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Research Article

PSYCHOTHERAPY VERSUS PHARMACOTHERAPY FOR POSTTRAUMATIC STRESS DISORDER: SYSTEMIC REVIEW AND META-ANALYSES TO DETERMINE FIRST-LINE TREATMENTS

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Background: *Current clinical practice guidelines (CPGs) for posttraumatic stress disorder (PTSD) offer contradictory recommendations regarding use of medications or psychotherapy as first-line treatment. Direct head-to-head comparisons are lacking.* **Methods:** *Systemic review of Medline, EMBASE, PILOTS, Cochrane Central Register of Controlled Trials, PsycINFO, and Global Health Library was conducted without language restrictions. Randomized clinical trials ≥8 weeks in duration using structured clinical interview-based outcome measures, active-control conditions (e.g. supportive psychotherapy), and intent-to-treat analysis were selected for analyses. Independent review, data abstraction, and bias assessment were performed using standardized processes. Study outcomes were grouped around conventional follow-up time periods (3, 6, and 9 months). Combined effect sizes were computed using meta-analyses for medication versus control, medication pre-/posttreatment, psychotherapy versus control, and psychotherapy pre-/posttreatment.* **Results:** *Effect sizes for trauma-focused psychotherapies (TFPs) versus active control conditions were greater than medications versus placebo and other psychotherapies versus active controls. TFPs resulted in greater sustained benefit over time than medications. Sertraline, venlafaxine, and nefazodone outperformed other medications, although potential for methodological biases were high. Improvement following paroxetine and fluoxetine treatment was small. Venlafaxine and stress inoculation training (SIT) demonstrated large initial effects that decreased over time. Bupropion, citalopram, divalproex, mirtazapine, tiagabine, and topiramate failed to differenti-*

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ate from placebo. Aripiprazole, divalproex, guanfacine, and olanzapine failed to differentiate from placebo when combined with an antidepressant.* Conclusions: *Study findings support use of TFPs over nontrauma-focused psychotherapy or medication as first-line interventions. Second-line interventions include SIT, and potentially sertraline or venlafaxine, rather than entire classes of medication, such as SSRIs. Future revisions of CPGs should prioritize studies that utilize active controls over waitlist or treatment-as-usual conditions. Direct head-to-head trials of TFPs versus sertraline or venlafaxine are needed. Depression and Anxiety 33:792–806, 2016.

Key words: ***PTSD; posttraumatic stress disorder; pharmacotherapy; psychotherapy; VA/DoD; ISTSS; NICE; WHO; Australian; Department of Defense; International Society for the Study of Traumatic Stress; National Institute for Clinical Excellence; World Health Organization***

INTRODUCTION

Current clinical practice guidelines (CPGs) for posttraumatic stress disorder (PTSD) offer contradictory recommendations regarding use of medications or psychotherapy as first-line treatment despite having basis in common clinical literature.[1–6] Veteran's Affairs/Department of Defense (VA/DoD), American Psychiatric Association (APA), and International Society for Traumatic Stress Studies (ISTSS) guidelines present medications and psychotherapy as equivalent first-line treatments.[1,3,6] Conversely, National Institute for Clinical Excellence (NICE), Australian, and World Health Organization (WHO) assert trauma-focused psychotherapies (TFPs) are superior to medications, and recommend against medication when TFPs are available.[2,4,5] Methodologically, VA/DoD, APA, and ISTSS prioritize number of positive trials and value uncontrolled data whereas other guidelines base recommendations on larger effects for TFPs against control.[1–6] Each guideline utilized different review methodologies and inclusion/exclusion criteria for studies considered.[1–6]

Medication recommendations differ across guidelines as well.[1–6] VA/DoD experts conclude all selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are roughly equivalent first-line treatments.[1] They advocate use of prazosin, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAO-Is), and nefazodone as second-line interventions. ISTSS experts recommend sertraline, paroxetine, fluoxetine, venlafaxine, mirtazapine, nefazodone, and prazosin for first-line use.[3] They advocate second-line use of phenelzine, amitriptyline, and bupropion. APA experts conclude SSRIs warrant first-line use, with all other second-generation antidepressants comprising second-line use. NICE experts find paroxetine, sertraline, amitriptyline, and phenelzine superior to other medications for second-line use.[2] Australian guidelines recommend SSRIs, and WHO recommends TCAs and MAO-Is.[4–6] All recommend against regular use of antiepileptics, antipsychotics, and benzodiazepines.[1–6] One reason for differing guideline recommendations is that psychotherapy effects are generally larger than those observed in medication studies. However, many psychotherapy studies involve waitlist and treatment-as-usual control conditions that inflate effect sizes, and do not control for time with a provider and other nonspecific treatment factors. Active-control conditions in psychotherapy studies, and particularly placebo-control in medication trials, tend to narrow efficacy margins between treatment and control conditions.

