liempt et al., 2006).

According to the present network meta-analysis, mirtazapine, paroxetine, nefazodone, and bupropion were not more beneficial than placebo for improving overall sleep quality in PTSD. Although nefazodone was the least effective according to the SUCRA ranking, these rankings do not have the magnitude to assist in decision making in clinical practice. Conversely, nefazodone could be associated with the exacerbation or maintenance of sleep complaints.

Sertraline has been approved by the US Food and Drug Administration for the treatment of PTSD and current evidence suggests that it improves overall PTSD symptoms (de Moraes Costa et al., 2020). According to the NMA results, sertraline seems to alleviate many of the sleep complaints associated with PTSD. The multiple treatment comparison revealed an improvement in sleep quality with sertraline versus placebo regarding measured symptoms of sleep. Furthermore, sertraline was generally

well tolerated and there was no significant difference between sertraline and placebo in terms of acceptability or tolerability. Sertraline is an SSRI that presumably increases serotonergic neurotransmission by blocking serotonin reuptake, resulting in the desensitization of serotonin receptors, particularly serotonin 1A receptors. Sertraline also has some ability to block dopamine reuptake, which could result in an increase in dopamine neurotransmission, and has moderate affinity with sigma 1 receptors, contributing to its therapeutic action (Stahl, 2013). As some sleep improvements found in individuals with PTSD who received sertraline are based on subjective measures of sleep (Buysse et al., 1989), there is no particular mechanism of action that we could outline as pharmacologically responsible for the effect of sertraline on sleep in this population. Despite improvements in sleep quality in patients with a diagnosis of PTSD, the beneficial effects of sertraline on sleep outcomes are derived from a network with a small body of trials, mostly compared to placebo, and predominantly of low quality according to the GRADE framework. Therefore, considerable uncertainty remains regarding the balance of benefits and risks in the use of sertraline for sleep disturbances in PTSD. More robust RCTs investigating the effects of sertraline are needed to enable more definitive conclusions with regards to its applicability in clinical practice.

Mirtazapine is a tetracyclic antidepressant that acts via antagonism at presynaptic α-2-adrenoreceptors and blocks postsynaptic serotonin 5-HT2 and 5-HT3 receptors as well as histamine H1 receptors (Stahl, 2013). These pharmacological effects suggest that it might be useful for improving sleep complaints in individuals with PTSD. However, this was not confirmed by the NMA. Therefore, the augmentation of antidepressant therapy with mirtazapine as a second antidepressant (e.g., combined mirtazapine plus sertraline or another SSRI) did not produce a clinically important benefit in improving overall sleep quality. Nevertheless, the evidence regarding the effects of augmenting antidepressant therapy with mirtazapine is currently insufficient, underscoring the need for well-designed RCTs with thorough eligibility criteria.

All-cause discontinuation has been used as a measure of effectiveness due to its relation to efficacy and tolerability. Noteworthy, there was no significant difference in the acceptability of the antidepressants used to alleviate sleep problems in individuals with PTSD. Moreover, discontinuations due to adverse events were not significantly greater for mirtazapine, sertraline, nefazodone, or bupropion compared to placebo. However, most trials recorded spontaneously reported adverse events rather than using a

reliable scale applied systematically (Davidson et al., 2001; Ramaswamy et al., 2017; McRae et al., 2004; Friedman et al., 2007). Therefore, most antidepressants are apparently well-tolerated, but passive collection, less frequent assessments, and shorter follow-up times may result in fewer recorded adverse events (Phillips et al., 2019).

For most antidepressants, factors related to drug administration do not seem to contribute to the lack of effectiveness in alleviating sleep complaints. Interestingly, when medication schedule, dose, and timing of delivery are set by the study protocol in a way that is closer to everyday practice, it is possible that treatment retention is improved with the reduction in sleep complaints due to adverse events. For example, in the trial conducted by Schneier et al. (2015), the medication dosage could be modified as clinically indicated (e.g., due to a complaint of an adverse event). In the same manner, the timing of vilazodone delivery (initially administered in the morning) could be switched to either the morning or evening, depending on the individual's reports of side effects (Ramaswamy et al., 2017). In the trial by Ramaswamy et al. (2017), differently from all other RCTs included in this systematic review, the inclusion criteria were diagnoses of PTSD and comorbid depression (at least mild). This comorbidity with depression could have contributed to the lack of efficacy of vilazodone (Dold et al., 2017).

Trials including only subjects exposed to combat-related trauma may not present consistent usefulness regarding antidepressant pharmacotherapy in the treatment of PTSD in civilians. However, only two trials (Ramaswamy et al., 2017; NCT00202449) were conducted exclusively with military personnel (in which the number of men exceeded the number of women), while most of the studies included in this systematic review were conducted with mixed (civilian and military) populations, enhancing the generalizability of our NMA results.

Limitations

The present NMA highlights the paucity of evidence on the use of antidepressants in alleviating sleep complaints during the course of PTSD. There were too few eligible RCTs (mostly comparing antidepressants to placebo), which is a major limitation regarding the reliability of the findings. The clinical interpretation of the network results is limited not only by the small number of trials in each node, but also because the poorly connected networks depend extensively on indirect comparisons, resulting in uncertainty around the estimates.

There were no RCTs involving several commonly prescribed drugs (e.g., trazodone and amitriptyline). Moreover, uncertainty remains regarding the balance between benefits and risks for these widely used "off-label" treatments in PTSD.

Although performing a comprehensive literature search, except for one trial (Schneier et al., 2015), we only identified data for the short-term use of antidepressants. While the antidepressants were generally well tolerated, there may have been limited reporting of adverse events. Considering that such drugs are often taken for long periods (a year or more), we acknowledge the limited evidence for their long-term use, as side effects play an important role in the decision to adopt an intervention or seek alternative management strategies. Moreover, several potentially confounding factors should be considered when sorting out the effectiveness of treatments for sleeping difficulties in PTSD, such as illness duration, failure to respond to previous treatment approaches, and clinical comorbidities not addressed in the trial protocols. Future studies should investigate the role of these variables as mediators of treatment outcomes. Additionally, future trials comparing polysomnographic features among subjects allocated to different drugs could assist in determining whether differences in sleep architecture emerge during the course of treatment (Freeman et al., 2020).

CONCLUSIONS

Sleep quality is a meaningful aspect of quality of life that is rarely measured in primary trials of pharmacotherapy for PTSD. Given this gap in primary research, we encourage researchers to address this critical outcome in future studies.

We found that mirtazapine, paroxetine, nefazodone, and bupropion were not more beneficial than placebo for improving overall sleep quality in PTSD. Importantly, there was no significant difference in acceptability or tolerability among these antidepressants. Although the NMA suggests that sertraline may have advantages in the symptomatic improvement of sleep in PTSD compared to placebo, due to the low certainty of evidence, these estimates are not robust enough to guide clinical decisions regarding antidepressant treatment for sleep problems in PTSD. Further robust RCTs with a broader range of subjects and an investigation of long-term effectiveness are needed to increase the certainty of these findings and draw clear conclusions on how antidepressants can be used to maximize sleep outcomes in PTSD.

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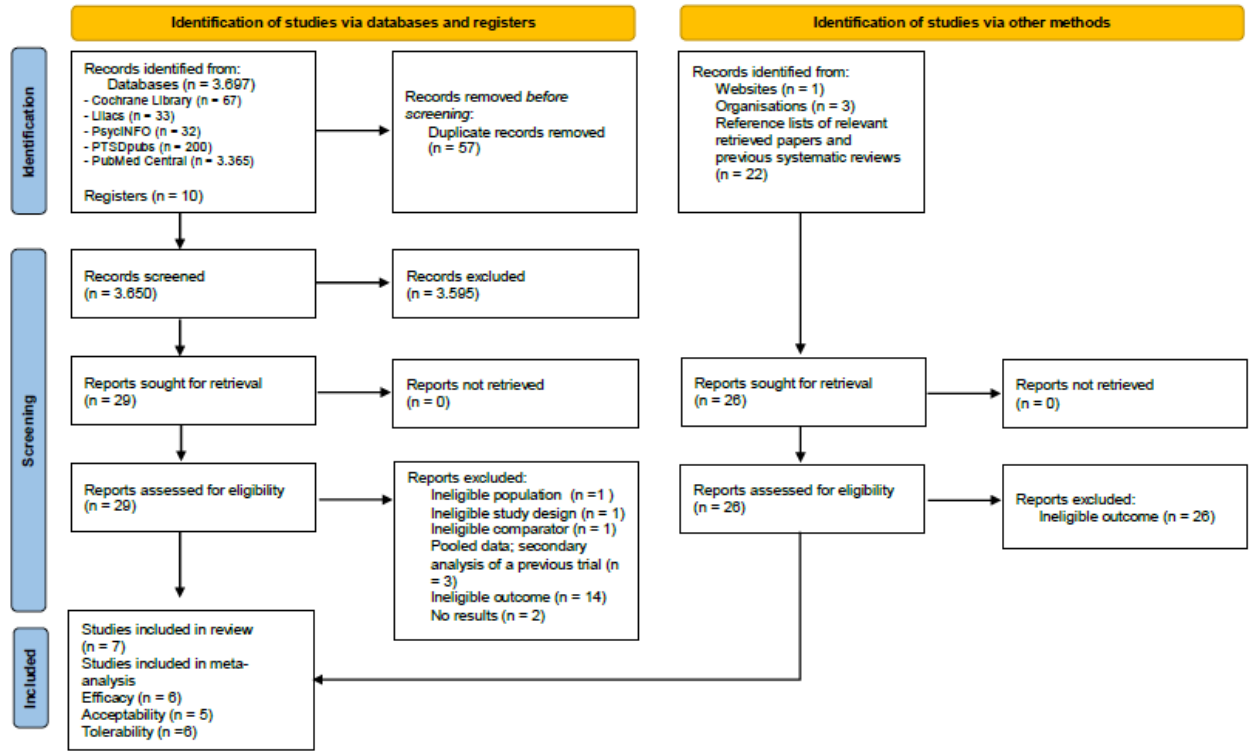
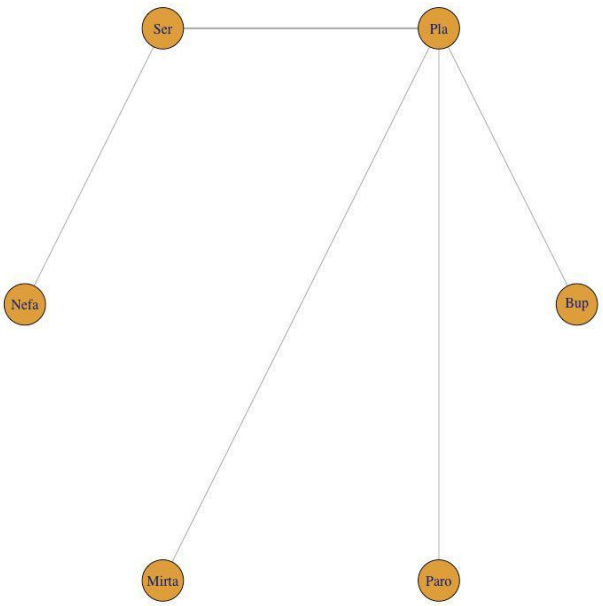
Figure 1. PRISMA 2020 flow diagram for new systematic reviews wich included searches of databases, registers and other sources