Discussion of PTSD psychotherapy is complicated by the term trauma-focused cognitive behavioral therapy (TF-CBT), which has two meanings. When used in guidelines, TF-CBT generally encompasses both meanings, and is synonymous with TFP, referring collectively to all types of psychotherapy with trauma-focus, including eye movement desensitization (EMDR), prolonged exposure (PE), cognitive processing therapy (CPT), imaginal exposure (IE), as well as a specific type of TFP used in some studies. NICE, WHO, Australian, and APA guidelines recommend TFP/TF-CBTs as a group.[2,4–6] VA/DoD guidelines recommend psychotherapy that includes components of exposure or cognitive restructuring such as EMDR, PE, CPT, IE, TF-CBT, or stress inoculation training (SIT). ISTSS guidelines highlight EMDR, PE, CPT, and SIT as first-line treatments.[3]

This series of meta-analyses was designed to answer the primary question of whether TFPs are superior to medications, or if both are generally equivalent first-line interventions in adult populations with PTSD. Although several recent expert reviews and meta-analyses of PTSD treatment have been published, they have methodological limitations, including unsystematic or overly stringent inclusion/exclusion criteria or statistical extrapolations made from uncontrolled open-label data.[7–12] Most, importantly, previous analyses were

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(posttraumatic stress disorder OR post-traumatic stress disorder OR PTSD) AND (sertraline OR paroxetine OR fluoxetine OR escitalopram OR citalopram OR fluvoxamine OR vilazodone OR vortioxetine OR nefazodone OR venlafaxine OR duloxetine OR desvenlafaxine OR milnacipran OR levomilnacipran OR bupropion OR mirtazapine OR amitriptyline OR nortriptyline OR imipramine OR desipramine OR doxepin OR maprotiline OR phenelzine OR tranylcypromine OR selegiline OR moclobemide OR brofaromine OR tianeptine OR prazosin OR risperidone OR paliperidone OR haloperidol OR olanzapine OR quetiapine OR lurasidone OR ileoperidone OR asenapine OR thioridazine OR fluphenazine OR ziprasidone OR aripiprazole OR topiramate OR divalproex OR lamotrigine OR lithium OR oxcarbazepine OR carbamazepine OR alprazolam OR diazepam OR clonazepam OR lorazepam OR temezapam OR guanfacine OR clonidine OR propranolol OR atomoxetine OR gabapentin OR pregabalin OR tiagabine OR eye movement desensitization reprocessing therapy OR EMDR OR cognitive behavioural therapy OR CBT OR prolonged exposure OR PE OR cognitive processing therapy OR CPT OR dialectal behavioural therapy OR DBT OR interpersonal therapy OR IPT OR narrative exposure therapy OR NET OR stress inoculation training OR SIT)

Figure 1. (A) Generic search strategy (interventions), (B) search strategy (syntax).

not designed to address the core question of whether TFPs have greater evidence of effectiveness than medications. Our goal in this analysis was to provide rigorous, transparent, and valid comparisons to inform clinical practice and improve existing CPGs. We compare medication and psychotherapy performance against placebo- or active-control conditions, as well as pre-/posttreatment symptom severity using gold-standard PTSD outcome measures. Based on evidence reviews in existing CPGs, we hypothesized that psychotherapy would outperform medications under controlled conditions, due to larger effect sizes observed in these studies, but would have generally comparable within-group pre-/posttreatment improvements, most strongly supporting VA/DoD and ISTSS guideline recommendations.