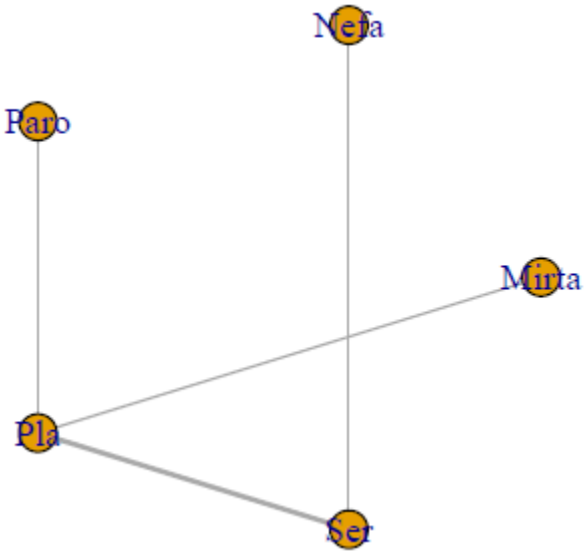
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 2. Networks of Eligible Comparisons for Efficacy, Acceptability and Tolerability

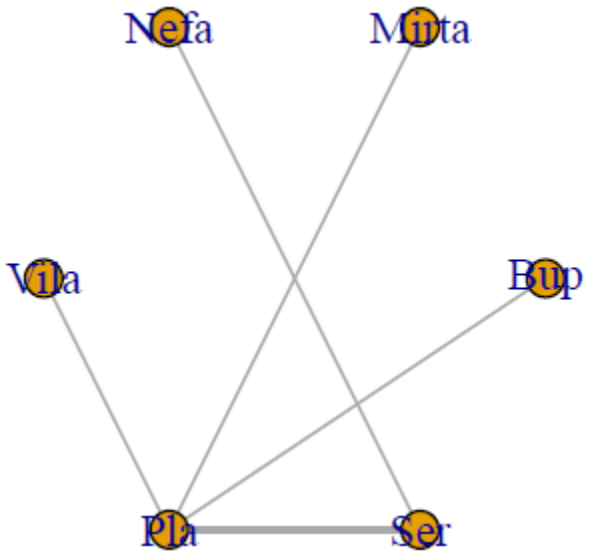
a) Efficacy



b) Acceptability



c) Tolerability



The width of the lines is proportional to the number of trials comparing every pair of treatments. Bup=bupropion. Mirta=mirtazapine. Nefa=nefazodone. Paro=paroxetine. Pla= placebo. Ser=sertraline. Vila=vilazodone.

Figure 3: League Table Showing Network Meta-analysis Results for Efficacy and Acceptability

Paro	1.10 (0.55, 2.25)		0.89 (0.47, 1.69)	0.89 (0.27, 2.94)	1.00 (0.57, 1.76)
0.29 (-6.9, 7.38)	**Mirta**		0.81 (0.47, 1.36)	0.81 (0.26, 2.53)	0.91 (0.58, 1.39)
-0.83 (-5.88, 4.18)	-1.07 (-7.29, 5.17)	**Bup**			
-2.65 (-7.00, 1.75)	-2.88 (-8.58, 2.85)	-1.80 (-4.28, 0.69)	**Ser**	1.00 (0.37, 2.75)	1.12 (0.83, 1.52)
-2.87 (-10.05, 4.31)	-3.09 (-11.12, 4.97)	-2.04 (-8.18, 4.17)	-0.27 (-5.85, 5.47)	**Nefa**	1.12 (0.39, 3.18)
-3.13 (-7.47, 1.26)	-3.35 (-9.06, 2.39)	-2.28 (-4.75, 0.21)	**-0.48 (-0.63, -0.32)**	-0.25 (-5.95, 5.38)	**Pla**

Drugs are reported in order of efficacy ranking according to SUCRAs. Data should be read from left to right: RR (95% CrI) for acceptability (upper triangle) and MD (95% CrI) for efficacy (lower triangle, blue). For efficacy (overall change in sleep quality) a MD below 0 favours the column-defining treatment. For acceptability (all-cause discontinuation) a RR below 1 favours the row-defining treatment.

Figure 4: League Table Showing Network Meta-analysis Results for Tolerability

Mirta					
0.87 (0.28, 2.50)	**Pla**				
0.23 (0.01, 2.58)	0.27 (0.01, 2.3)	**Vila**			
0.5 (0.13, 1.76)	0.58 (0.28, 1.14)	2.16 (0.22, 59.89)	**Ser**		
0.33 (0.01, 3.16)	0.4 (0.02, 2.75)	1.44 (0.03, 62.86)	0.68 (0.02, 5.49)	**Bup**	
0.31 (0.03, 2.78)	0.36 (0.04, 2.45)	1.39 (0.06, 56.62)	0.63 (0.08, 3.75)	0.96 (0.05, 38.18)	**Nefa**

Drugs are reported in order of tolerability ranking according to SUCRAs. Data should be read from left to right. For tolerability a RR (95% CrI) below 1 favours the column-defining treatment. Significant results are shown in bold. CrI=credible interval. RR= relative risk. SUCRA=surface under the cumulative ranking curve. Bup=bupropion. Mirta=mirtazapine. Nefa=nefazodone. Pla= placebo. Ser=sertraline. Vila= vilazodone.

ROLE OF THE FUNDING SOURCE

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CONTRIBUTORS

GMC, FBZ and CFM conceived the idea and designed the study; GMC and FBZ wrote the protocol. GMC and PMC searched the literature; GMC and PMC selected studies; GMC, FBZ and PKZ extracted data. PKZ performed the statistical analysis. GMC and PMC undertook the risk of bias analysis. GMC and CCM assessed the certainty of evidence. GMC, FBZ, and PKZ wrote the first draft of the manuscript. All authors have made significant contributions to the study, have read, and approved the final version of the manuscript.

CONFLICT OF INTEREST

GMC reports honoraria for lectures from Pfizer. All other authors declare no potential conflict of interest.

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SUPPLEMENTARY DATA

Appendix S1. PRISMA Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-Analysis (NMA)

Appendix S2. Search Strategy in the Cochrane Library, LILACS (Literatura Latino-americana e do Caribe em Ciências da Saúde), MEDLINE/PubMed (via National Library of Medicine), PsycInfo, and PTSDpubs Database – ProQuest (formerly called PILOTS).

Appendix S3. The certainty of evidence produced by the synthesis for each outcome, assessed through GRADE approach for network meta-analysis (NMA)

Table S1. Characteristics of the Randomized Controlled Trials Included in the Systematic Review

Figure S1. Pairwise Meta-analysis Results: Efficacy

Figure S2. Pairwise Meta-analysis Results: Acceptability

Figure S3. Pairwise Meta-analysis Results: Tolerability

Figure S4. The ranking of treatments based on cumulative probability plots and SUCRAs

Figure S5. Risk of bias assessments (RoB 2.0 risk of bias domains for all eligible trials and overall risk of bias graph)

References S1. List of Randomized Controlled Trials Included in the Systematic Review

References S2. List of Randomized Controlled Trials of Antidepressants in PTSD Patients that Met Many but Not All Inclusion Criteria (‘Near-misses’)

Appendix S1. PRISMA Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-Analysis (NMA)

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
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.	3
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.*	4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
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.	6
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).*	6
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.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, Appendix S2

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).	7, 8
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.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8, 9
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.	
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.	10
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.*	9, 10
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.*	10
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.	11
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).	12
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).*	
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at	12, Figure 1

		each stage, 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.	Figure 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.	12
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.	Table S1; References S1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	12, Figure 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 networks.*	Table S1
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.	12, 13, 14, Figure S1, Figure S2, Figure 3, Appendix S3, Figure S5, Figure S4
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.	11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	
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).	
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).	15, 16, 17, 18
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).*	18, 19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20

FUNDING			
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.	21

Appendix S2. Search Strategy in the Cochrane Library, LILACS (Literatura Latino-americana e do Caribe em Ciências da Saúde), MEDLINE/PubMed (via National Library of Medicine), PsycInfo, and PTSDpubs Database (ProQuest) - formerly called PILOTS.