METHODS

This report adheres to PRISMA guidelines.[13] Four authors (D.L., C.S., J.W., C.H.) searched Medline (1900-July 2015), EMBASE (1860-July 2015), PILOTS, Cochrane Central Register of Controlled Trials, PsycINFO (1806-July 2015), and Global Health Library without language restrictions. Our full search strategy is online (Fig. 1A and B). Search involved combinations of PTSD and generic medication names, psychotherapy names, and psychotherapy abbreviations. Bibliographies of included studies and guidelines were reviewed for citations to supplement the search.

We searched for published and unpublished randomized adult clinical trials of any therapy or medication compared with active/placebo-control conditions utilizing intention-to-treat analyses. We defined 8 weeks of medication or eight sessions of psychotherapy as the minimum length necessary for inclusion, a broad definition often used in health services research.[14] We included every medication for which we could find qualifying studies. Psychotherapy sessions for both treatment and control conditions were required to be individual, in-person, manualized, and ≥45 min in duration. The in-person criterion was required to avoid potentially confounding results due to differences in nonspecific effects associated with direct interaction with the therapist in the room. Group therapies were excluded due to their limited evidence, nonspecific social effects of the group environment, and clinical challenges delivering core trauma-focused components in this manner. Psychotherapies deviating from traditional manualized approaches were excluded. For this study, the term "TF-CBT" is used only to refer to a specific psychotherapy type and TFPs refer to the entire group of psychotherapies.

PTSD diagnosis using DSM-III-R or DSM-IV-TR criteria was required prior to treatment initiation. PTSD trials with 100% prevalence of comorbid conditions, such as borderline personality disorder, primary thought disorder, or substance use disorder were excluded as these were not generalizable to standard patient populations. However, many studies included samples with high percentages of comorbid substance abuse, depression, and anxiety disorders at rates typical of PTSD study populations. Gold standard, interview-based outcome measures required for inclusion were Clinician-Administered PTSD Scale (CAPS), Short PTSD Rating Interview (SPRINT), and PTSD

B

PubMed

("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 ("posttraumatic"[All Fields] AND "stress"[All Fields] AND "disorder"[All Fields]) OR "posttraumatic stress disorder"[All Fields]) AND ("generic drug name/therapy name/therapy abbreviation"[MeSH Terms] OR "generic drug name/therapy name/therapy abbreviation"[All Fields] OR "generic drug name/therapy name/therapy abbreviation"[All Fields])

EMBASE

"posttraumatic" AND "stress" AND "disorder" AND "generic drug name/full therapy name"

Cochrane

- Search terms used: posttraumatic stress disorder, generic drug name/full therapy name

PILOTS

("generic drug name") OR ("full therapy name") OR ("therapy abbreviation")

PsycINFO

(posttraumatic stress disorder and generic drug name/full therapy name).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

- Search terms used: disorder, posttraumatic, generic drug name/full therapy name, Stress

Figure 1. *Continued.*

Symptom Scale-Interview (PSS-I), which have been validated against the Structured Clinical Interview for DSM-IV and CAPS and widely adopted in PTSD research. Outcome measures created for specific RCTs or validated as part of an RCT design were excluded. These included standardized interview for PTSD (SI-PTSD), revised standardized interview for PTSD (SIP), and several outcome measures named for Duke University.[15–18]

Study outcomes were grouped by follow-up duration (8–12 weeks, 14–27 weeks, and 32+ weeks) and consolidated into overall effect using meta-analysis. Our intent was to separate outcome measures into traditional 3-, 6-, and 9-month end points as a surrogate for performance over time. Selected ranges allowed for capture of outcome measurements occurring at or closely around these time points. Outcomes beyond 32 weeks were grouped together due to variable end points. Many medication trials longer than 12 weeks involved maintenance (continuing medication after response) and relapse prevention (determining if switch to placebo after response causes loss of efficacy). Both designs were retained because they began from similar baselines and their exclusion would have eliminated most long-term medication trials. Although most psychotherapy trials involved weekly treatment, if treatment was provided more or less frequently, outcomes collected immediately posttreatment were included within the 8- to 12-week grouping. Later measures were grouped normally.