Cochrane Library:

#1 MeSH descriptor: [Stress Disorders, Post-Traumatic] explode all trees MeSH 2609

#2 MeSH descriptor: [Combat Disorders] explode all trees MeSH 129

#3 PTSD Limits 4477

#4 MeSH descriptor: [Drug Therapy] explode all trees MeSH 140471

#5 MeSH descriptor: [Antidepressive Agents] explode all trees MeSH 5760

#6 MeSH descriptor: [Antidepressive Agents, Tricyclic] explode all trees MeSH 970

#7 MeSH descriptor: [Antidepressive Agents, Second-Generation] explode all trees MeSH 1335

#8 MeSH descriptor: [Serotonin Uptake Inhibitors] explode all trees MeSH 2744

#9 MeSH descriptor: [Serotonin and Noradrenaline Reuptake Inhibitors] this term only MeSH 55

#10 MeSH descriptor: [Monoamine Oxidase Inhibitors] this term only MeSH 385

#11 MeSH descriptor: [Neurotransmitter Uptake Inhibitors] explode all trees MeSH 3451

#12 amitriptyline OR brofaromine OR bupropion OR citalopram OR desipramine OR duloxetine OR desvenlafaxine OR escitalopram OR fluoxetine OR fluvoxamine OR imipramine OR mirtazapine OR nefazodone OR paroxetine OR phenelzine OR reboxetine OR sertraline OR venlafaxine OR vilazodone Limits 19745

#13 #1 OR #2 OR #3 Limits 5054

#14 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 Limits 160769

#15 #13 AND #14 Limits 459

#16 MeSH descriptor: [Sleep] explode all trees MeSH 5669

#17 MeSH descriptor: [Sleep Initiation and Maintenance Disorders] explode all trees MeSH 2449

#18MeSH descriptor: [Sleep Wake Disorders] explode all trees MeSH 8155

#19 insomnia Limits 11365

#20 nightmare Limits 463

#21 Pittsburgh sleep quality index Limits 2771

#22 #16 OR #17 OR #18 OR #19 OR #20 OR #21 Limits 22328

#23 #15 AND #22 Limits 67

LILACS (Literatura Latino-americana e do Caribe em Ciências da Saúde):

Stress Disorders, Post-Traumatic [DeCS Category] or ptsd [Words] and Antidepressive Agents [DeCS Category] or Antidepressants [Words] or amitriptyline OR brofaromine OR bupropion OR citalopram OR desipramine OR duloxetine OR desvenlafaxine OR escitalopram OR fluoxetine OR fluvoxamine OR imipramine OR mirtazapine OR nefazodone OR paroxetine OR phenelzine OR reboxetine OR sertraline OR venlafaxine OR vilazodone [Words] and Sleep Initiation and Maintenance Disorders [DeCS Category] or Sleep Wake Disorders [DeCS Category] or sleep [Words]

MEDLINE/PubMed (via National Library of Medicine):

((("stress disorders, post-traumatic"[MeSH Terms] OR "combat disorders"[MeSH Terms]) OR ("stress disorders, post-traumatic"[MeSH Terms] OR ("stress"[All Fields] AND "disorders"[All Fields] AND "post-traumatic"[All Fields]) OR "post-traumatic stress disorders"[All Fields] OR "ptsd"[All Fields])) AND (((((((("drug therapy"[MeSH Terms] OR ("drug therapy"[Subheading] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "pharmacotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "pharmacotherapy"[All Fields])) OR "antidepressive agents"[MeSH Terms]) OR ("antidepressive agents"[All Fields] OR "antidepressive agents"[MeSH Terms] OR ("antidepressive"[All Fields] AND "agents"[All Fields]) OR "antidepressive agents"[All Fields] OR "antidepressants"[All Fields])) OR "antidepressive agents, tricyclic"[MeSH Terms]) OR "antidepressive agents, second-generation"[MeSH Terms]) OR "serotonin uptake inhibitors"[MeSH Terms]) OR "neurotransmitter uptake inhibitors"[MeSH Terms]) OR "monoamine oxidase inhibitors"[MeSH Terms]) OR (("amitriptyline"[MeSH Terms] OR "amitriptyline"[All Fields]) OR ("brofaromine"[Supplementary Concept] OR "brofaromine"[All Fields]) OR ("bupropion"[MeSH Terms] OR "bupropion"[All Fields]) OR ("citalopram"[MeSH Terms] OR "citalopram"[All Fields]) OR ("desipramine"[MeSH Terms] OR "desipramine"[All Fields]) OR ("duloxetine hydrochloride"[MeSH Terms] OR

("duloxetine"[All Fields] AND "hydrochloride"[All Fields]) OR "duloxetine hydrochloride"[All Fields] OR "duloxetine"[All Fields]) OR ("desvenlafaxine succinate"[MeSH Terms] OR ("desvenlafaxine"[All Fields] AND "succinate"[All Fields]) OR "desvenlafaxine succinate"[All Fields] OR "desvenlafaxine"[All Fields]) OR ("citalopram"[MeSH Terms] OR "citalopram"[All Fields] OR "escitalopram"[All Fields]) OR ("fluoxetine"[MeSH Terms] OR "fluoxetine"[All Fields]) OR ("fluvoxamine"[MeSH Terms] OR "fluvoxamine"[All Fields]) OR ("imipramine"[MeSH Terms] OR "imipramine"[All Fields]) OR ("mirtazapine"[MeSH Terms] OR "mirtazapine"[All Fields]) OR ("nefazodone"[Supplementary Concept] OR "nefazodone"[All Fields]) OR ("paroxetine"[MeSH Terms] OR "paroxetine"[All Fields]) OR ("phenelzine"[MeSH Terms] OR "phenelzine"[All Fields]) OR ("reboxetine"[MeSH Terms] OR "reboxetine"[All Fields]) OR ("sertraline"[MeSH Terms] OR "sertraline"[All Fields]) OR ("venlafaxine hydrochloride"[MeSH Terms] OR ("venlafaxine"[All Fields] AND "hydrochloride"[All Fields]) OR "venlafaxine hydrochloride"[All Fields] OR "venlafaxine"[All Fields]) OR ("vilazodone hydrochloride"[MeSH Terms] OR ("vilazodone"[All Fields] AND "hydrochloride"[All Fields]) OR "vilazodone hydrochloride"[All Fields] OR "vilazodone"[All Fields])))) AND ((((("sleep disorders, intrinsic"[MeSH Terms] OR "sleep"[MeSH Terms]) OR ("sleep initiation and maintenance disorders"[MeSH Terms] OR ("sleep"[All Fields] AND "initiation"[All Fields] AND "maintenance"[All Fields] AND "disorders"[All Fields]) OR "sleep initiation and maintenance disorders"[All Fields] OR "insomnia"[All Fields])) OR ("dreams"[MeSH Terms] OR "dreams"[All Fields] OR "nightmares"[All Fields])) OR "Pittsburgh sleep quality index"[All Fields])

Filter: humans

PsycInfo:

((((MeSH: (post-traumatic stress disorders))) OR ((MeSH: (posttraumatic stress disorder))) OR ((MeSH: (PTSD)))) AND (((MeSH: (Pharmacotherapy))) OR ((MeSH: (antidepressant drugs))) OR ((MeSH: (antidepressive agents))) OR ((MeSH: (Antidepressant))) OR ((MeSH: (selective serotonin reuptake inhibitor))) OR ((MeSH: (monoamine oxidase inhibitors))) OR ((MeSH: (tricyclic antidepressant))) OR ((MeSH: (serotonin)) AND (MeSH: (norepinephrine reuptake inhibitor))) OR ((Any Field: (atypical antidepressants))) OR ((Any Field: (amitriptyline)) OR (Any Field: (brofaromine)) OR (Any Field: (bupropion)) OR (Any Field: (citalopram)) OR (Any Field: (desipramine)) OR (Any Field: (duloxetine)) OR (Any Field: (desvenlafaxine)) OR (Any Field: (escitalopram)) OR (Any Field: (fluoxetine)) OR (Any Field: (fluvoxamine)) OR (Any Field: (imipramine)) OR (Any Field: (mirtazapine)) OR (Any Field: (nefazodone ORparoxetine)) OR (Any Field: (phenelzine)) OR (Any Field: (reboxetine)) OR (Any Field: (sertraline)) OR (Any Field: (venlafaxine)) OR (Any Field: (vilazodone))))) AND ((MeSH: (Intrinsic Sleep Disorders)) OR (MeSH: (sleep initiation) AND MeSH: (maintenance disorders)) OR (MeSH: (sleep arousal disorders)) OR (MeSH: (sleep disorders)) OR (MeSH: (sleep)) OR (MeSH: (insomnia)) OR (MeSH: (nightmares)) OR (Any Field: (pittsburgh sleep quality index)))

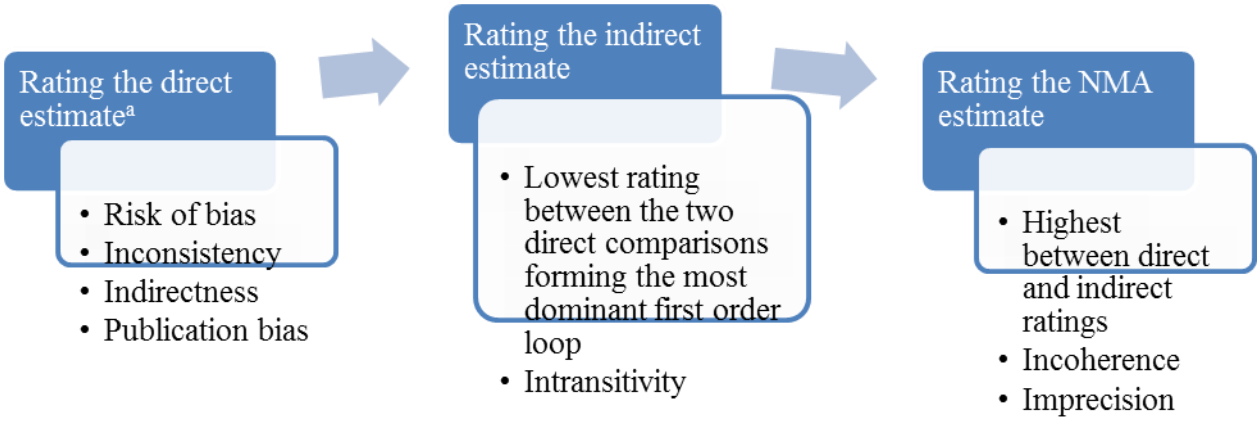
PTSDpubs Database – ProQuest (formerly called PILOTS):

(((Post-Traumatic Stress Disorder) OR (Posttraumatic Stress Disorder) OR PTSD) AND (Pharmacotherapy OR (antidepressant drug) OR antidepressant OR (Selective Serotonin Reuptake Inhibitors) OR (monoamine oxidase inhibitors) OR tricyclics OR (serotonin and noradrenaline reuptake inhibitors) OR (atypical antidepressant) OR (new antidepressants) OR (amitriptyline OR brofaromine OR bupropion OR citalopram OR desipramine OR duloxetine OR desvenlafaxine OR escitalopram OR fluoxetine OR fluvoxamine OR imipramine OR mirtazapine OR nefazodone OR paroxetine OR phenelzine OR reboxetine OR sertraline OR venlafaxine OR vilazodone))) AND ((Intrinsic Sleep Disorders) OR (sleep initiation and maintenance disorders) OR (sleep initiation dysfunction) OR Insomnia OR nightmare OR Sleep OR (pittsburgh sleep quality index))

Applied filters: Scholarly Journals

Appendix S3. The certainty of evidence assessed for each outcome

The following criteria was used to assess the certainty of evidence through GRADE approach for network meta-analysis (NMA): [1,2,3,4]



[a] Starting with high evidence (randomized controlled trials).

[1]Bonner A, Alexander PE, Brignardello-Petersen R, Furukawa TA, Siemieniuk RA, Zhang Y, Wiercioch W, Florez ID, Fei Y, Agarwal A et al. 2018. Applying GRADE to a network meta-analysis of antidepressants led to more conservative conclusions. J Clin Epidemiol. 102:87-98.

[2]Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, Hazlewood GS, Alhazzani W, Mustafa RA, Murad MH et al. 2018a. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. J Clin Epidemiol. 93:36-44.

[3]Martins CC, Firmino RT, Riva JJ, Ge L, Carrasco-Labra A, Brignardello-Petersen R, Colunga-Lozano LE, Granville-Garcia AF, Costa FO, Yepes-Nuñez JJ, Zhang Y, Schünemann HJ. Desensitizing Toothpastes for Dentin Hypersensitivity: A Network Meta-analysis. J Dent Res. 2020 May;99(5):514-522. doi: 10.1177/0022034520903036. Epub 2020 Feb 8. PMID: 32037944.

[4]Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, Kessels AG, Guyatt GH; GRADE Working Group. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ. 2014 Sep 24;349:g5630. doi: 10.1136/bmj.g5630. Erratum in: BMJ. 2015;350:h3326. PMID: 25252733.

a) Summary of findings (SoF) table showing effect estimates, credible intervals (Crl) and certainty of evidence for the outcome <u>efficacy</u>

Treatment	Comparison	Effect MD (95% CrI)	Certainty of Evidence
Bupropion	Placebo	-2.28 (-4.75, 0.21)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision
Sertraline	Placebo	-0.48 (-0.63; -0.32)	⊕⊕◯◯ LOW Due to inconsistency and imprecision
Nefazodone	Sertraline	-0.27 (-5.85, 5.47)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]
Paroxetine	Placebo	-3.13 (-7.47, 1.26)	⊕◯◯◯ VERY LOW Due to risk of bias[a], publication bias and imprecision[a]
Mirtazapine	Placebo	-3.35 (-9.06, 2.39)	⊕⊕◯◯ LOW Due to imprecision[a]
Paroxetine	Mirtazapine	0.29 (-6.9, 7.38)	⊕◯◯◯ VERY LOW Due to risk of bias[a], publication bias and imprecision[a]
Paroxetine	Bupropion	-0.83 (-5.88, 4.18)	⊕◯◯◯ VERY LOW Due to risk of bias[a], publication bias and imprecision[a]

Treatment	Comparison	Effect MD (95% CrI)	Certainty of Evidence
Paroxetine	Sertraline	-2.65 (-7.00, 1.75)	⊕◯◯◯ VERY LOW Due to risk of bias[a], publication bias and imprecision[a]
Paroxetine	Nefazodone	-2.87 (-10.05, 4.31)	⊕◯◯◯ VERY LOW Due to risk of bias[a], publication bias and imprecision[a]
Mirtazapine	Bupropion	-1.07 (-7.29, 5.17)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]
Mirtazapine	Sertraline	-2.88 (-8.58, 2.85)	⊕⊕◯◯ LOW Due to imprecision[a]
Mirtazapine	Nefazodone	-3.09 (-11.12, 4.97)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]
Bupropion	Sertraline	-1.80 (-4.28, 0.69)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]
Bupropion	Nefazodone	-2.04 (-8.18, 4.17)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]

CrI: Credible interval; MD: Mean difference

[a] Downgraded by two levels; due to imprecision: wide 95% CrI, and CrI including zero, reflecting uncertainty with regards to the direction of the effect

b) SoF table showing effect estimates, credible intervals (Crl) and certainty of evidence for the outcome accetability

Treatment	Comparison	Effect RR (95%CrI)	Certainty of Evidence
Sertraline	Placebo	1.12 (0.83, 1.52)	⊕◯◯◯ VERY LOW Due to inconsistency and imprecision[a]
Nefazodone	Sertraline	1.00 (0.37, 2.75)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]
Paroxetine	Placebo	1.00 (0.57, 1.76)	⊕◯◯◯ VERY LOW Due to risk of bias[a], publication bias, and imprecision[a]
Mirtazapine	Placebo	0.91 (0.58, 1.39)	⊕⊕◯◯ LOW Due to imprecision[a]
Paroxetine	Mirtazapine	1.10 (0.55, 2.25)	⊕◯◯◯ VERY LOW Due to risk of bias[a], publication bias, and imprecision[a]
Paroxetine	Sertraline	0.89 (0.47, 1.69)	⊕◯◯◯ VERY LOW Due to risk of bias[a], publication bias, and imprecision[a]
Paroxetine	Nefazodone	0.89 (0.27, 2.94)	⊕◯◯◯ VERY LOW Due to risk of bias[a], publication bias, and imprecision[a]

Treatment	Comparison	Effect RR (95%CrI)	Certainty of Evidence
Mirtazapine	Sertraline	0.81 (0.47, 1.36)	⊕⊕◯◯ LOW Due to imprecision[a]
Mirtazapine	Nefazodone	0.81 (0.26, 2.53)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]

SoF = Summary of findings; RR = relative risk; CrI = credible interval.

[a] Downgraded by two levels; due to imprecision: wide 95% CrI, and CrI including a RR of 1.0

c) SoF table showing effect estimates, credible intervals (Crl) and certainty of evidence for the outcome <u>tolerability</u>

Treatment	Comparison	Effect RR (95%CrI)	Certainty of Evidence
Bupropion	Placebo	0.4 (0.02, 2.75)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]
Sertraline	Placebo	0.58 (0.28, 1.14)	⊕⊕◯◯ LOW Due to imprecision[a]
Nefazodone	Sertraline	0.63 (0.08, 3.75)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]

Treatment	Comparison	Effect	Certainty of Evidence
		RR (95%CrI)	
Vilazodone	Placebo	0.27 (0.01, 2.3)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]
Mirtazapine	Placebo	0.87 (0.28, 2.50)	⊕⊕◯◯ LOW Due to imprecision[a]
Mirtazapine	Vilazodone	0.23 (0.01, 2.58)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]
Mirtazapine	Sertraline	0.5 (0.13, 1.76)	⊕⊕◯◯ LOW Due to imprecision[a]
Mirtazapine	Bupropion	0.33 (0.01, 3.16)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]
Mirtazapine	Nefazodone	0.31 (0.03, 2.78)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]
Vilazodone	Sertraline	2.16 (0.22, 59.89)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]
Vilazodone	Bupropion	1.44 (0.03, 62.86)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]
Vilazodone	Nefazodone	1.39 (0.06, 56.62)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]

Treatment	Comparison	Effect	Certainty of Evidence
		RR (95%CrI)	
Sertraline	Bupropion	0.68 (0.02, 5.49)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]
Bupropion	Nefazodone	0.63 (0.08, 3.75)	⊕◯◯◯ VERY LOW Due to risk of bias[a] and imprecision[a]

SoF = Summary of findings; RR = relative risk; CrI = credible interval. [a] Downgraded by two levels; due to imprecision: wide 95% CrI, and CrI including a RR of 1.0.

Table S1. Characteristics of the Randomized Controlled Trials Included in the Systematic Review

First author; year	Participants (N randomized)	Intervention (N analized)	Duration, weeks	Trauma type (% predominant)	Age, years, mean	Gender, female, n (%)	PTSD Diagnostic criteria	Sponsor	Overall RoB 2.0
Becker et al. 2007	A: 20 C: 10	A: Bupropion SR 100 to 300 mg/d (18) C: Placebo (7)	8	Mixed (79% combat-related)	50.39 (overall) A: NR C: NR	21 (overall) A: NR C: NR	DSM-IV	Pharmaceutical industry; Veterans Affairs Merit Awards	High risk
Davidson JR et al. 2001	A: 100 C: 108	A: Sertraline 25 to 200 mg/d (98) C: Placebo (104)	12	Mixed (64% physical or sexual assault)	A: 37.6 C: 36.6	A: 84 C: 72	DSM-III-R	Pharmaceutical industry	Low risk
Friedman et al. 2007	A: 86 C: 83	A: Sertraline 25 to 200 mg/d (84) C: Placebo (82)	12	Mixed (71% combat-related)	A:45 C:46	A: 20.93 (18) C: 19.27 (16)	DSM-III-R	Pharmaceutical industry	Low risk
McRae AL et al. 2004	A: 18 C:19	A: Nefazodone 100 to 600 mg/d (13) C: Sertraline 50 to 200 mg/d (13)	12	Mixed (30.8% sexual assault)	A:41.85 C: 38.69	A: 77 C: 77	DSM-IV	Pharmaceutical industry	High risk
NCT00202449	A: 18[a] B: 20	A: Prazosi	12	Veterans	Overall: 30	A: 5.6 B: 5.0	DSM-IV	Seattle Institut	High risk