Given the paucity of psychotherapy studies that excluded concomitant medications, we allowed psychotherapy trials in which participants were taking medications, provided these were similar for treatment and control. All included medication studies involved placebo control. Medication studies wherein >25% of the study population was maintained on an antidepressant were considered adjunctive trials as they differed significantly from monoagent trials requiring discontinuation of all other medications. Psychotherapy controls included supportive psychotherapy, biofeedback, and relaxation training. Waitlist and treatment-as-usual controls were deemed insufficient to account for nonspecific treatment effects and were excluded.

For studies meeting above inclusion criteria, we avoided exclusions based on study quality or risk of bias, since differing inclusion/exclusion criteria appeared to be a major factor in variation between guideline recommendations. Most importantly, exclusion of studies deemed at high risk of bias would have resulted in exclusion of most medication trials; we prioritized answering our research question, even if this meant inclusion of biased studies.

STUDY SELECTION AND DATA ABSTRACTION

We utilized a two-stage study selection process. In stage one, four authors (D.L., C.S., J.W., C.H.) independently reviewed titles and abstracts to select full text articles. If based on abstract or title, a study was determined to be randomized, but study length or session number could not be determined (or vice versa), we erred toward retrieval. If neither could be determined, it was excluded. During stage two, D.L. and C.S., J.W., M.V., A.R., or C.H. independently applied inclusion/exclusion criteria using standardized forms, assessed article quality using Cochrane's bias assessment tool,[19] and extracted data. Interrater agreement was high for these measures (>95%). Disagreements centered on handling of unanticipated outcome measures and psychotherapy controls and were resolved by consensus. Extracted demographic information appears in Table 1.

STATISTICAL ANALYSIS

Meta-regression was considered, but rejected in favor of meta-analysis, which was deemed more accurate for nonlinear data and time intervals driven by clinical convention. Due to differences between CAPS, SPRINT, and PSS-I, we computed study effect sizes to determine overall effect size for each intervention. By convention, effect sizes greater than 0.8 are considered large, those between 0.6 and 0.8 moderate, and those between 0.2 and 0.5 small.[20] Performance versus control was computed using treatment and control measures taken at the same time. Pre-/posttreatment analyses compared treatment group measures against group baseline. Guideline comparisons were done by combining effects for all first-line or second-line interventions recommended in the guidelines using meta-analysis. For example, the VA/DoD guideline recommends SSRIs and SNRIs as first-line pharmacological treatments, and TFT or SIT as first-line psychotherapies. Thus, we ran separate meta-analyses involving the various combinations of studies using these different first-line treatments.

Studies analyzing different aspects of the same study population were combined into a single study for analysis. Studies with multiple treatment arms measured against a single active-control condition were analyzed as separate studies (e.g., PE vs. interpersonal therapy (IPT) vs. control became PE vs. control and IPT vs. control). All uncontrolled data points were excluded. Data points were excluded if they involved exclusion of treatment responders or treatment nonresponders. Heterogeneity was assessed using the I^2 statistic, though large heterogeneity was expected due to inclusion of many interventions (Fig. 2).[21] We estimated number of unpublished trials needed to invalidate our findings using file drawer/fail safe (FDFS).[22] All analyses were completed using Stata's metan command (v.11). Meta-analyses utilized inverse variance weighting with random effects.

RESULTS

Of 61,268 initial search results, 285 potential articles were identified, retrieved, and assessed for eligibility (Fig. 3). Sixty-three articles met inclusion criteria; seven of these articles[23–29] described outcomes from three research populations. These results were combined into three studies, leaving 58 independent studies. Three studies replicated data from other included studies, leaving 55 total studies. Interventions that met inclusion criteria and number of studies using them included aripiprazole (1),[30] brofaromine (2),[31,32] bupropion (1),[33] TF-CBT (2),[23,24,34] citalopram (1),[35] CPT (1),[36] divalproex (2),[37,38] EMDR (2),[39,40] fluoxetine (5),[25,26,41–44] guanfacine (2),[45,46] IPT (1),[47] mirtazapine (1),[16] nefazodone (1),[48] olanzapine (3),[18,49,50] paroxetine (7),[51–57] PE with cognitive restructuring (PE/CR) (2),[58,59] PE (7),[40,47,58–62] prazosin (3),[63–65] risperidone (5),[66–70] sertraline (5),[27–29,35,71–73] SIT (1),[60] tiagabine (2),[17,74] topiramate (2),[75,76] and venlafaxine (2).[71,77]