First author; year	Participants (N randomized)	Intervention (N analized)	Duration, weeks	Trauma type (% predominant)	Age, years, mean	Gender, female, n (%)	PTSD Diagnostic criteria	Sponsor	Overall RoB 2.0
	C:21	n 1 to 30 mg/d (6) B: Paroxetine 20 mg/d (9) C: Placebo (9)		(100% combat-related)	A: 29 B: 28 C: 32	C: 4.8		e for Biomedical and Clinical Research	
Ramaswamy S et al. 2017	A: 29 C:30	A: Vilazodone 10 to 40 mg/d (25) C: Placebo (22)	12	Veterans (100% combat-related)	A: 33.6 C: 31.8	A: 3 C: 3	DSM-IV	Pharmaceutical industry	High risk
Schneier FR et al. 2015	A: 18 C: 20	A: Sertraline 25 to 200 mg/d + Mirtazapine 30 to 45 mg/d (18) C: Sertraline 25 to 200 mg/d + Placebo (18)	24	Violence among civilians (68.8% interpersonal, e.g. assault)	A: 37.6 C: 42.4	A: 66.7 C: 61.1	DSM-IV	Research Foundation for Mental Hygiene, Incorporated.	Low risk

NR= not reported. Ns= nonsignificant. RoB 2.0= Cochrane revised tool for assessing risk of bias in randomized trials.

[a] Prazosin, an alpha-1 adrenal receptor antagonist, is not an antidepressant drug, therefore it was not included in the quantitative analyses.

Figure S1. Pairwise Meta-analysis Results: Efficacy

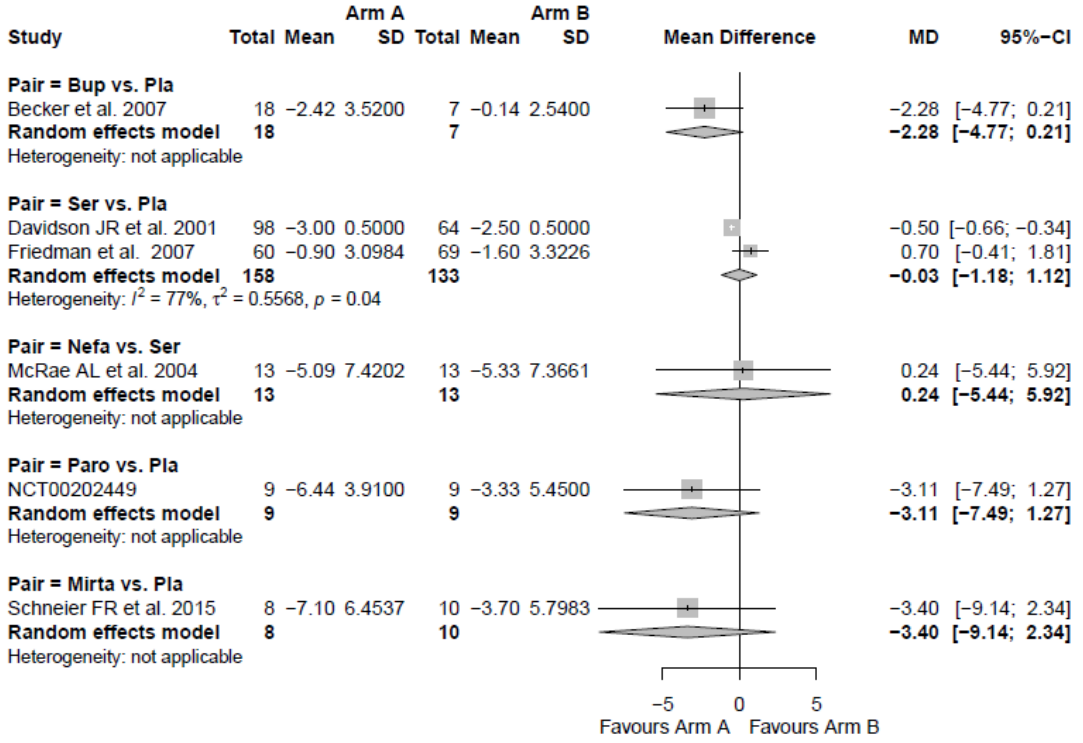


Figure S2. Pairwise Meta-analysis Results: Acceptability

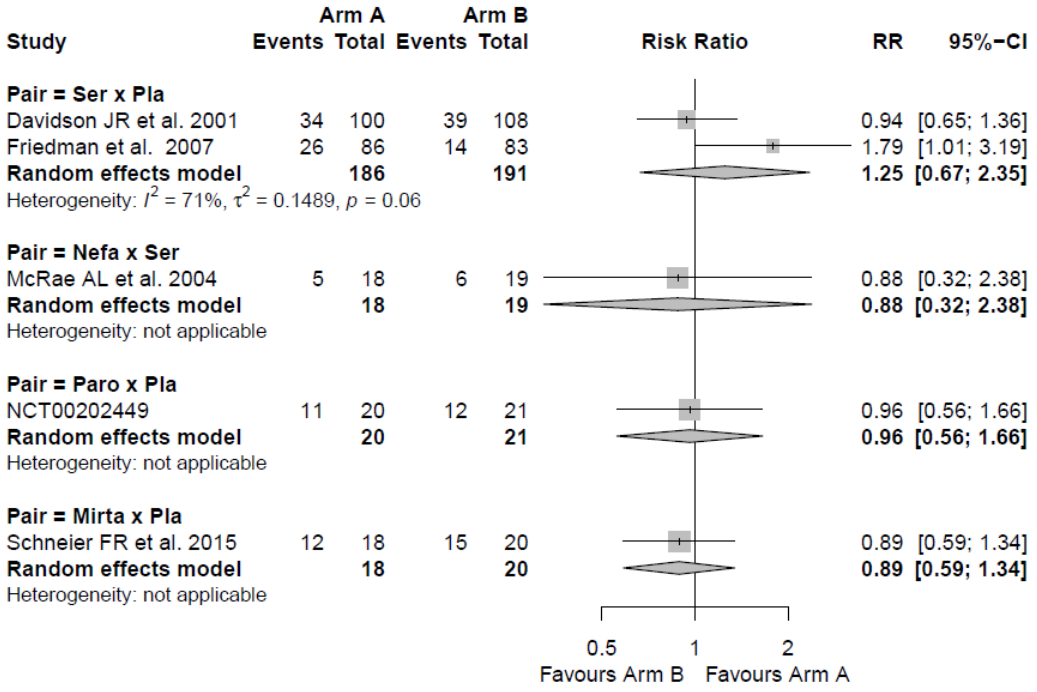


Figure S3. Pairwise Meta-analysis Results: Tolerability

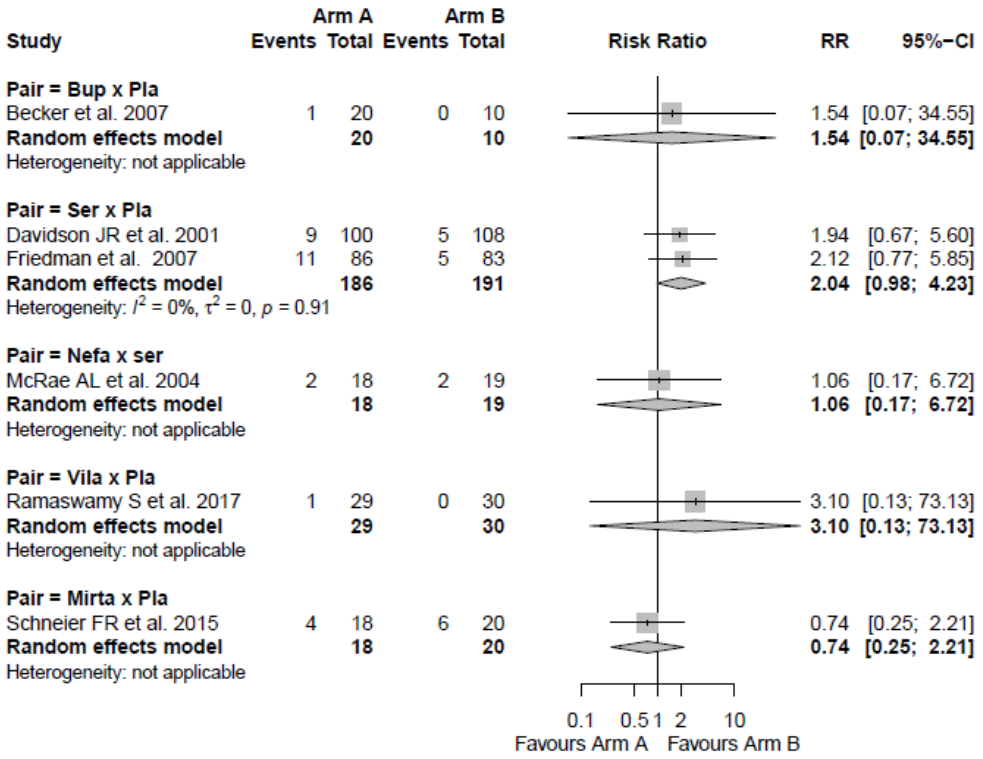


Figure S4. The ranking of treatments based on cumulative probability plots and SUCRAs

a) Ranking of Efficacy

DRUG	SUCRA
Paroxetine	0.7126300
Mirtazapine	0.7164375
Bupropion	0.6479350
Sertraline	0.3336850
Nefazodone	0.3086875
Placebo	0.2806250

b) Ranking of Acceptability

DRUG	SUCRA
Mirtazapine	0.6802100
Placebo	0.5451925
Paroxetine	0.5272450
Nefazodone	0.4211375
Sertraline	0.3262150

c) Ranking of Tolerabiliy

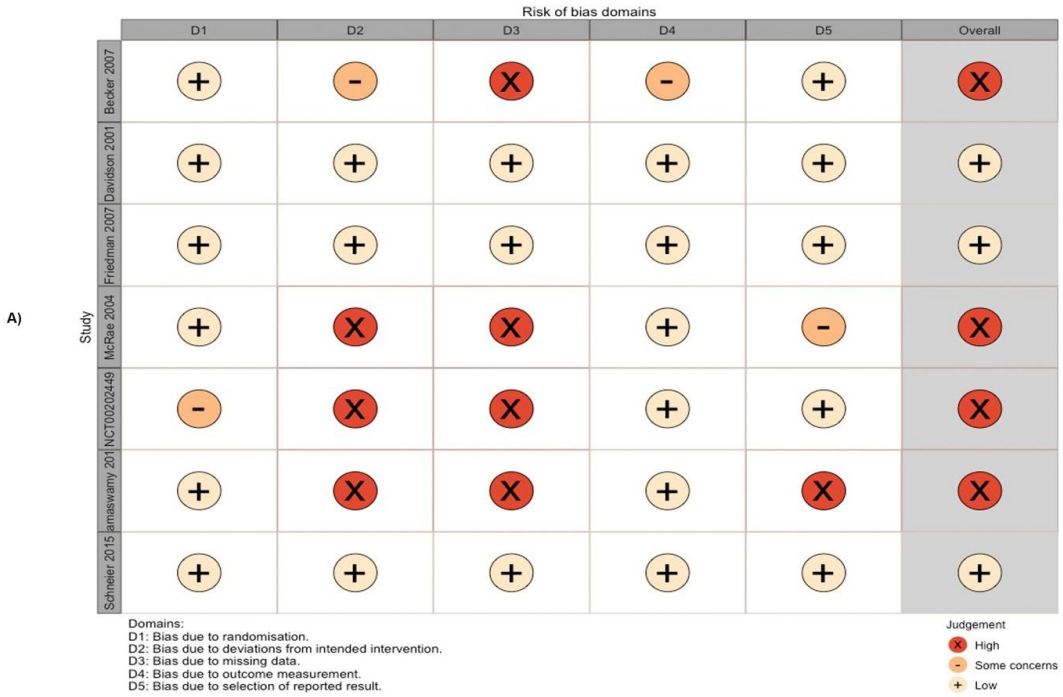
DRUG	SUCRA
Mirtazapine	0.742356
Placebo	0.704472
Vilazodone	0.610354
Sertraline	0.367730
Bupropion	0.310110
Nefazodone	0.264978

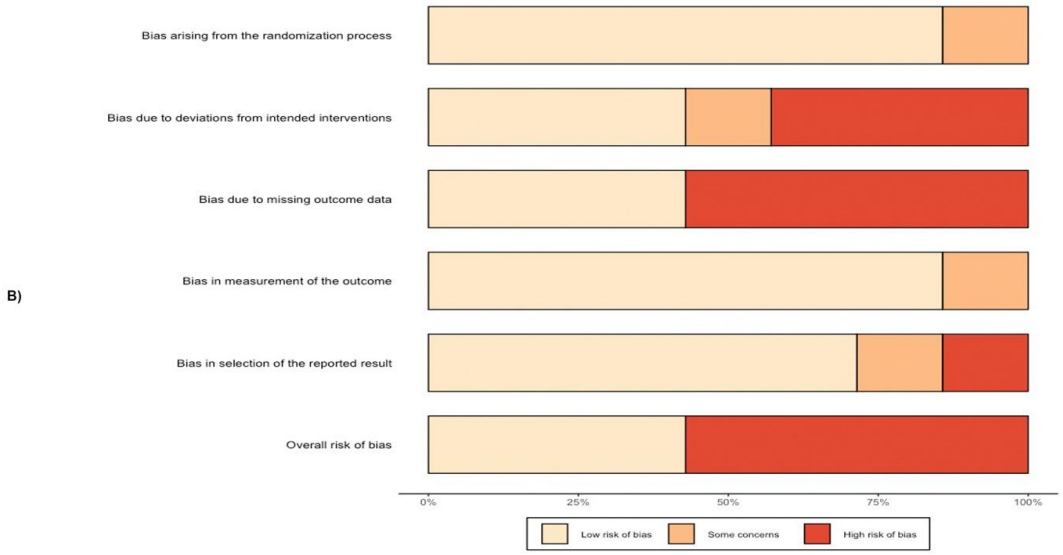
The hierarchy of competing interventions of the network meta-analysis exhibits the probabilities estimated for each drug in the network of achieving a particular placement in a ranking of treatment effects, from best to worst, in terms of treatment rankings for efficacy (a), acceptability (b), and tolerability (c).
SUCRA=surface under the cumulative ranking curve. Bup=bupropion. Mirta=mirtazapine. Nefa=nefazodone. Paro=paroxetine. Pla= placebo. Ser=sertraline. Vila=vilazodone.

Figure S5. Risk of bias assessments

A) Risk of bias domains for all eligible trials according to Cochrane's RoB 2.0

B) Overall risk of bias graph





References S1. List of Randomized Controlled Trials Included in the Systematic Review

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5. NCT00202449. (Unpublished results). Prazosin vs Paroxetine in Combat Stress-Related Post-Traumatic Stress Disorder (PTSD) Nightmares & Sleep Disturbance. ClinicalTrials.gov Identifier: NCT00202449.
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7. Schneier FR, Campeas R, Carcamo J, Glass A, Lewis-Fernandez R, Neria Y, et al.(2015): Combined mirtazapine and SSRI treatment of PTSD: a placebo-controlled trial. Depress Anxiety. 32(8):570-9. doi: 10.1002/da.22384.

References S2. List of Randomized Controlled Trials of Antidepressants in PTSD Patients that Met Many but Not All Inclusion Criteria ('Near-misses')

These studies were excluded from the Systematic Review due to ineligible outcome (e.g., sleep outcomes were not measured; lack of a reliable or valid screening tool for sleep dysfunction; treatment of secondary/ subset of symptoms; treatment of comorbidities in PTSD) and/or ineligible study design (e.g., continuation or maintenance treatment; relapse prevention trial; concurrent treatment).

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3. Brady KT, Sonne S, Anton RF, Randall CL, Back SE, Simpson K (2005): Sertraline in the treatment of co-occurring alcohol dependence and posttraumatic stress disorder. Alcohol Clin Exp Res. 29(3):395-401. PMID: 15770115.
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month randomized controlled trial. Arch Gen Psychiatry. 63(10):1158-65. DOI: 10.1001/archpsyc.63.10.1158.

6. Davidson J, Kudler H, Smith R, Mahorney SL, Lipper S, Hammett E, et al. (1990): Treatment of posttraumatic stress disorder with amitriptyline and placebo. Arch Gen Psychiatry. 47(3):259-66. PMID: 2407208.
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4 CONCLUSÕES

A intenção primaz da presente tese foi, além de apresentar as evidências atuais acerca da efetividade do tratamento farmacológico do TEPT em adultos, trazer em tela o debate acerca das aplicações práticas do uso de antidepressivos no manejo das alterações do sono nesses pacientes, haja vista a elevada frequência com que estão presentes no transtorno e as suas implicações prognósticas. Em final análise, conclui-se que:

- As evidências sugerem benefícios com o uso de topiramato, risperidona, quetiapina, paroxetina, venlafaxina, fluoxetina e sertralina devido à sua eficácia superior ao placebo na redução de sintomas do TEPT.

- Dentre esses psicofármacos eficazes na redução global dos sintomas do TEPT, apenas a fluoxetina apresentou aceitabilidade superior ao placebo.

- De acordo com os dados da metanálise em rede apenas o antidepressivo sertralina teve eficácia superior ao placebo na melhora da qualidade do sono de pacientes com TEPT.

- O placebo e os antidepressivos paroxetina, mirtazapina, sertralina e nefazodona apresentaram aceitabilidade semelhante para a melhora da qualidade do sono em pacientes com TEPT.

- O placebo e os antidepressivos mirtazapina, vilazodona, sertralina, bupropiona e nefazodona tiveram tolerabilidade semelhante na avaliação da qualidade do sono no TEPT.

- Exceto pela sertralina, não há evidências de diferenças significativas na efetividade dos antidepressivos para a melhora da qualidade do sono no TEPT. A baixa qualidade das evidências coaduna com essa informação, de maneira que a ausência de recomendação de um antidepressivo com essa finalidade parece apropriada.

A medicina baseada em evidências, nas inovações trazidas pela técnica da metanálise em rede, se corretamente utilizada caracteriza-se como alicerce valioso a fim de que o prescritor execute a sua atividade a contento. Cumpre ao médico decidir com a máxima cautela, perscrutando desfechos relevantes e a sua aplicabilidade nos casos concretos. O que se espera, ante todo o exposto neste trabalho, é que a qualidade da evidência seja observada

com especial atenção pelos psicofarmacologistas, mormente dos médicos psiquiatras, a fim de que os benefícios esperados pela farmacoterapia no TEPT superem os potenciais malefícios.

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6 ANEXOS

Anexo A – Registro do protocolo de pesquisa do artigo 1

UNIVERSITY of York
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NHS
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PROSPERO International prospective register of systematic reviews

Comparative effectiveness of pharmacological treatments for post-traumatic stress disorder (PTSD): a systematic review and network meta-analysis

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Review question(s)
What is the best pharmacological treatment for patients with a PTSD diagnosis, based on efficacy (FQ1) and acceptability (FQ2)?

Searches
The following electronic databases will be searched through April 2017: PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), PILOTS, LILACS, PsycINFO and Web of Science. Language restriction will be not applied.

For unpublished trials, we will perform a separate search on ongoing randomized clinical trials on International Clinical Trials Registry Platform (http://apps.who.int/trialsearch) and clinicaltrials.gov. For unpublished systematic reviews, PROSPERO platform will be searched. For grey literature, we will search Open Grey and Google scholar (up to 300 citations) to identify eligible trials. In addition, we will search the reference lists of relevant articles and systematic reviews for studies not identified through electronic searches. To avoid duplicate study selection, we will compare author names and affiliations, as well as study characteristics, and where uncertainty remains, we will contact corresponding authors for clarification.