A total of 6,313 participants were enrolled across all trials (Table 1). Average study duration was 18 weeks (range 8–104) with the average medication study running 17 weeks (8–64) and the average psychotherapy study running ten sessions (8–12). A mean of 115 participants (10–551) took part in each study. Forty-nine percent of participants were women (0–100%). Mean age of participants was 42 (30–55). All included studies were in English. Thirty-one medication trials (72%) were industry supported. Average percentage of veterans was 40% (0–100%). Dropout average was 29% (0–79%). In 36 studies specifying major depressive disorder prevalence at initiation, average comorbidity was 41% (0–86%).

QUALITY AND RISK OF BIAS

Quality varied, with most studies having important limitations in design, reporting, or both (Table 2). Double-blinding was not possible for psychotherapy studies, and it is unlikely nonspecific placebo effects were fully controlled for, even with optimal methods. Nevertheless, psychotherapy trials were generally better designed, executed, and reported than medication studies. Cochrane criteria demonstrated considerable differences in risk of bias between medication and psychotherapy studies (Table 2). Most psychotherapy trials were rated low or very low risk of bias and most medication trials were rated high or very high risk of bias, despite the fact they were placebo controlled. Differences were noted for allocation concealment, adherence, sequence generation, and industry sponsorship, suggesting fundamental design and reporting differences. A typical medication study was conducted by one of a handful of industry-sponsored researchers, selectively reported data, and failed to disclose methods for randomization, allocation concealment, or adherence. Failure to perform pill counts, having treating providers assess outcome measures, and nonrandom group assignments allowed possible influence toward desired outcomes. Randomization and blinding success were also questionable in some medication studies with groups differing significantly in adverse effects and attrition, which could easily jeopardize allocation concealment. Data reporting, standardized across psychotherapy studies, varied across medication studies, particularly among industry-sponsored trials. Most medication studies and

TABLE 1. Demographic information for included studies

Intervention	Author (year)	*N*	Veterans (%)	Women (%)	Mean age	Depression %	Mean dose/ No. of sessions
Aripiprazole	Naylor (2015)	16	100	31	34	86	10 mg
Brofaromine	Baker (1995)	118	60	19	44	Uncertain	Uncertain
Brofaromine	Katz (1995)	45	18	24	39	0	Uncertain
Bupropion	Becker (2007)	28	50	21	50	Uncertain	300 mg
CPT	Suris (2013)	86	0	85	46	Uncertain	10 sessions
Divalproex	Davis (2008)	85	100	Uncertain	55	Uncertain	2309 mg
Divalproex	Hamner (2009)	29	100	3	52	69	1196 mg
EMDR	Carlson (1998)	35	100	0	48	Uncertain	Uncertain
EMDR, PE, PE/CR	Taylor (2003)	60	0	75	37	42	8 sessions
Fluoxetine	Davidson (2005)	123	32	50	44	Uncertain	49 mg
Fluoxetine	Martenyi (2007)	411	5	72	41	Uncertain	30 mg
Fluoxetine	Martenyi (2002), Martenyi (2002)	301	31	19	38	0	57 mg
Fluoxetine	Martenyi (2006)	144	100	1	36	0	65 mg
Fluoxetine	van der Kolk (2007)	59	0	83	36	Uncertain	30 mg
Guanfacine	Davis (2008)	35	100	6	53	57	2 mg
Guanfacine	Neylan (2006)	56	100	Uncertain	Uncertain	Uncertain	2 mg
IE, IE/CR	Bryant (2003)	58	0	52	35	Uncertain	Uncertain
Mirtazapine	Davidson (2003)	29	14	50	47	73	39 mg
Nefazodone	Davis (2004)	41	98	2	54	39	435 mg
Olanzapine	Butterfield (2001)	15	60	93	43	53	14 mg
Olanzapine	Carey (2012)	28	0	61	41	0	9 mg
Olanzapine	Stein (2002)	21	100	0	53	Uncertain	15 mg
Paroxetine	GlaxoSmithKline (2001)	263	0	66	43	0	Uncertain
Paroxetine	Marshall (2001)	551	8	67	42	45	30 mg
Paroxetine	Marshall (2007)	52	0	67	40	63	Uncertain
Paroxetine	Schneier (2012)	37	0	54	50	66*	32 mg
Paroxetine	Tucker (2000)	323	7	66	41	35	28 mg
Paroxetine	Fani (2009)	18	Uncertain	56	41	Uncertain	Uncertain
Paroxetine	Fani (2011)	13	8	54	40	85	Uncertain
PE	Schnurr (2007)	284	100	100	45	64*	9 sessions
PE	Rauch (2014)	30	100	8	32	47	11 sessions
PE, IPT	Markowitz (2015)	110	0	77	40	50	8 PE/13 IPT
PE, PE/CR	Marks (1998)	87	3	36	38	49	Uncertain
PE, SIT	Foa (1991)	45	0	100	32	Uncertain	Uncertain
Prazosin	Raskind (2007)	38	100	5	56	Uncertain	13 mg
Prazosin	Raskind (2013)	67	100	15	30	34	20 mg men / 9 mg women
Prazosin	Raskind (2003)	10	100	0	53	Uncertain	10 mg
Risperidone	Padala (2006)	20	0	100	41	Uncertain	3 mg
Risperidone	Reich (2004)	21	0	100	28	62	1 mg
Risperidone	Bartzokis (2004)	65	100	0	52	Uncertain	3 mg
Risperidone	Krystal (2011)	296	100	3	54	70	3 mg
Risperidone	Rothbaum (2008)	20	0	80	34	80	2 mg
Sertraline	Brady (2000), Davidson (2001), Davidson (2001)	385	5	76	38	37	139 mg
Sertraline	Friedman (2007)	169	100	20	46	0	135 mg
Sertraline	Zohar (2002)	42	100	12	40	0	120 mg
Sertraline, citalopram	Tucker (2003)	58	3	74	39	78	Sert 134 mg/cit 36 mg
Sertraline, venlafaxine	Davidson (2006)	531	9	Uncertain	Uncertain	0	Sert 110 mg/ven 164 mg
TF-CBT	Blanchard (2003), Blanchard (2003)	98	0	73	40	49	10 sessions
TF-CBT	McDonaugh (2005)	74	0	100	40	Uncertain	Uncertain
TF-CBT	Ehlers (2014)	121	0	59	39	36	12 sessions
Tiagabine	Connor (2005)	26	4	73	41	Uncertain	11 mg
Tiagabine	Davidson (2007)	232	9	66	43	38	11 mg
Topiramate	Tucker (2007)	40	0	79	42	61	150 mg
Topiramate	Yeh (2011)	35	0	68	40	13	103 mg
Venlafaxine	Davidson (2006)	329	12	54	41	0	182 mg

CPT, cognitive processing therapy; EMDR, eye movement desensitization reprocessing therapy; IE, imaginal exposure; PE, prolonged exposure; PE/CR, prolonged exposure with cognitive restructuring; SIT, stress inoculation training; TF-CBT, trauma-focused cognitive behavioral therapy.
*Reporting of mood disorder rather than depression.

I^2 Statistic		
8-12 Wk vs. Control	14-27 Wk vs. Control	34+ Wk vs. Control
84.80%	68.20%	79.40%
8-12 Wk Pre/Post	14-27 Wk Pre/Post	34+ Wk Pre/Post
94.20%	96.00%	95.90%

Figure 2. I^2 statistic.

several psychotherapy studies reported outcome data selectively or in a misleading manner. Examples included partial/nonstandard reporting between text and charts,[19,20,22–27,32–35,37–39,42,44–46,49,52,56,58,60,62,63,65–69] switching between mean/mean change,[25,26,38,43–45,48,50,52,66,69,71–75] switching between standard deviations(SD)/confidence intervals/standard errors,[25,26,28,30,43,44,51,55,62,64,67,71,72] omitting baseline outcome data,[28,33,68] omitting variance measures completely,[28,31,68] omitting outcome measures at specific time points,[28,40,68] creation of nonstandard outcome measures by combining standard measures with other variables,[25,28,32,41,44,51,73] splitting outcome measures into subscales without providing total score,[39,58] failure to cross-reference data spread over several publications,[25,26,43,44] and including nonscaled graphs without providing corresponding means.[28,40,68]