Types of study to be included
Studies will be included according to the following hierarchical structure: Level I - Randomized clinical trials (RCTs); Level II – Non-randomized studies [Controlled before-and-after studies, quasi-randomized studies (studies that use inappropriate randomization strategies or that the allocation to different interventions used a method that were not random) and cohort studies.

Condition or domain being studied
Exposure to a traumatic life event (such as interpersonal violence, natural disaster, military combat or life-threatening accident) has been associated with substantial long-term psychiatric consequences, including an increased risk for suicide and Post-traumatic stress disorder (PTSD).

Although a wide range of symptoms may occur in response to trauma, the intensity and duration of these responses will differentiate them between acute non-pathological reactions and a mental illness. Acute stress disorder is distinguished from PTSD because its symptoms pattern is restricted to a duration of three days to one month following trauma exposure, while the severe lasting psychological effects of PTSD must be present for more than one month. PTSD represents a leading contributor to post-trauma disability and premature mortality, requiring elevated healthcare utilization.

A recent meta-analysis of PTSD treatment has shown that effect sizes for trauma-focused psychotherapies (TFPs) versus active control conditions were greater than medications versus placebo and other psychotherapies versus active controls. Notwithstanding, it has been argued that lower effect sizes might partly result from higher but considerable placebo effects in medication trials that are more difficult to control for, while many psychotherapy studies in PTSD

involve waitlist and treatment-as-usual control, conditions that inflate effect sizes. In addition, pharmacotherapy may help by correcting dysfunctions of neurotransmitter and neuroendocrine systems, as well as functional neuranatomical abnormalities thought to play a role in causing and/or maintaining PTSD symptoms. In spite of that, the optimal pharmacological strategy is challenging, including the most favorable window for drug administration, risk of substance abuse, presence of physical sequelae and psychiatric comorbidities. Likewise, almost half of PTSD patients show no remission after a period of more than three years, stressing a significant unmet need for pharmacotherapy that is scientifically sound and supported by clinical practice.

At present, drug recommendations differ across guidelines. Additionally, it is unclear which strategy is most effective for PTSD treatment, as few drugs have been directly compared and current research is based on traditional pair-wise meta-analytic techniques.

In order to provide a clinically useful summary that can guide treatment decisions we will use the method of multiple-treatments meta-analysis (network meta-analysis), to allow the integration of data from direct and indirect comparisons about the effectiveness of medications in the treatment of PTSD. Furthermore, this study will put the link between PTSD pharmacological treatments and their efficacy into proportion, determining first-line drugs in view of the evidence and signaling a path towards sequential treatment in non-responders.

Participants/ population

Adults (>= 18 years) treated in any setting (e.g. hospital or community) with diagnosis of PTSD based on the diagnostic and Statistical Manual of Mental Disorders (DSM) criteria and reporting a valid PTSD symptom measure. No restrictions will be placed on study selection based on sex, ethnicity or comorbid condition.

Intervention(s), exposure(s)

Studies that evaluate any pharmacological strategy in PTSD adults, compared with a placebo or with another active drug. We will include every medication for which we can find qualifying trials. Studies of medication prophylaxis for PTSD will not be included. Further, we will utilize eight weeks of medication as the minimum length necessary for inclusion, accordingly to clinical recommendations about appropriate duration of pharmacological treatment in PTSD. Additionally, studies designed to treat only specific subsets of PTSD clusters or symptoms (e.g. sleep disturbances) will be excluded from our systematic review.

Comparator(s)/ control

Studies that evaluate any pharmacological strategy in PTSD adults, compared with a placebo or with another active drug.

Studies in which the active comparator is not specifically defined will be excluded, as well as studies with psychotherapy as the only comparator.

Context

Both randomized controlled trials (RCTs) and non-randomized studies will be sought. Reasons for inclusion of both designs are because relevant non-randomized data are available. We will include cohort studies that (a) use propensity matching techniques to minimize the risk of residual confounding or (b) adjust for a minimum of two factors that could potentially affect pharmacotherapy response (e.g. trauma severity, the duration of the symptoms, prior/ongoing trauma, comorbid psychiatric conditions, lack of social support and ongoing litigation/financial compensation).

Of note, a recent study (Efthimiou O et al 2017) has stated that "the inclusion of real-world evidence from non-randomized studies in network meta-analysis "has the potential to corroborate findings from RCTs, increase precision and enhance the decision-making process".

Outcome(s)

Primary outcomes

Our primary outcomes are PTSD treatment efficacy and acceptability.

We defined efficacy as mean change scores on continuous measures of symptom severity. We defined acceptability (treatment discontinuation) as the number of patients who left the study early for any reason during the first eight

weeks of treatment of the total number of patients randomly assigned to each treatment group.

Secondary outcomes

Our secondary outcomes include the following: potential and actual adverse effects; mortality by suicide; health-related quality of life; estimated proportion of patients who responded to treatment.

Additionally, treatment response (responders versus non-responders) will be determined from the Clinical Global Impressions scale – improvement item (CGI-I)52, or closely related measure as shown in a previous study (by Stein DJ et al 2006). As mortality may be defined at various time points, we will extract all reported mortality outcomes and create subgroups where needed for descriptive and analytical purposes.

Data extraction, (selection and coding)

Two authors (G.M.C. and A.J.S.B.) will independently screen papers to identify eligible studies. First, we will examine paper title and abstracts. Studies without abstracts but with titles suggesting that they are related to the objectives of this review will also selected for full-text screening. In each step, reasons for study exclusion will be registered and a kappa score will be calculated to verify the agreement between both reviewers. The following data will be extracted from the studies selected: (1) citation (e.g., name of journal, names of authors and year of publication); publication status (unpublished, accepted for publication, published journal) and source of funding; (2) location (setting/country); (3) characteristics of the participants (number of patients per group, age, gender, PTSD in conjunction with other psychiatric disorders - e.g, major depressive disorder, bipolar disorder, substance use disorder - per intervention group; (4) follow-up time; (5) criteria for definition of PTSD, the nature of trauma and severity of PTSD; (6) details of drug interventions (class of drugs, mode of delivery, dosages, number of times per day and the schedule of use, duration of treatment, when drug regimen was initiated) and co-interventions - e.g. psychotherapy (PST), duration of PST session, number of PST sessions, interval between PST sessions or another associated drug therapy); (7) control of adherence to drugs protocols; (9) side effects (e.g., diarrhea, headache, nausea, vomiting, irritability, gastrointestinal discomfort, etc.); (10) data on outcomes and significant differences between baseline and final evaluation in both test and control groups. In order to address incomplete, inaccurate, or missing data we will contact the corresponding authors of the studies via electronic mail for additional information.

Risk of bias (quality) assessment

Two review authors will independently assess the risk of bias for each included study. The authors assessing risk of bias will not be blinded to the names of the researchers, institutions, journal and results of a study when they assess its methods.

For intervention trials, the Cochrane revised “Risk of bias tool” will be used. The risk of bias will be deemed as low, high (one or more domains are considered to be at high risk of bias) or unclear (if insufficient detail is reported and cannot be obtained from study authors) in each of the following domains:

1. Sequence generation, allocation concealment and occurrence of uneven groups with regard to important prognostic factors (selection bias);

2. Blinding of participants and personnel and other potential threats to validity (performance bias);

3. Blinding of outcome(s) assessment and other potential threats to validity (detection bias);

4. Incomplete outcome data or absence of intention-to-treat analysis (attrition bias);

5. Selective outcome reporting (reporting bias).

Strategy for data synthesis

We will perform a two stage approach to evidence synthesis: in the first stage data from randomized controlled trials alone will be pooled and in the second stage we will add data from non-randomized trials, allowing for the assessment of the additional contribution from them. For each outcome of interest we will carry out the mixed treatment comparisons approach for network meta-analysis. To estimate posterior densities for unknown variables we will use Markov Chain Monte Carlo methods through R software (meta, metafor, gemtc, coda and rjags packages). All results from network meta-analyses will be reported with point estimates and corresponding 95% credible intervals. The

ranking/probability profile of each therapy, the probability of each odds ratio being larger than 1 and the probability of a therapy being associated with the lowest risk of harm will be estimated. To assess model convergence, two chains will fit, each employing 50 000 or more iterations, with a burn-in of 50 000 iterations. We will assess the model fit by comparing the residual deviance from each model with the total number of unconstrained data points. We will explore model fit and compare alternative models by reviewing the residual deviance and the deviance information criteria from each model. We will look for any statistical inconsistency in the findings from direct and indirect evidence by fitting inconsistency models as described elsewhere (by Cipriani A et al 2009 and Yildiz A et a 2015).

Analysis of subgroups or subsets
We will investigate the effect of sponsorship on outcome estimate by performing a meta-regression analysis. Furthermore, if sufficient information is identified, we will perform subgroup analyses and/or meta-regression to determine the impact of covariates on our findings in order to establish their robustness (e.g. setting; comorbidities; severity of PTSD; cointerventions; high/unclear versus low risk of bias)

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Anticipated or actual start date
24 January 2017

Anticipated completion date
18 January 2019

Funding sources/sponsors
The present research has no specific grant/sponsors from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of interest
None known

Language
English

Country
Brazil

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Humans; Network Meta-Analysis; Stress Disorders, Post-Traumatic

Stage of review
Ongoing

Date of registration in PROSPERO
20 January 2017

Date of publication of this revision
20 January 2017

Stage of review at time of this submission	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Anexo B – Registro do protocolo de pesquisa do artigo 2

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

The Efficacy, Acceptability and Tolerability of Antidepressants for PTSD-related sleep disturbance: Protocol for a Systematic Review and Meta-analysis

Gabriela de Moraes Costa, Fabricio Batistin Zanatta, Patricia Klarmann Ziegelmann, Patricia de Moraes Costa, Carlos Fernando Mello

To enable PROSPERO to focus on COVID-19 registrations during the 2020 pandemic, this registration record was automatically published exactly as submitted. The PROSPERO team has not checked eligibility.

Citation

Gabriela de Moraes Costa, Fabricio Batistin Zanatta, Patricia Klarmann Ziegelmann, Patricia de Moraes Costa, Carlos Fernando Mello. The Efficacy, Acceptability and Tolerability of Antidepressants for PTSD-related sleep disturbance: Protocol for a Systematic Review and Meta-analysis. PROSPERO 2021 CRD42021234399
Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021234399

Review question

This systematic review and meta-analysis aims to answer the following questions:
(a) Are antidepressants effective for the treatment of sleep disturbances in adults with PTSD?
(b) Are antidepressants a well-accepted form of treatment for sleep disturbances in adults with PTSD, compared with placebo (or another active drug)?
(c) Are antidepressants a well-tolerated form of treatment for sleep disturbances in adults with PTSD, compared with placebo (or another active drug)?

Searches

The following electronic databases will be systematically searched from database inception up to November 29, 2020: Cochrane Library, LILACS, PsycINFO, PTSDpubs and PubMed Central. Two authors (GMC and PMC) will independently search the aforementioned databases and other sources ("grey literature"), including clinical trials registers, clinical study reports, and reference lists of selected studies to find possible additional articles. Relevant individuals and organizations will be contacted for information about incomplete, unpublished or ongoing studies (e. g. pharmaceutical industry; sponsors; regulatory agency sources). The full search strategies for all databases and registers, including the filters and limits used, will be presented in the supplementary material of the manuscript.

Types of study to be included

We will employ a methodical, comprehensive, replicable and systematic search process in order to synthesize evidence from Randomized controlled trials (RCTs) of antidepressants in adults with PTSD.
Both experimental and comparator interventions had no restrictions regarding drug preparation, route of administration, dose, timing of delivery, and frequency. With regard to duration we excluded studies in which the intervention was a single dose.
We will exclude studies in which the subjects have obstructive sleep apnoea syndrome. Similarly, PTSD patients with a comorbid substance use disorder will be excluded from the SR.

Condition or domain being studied

Sleep disturbance is frequently observed over the course of Post-traumatic Stress Disorder (PTSD). Moreover, it may remain after the evidence-based treatment for PTSD has been implemented, thus greater emphasis on diagnosis and treatment of sleep problems is warranted. Noteworthy, sleep disturbance is an independent risk factor for PTSD that exacerbates and maintains the disorder, and successful efforts to improve sleep could result in more positive PTSD treatment outcomes.
Managing residual insomnia and nightmares of PTSD patients is quite challenging owing to the fact that they are prevalent, persistent, and distressing. Nevertheless, we still do not know which drugs are most effective and acceptable for people with PTSD and sleep complaints and daily practice should be based on a sound rationale.
Therefore, the scarce available evidence suggests the need to explore the effectiveness of commonly-used pharmacotherapies for PTSD, such as antidepressants, on sleep outcomes.

Participants/population

Adults diagnosed with PTSD using validated criteria, such as the Diagnostic and Statistical Manual (DSM) or International Classification of Disease (ICD) criteria.

Intervention(s), exposure(s)

Antidepressants of various pharmacological classes: selective serotonin reuptake inhibitor (e.g. fluoxetine, paroxetine, sertraline, citalopram, fluvoxamine); serotonin - noradrenaline reuptake inhibitor (e.g. venlafaxine, desvenlafaxine); dopamine reuptake inhibitor (e.g bupropion); monoamine oxidase inhibitor (e. g. brofaromine, phenelzine); tricyclic (e. g. amitriptyline, desipramine, imipramine); second-generation antidepressant (e. g. mirtazapine, nefazodone, trazodone); selective norepinephrine reuptake inhibitor (e.g. reboxetine); serotonin partial agonist and reuptake inhibitor (e.g. vilazodone).

Comparator(s)/control

Placebo or any other drug.

Context

Regarding our eligibility criteria, we placed no restrictions on the basis of age, gender, duration or severity of PTSD, duration or severity of the sleep complaints, patient's treatment setting (inpatient or community), or type of trauma (combat versus noncombat).

Main outcome(s)

The primary outcome measure is efficacy in reducing sleep disturbances.

Measures of effect

We will extract the mean overall change in symptoms (and its standard deviation) from baseline to endpoint, as measured by the PSQI, or related measure of sleep (e.g. CAPS item B2).
To compare the efficacy of the selected studies, the results will be pooled and analyzed using weighted differences (MD), when studies use the same scales, or standardized mean differences (SMD), when studies use different scales, and 95% confidence intervals (CI).

Additional outcome(s)

The secondary outcomes are: acceptability and tolerability

Measures of effect

Acceptability was defined as the number of patients leaving the study early due to any reason and tolerability as withdrawal of intervention/comparison due to adverse events.

//www.crd.york.ac.uk/prospero/display_record.php?RecordID=234399

Relative risk (RR) of withdrawal from treatment will be used as the summary statistic for these dichotomous outcomes of interest, with 95% confidence intervals (CI).

Data extraction (selection and coding)

To ensure that the eligibility criteria will be consistently applied, all records will be double-screened by two authors (GMC and PMC) working independently. Multiple reports of the same study will be identified and associated with each other manually by the review authors. In order to reach a decision on inclusion the full texts of potentially eligible studies will be screened, after an initial review of titles and abstracts. Consensus meetings will be held at regular intervals to resolve unclear decisions at all screening phases. A senior researcher will be consulted to resolve disagreements (CFM). No automation tools will be used in the process. Data extraction will be conducted by a single author (GMC) and verified by other two (FBZ and PKZ). Data will be obtained from the original reports and by contacting the authors when necessary. The data collection process will be held without the aid of an automation tool. The data regarding outcomes and subjects characteristics will be extracted and compiled in a spreadsheet. Where presented, intention-to-treat data will be extracted instead of completer's analysis.

Risk of bias (quality) assessment

The Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) will be used to assess risk of bias. The ROB2 tool includes a fixed set of bias domains, which are intended to cover all issues that might lead to a risk of bias, including risk of bias due to missing results in a synthesis (arising from reporting biases). Also, the assessment is typically specific to a particular result. Importantly, we will use the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach to assess certainty in the body of evidence for each outcome, with the aid of the GRADEpro tool.

Strategy for data synthesis

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and flow-chart will be used for the systematic selection process of articles.
In order to enable syntheses and the risk of bias assessment we will collect as many details as possible about the methods, participants, setting, context, interventions, outcomes, results, publications, and investigators of each retrieved report. The following data will be sought:
- Recruitment and sampling procedures used; length of participant follow-up; details of random sequence generation, allocation sequence concealment, and masking for randomized trials, and methods used to prevent and control for confounding; source(s) of funding; statistical methods used, including methods used to prevent and address missing data;
- Setting; countries from which study participants were recruited; study eligibility criteria, including diagnostic criteria; age, gender, type of trauma; comorbidity of participants at the beginning (or baseline) of the study;
- Components, dose, timing, and frequency of the intervention(s) and comparison (s);
- Instrument used to assess the outcomes (name of the scale, upper and lower limits, and whether a high or low score is more favourable); number of participants randomly assigned and included in the analysis for each outcome; timing of outcome measurements.
Following independent peer review of titles and abstracts, the studies must be RCTs of the relevant interventions and have the outcomes of interest measured (efficacy, acceptability, tolerability). They will be initially included irrespective of whether they report all outcome data; ultimately, they will be legitimately excluded after full-text review if sleep outcomes were not measured.
Meta-analyses will be performed whenever the studies are judged to be sufficiently homogeneous, clinically and methodologically. Results will be synthesized using the R statistical software, version 4.0.4 (data were analyzed using the coda, meta, metafor, and robvis packages).

Analysis of subgroups or subsets

We plan to investigate whether the intervention effect was modified by the addition of any supplementary intervention, type of trauma, or risk of bias, through subgroup analysis.

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Professor Patricia de Moraes Costa. Federal University of Santa Maria
Professor Carlos Fernando Mello. Federal University of Santa Maria

Type and method of review

Meta-analysis, Systematic review

Anticipated or actual start date

11 November 2020

Anticipated completion date

01 May 2021

Funding sources/sponsors

None

Grant number(s)
State the funder, grant or award number and the date of award
None

Conflicts of interest

Language

English

Country

Brazil

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

02 March 2021

Date of first submission

31 January 2021

Stage of review at time of this submission

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

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

02 March 2021
02 March 2021

Anexo C – Comprovante de submissão do artigo científico 2

UFSM

GABRIELA DE MORAES COSTA <gabriela.m.costa@ufsm.br>

Submission Confirmation

1 mensagem

European Neuropsychopharmacology <em@editorialmanager.com> 25 de julho de 2021 20:54
Responder a: European Neuropsychopharmacology <support@elsevier.com>
Para: Gabriela de Moraes Costa <gabriela.m.costa@ufsm.br>

Efficacy, Acceptability, and Tolerability of Antidepressants for Sleep Disturbance in Post-Traumatic Stress Disorder: a Systematic Review and Network Meta-Analysis
by Gabriela de Moraes Costa; Patricia Klarmann Ziegelmann; Fabricio Batistin Zanatta; Carolina Castro Martins; Patricia de Moraes Costa; Carlos Fernando Mello
Review article

Dear Dr de Moraes Costa

Your submission entitled "Efficacy, Acceptability, and Tolerability of Antidepressants for Sleep Disturbance in Post-Traumatic Stress Disorder: a Systematic Review and Network Meta-Analysis" has been received by European Neuropsychopharmacology

You may check on the progress of your paper by logging on to the Editorial Manager as an author.
The URL is https://www.editorialmanager.com/neupsy/.

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Thank you for submitting your work to this journal.

Kind regards

Editorial Manager
European Neuropsychopharmacology

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