Data abstraction for most medication studies required mathematical conversion of provided data into mean total CAPS/SPRINT/PSS-I and SD. Data extraction for

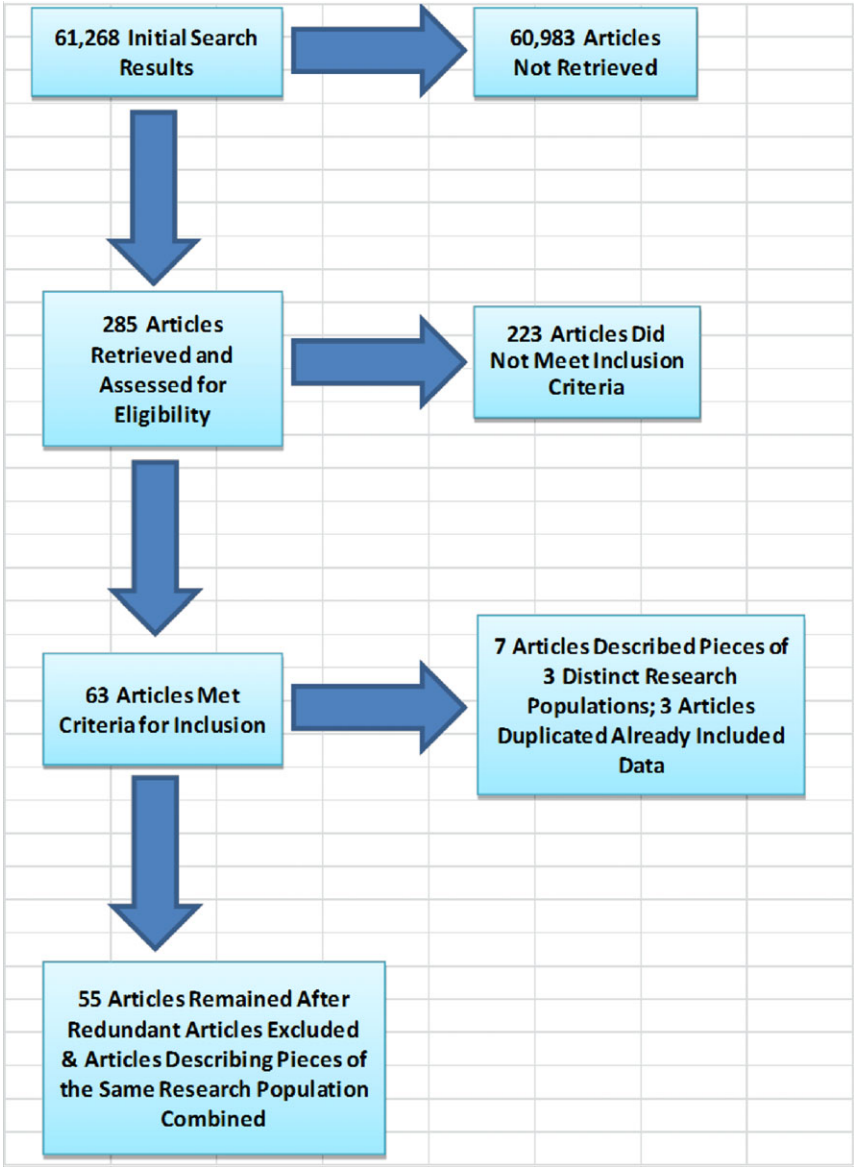

Figure 3. Flow of Studies, Reasons for nonretrieval or exclusion involved one or more of the following: (1) not pertinent to research question, (2) duration was too short, (c) wrong outcome measure(s), and/or (d) study involved acute stress disorder or subdiagnostic PTSD.

TABLE 2. Application of Cochrane bias assessment to all included studies

Bias risk	Intervention	Author (year)	Dropout (%)	Adherence	Sequence generation	Allocation concealment	Industry support	Selective reporting
Very low	CPT	Suris (2013)	28	Yes	Yes	Yes	No	No
Very low	IE, IE/CR	Bryant (2003)	22	Yes	Yes	Yes	No	No
Very low	PE, PE/CR	Marks (1998)	60	Yes	Yes	Yes	No	Yes
Very low	PE	Schnurr (2007)	29	Yes	Yes	Yes	No	No
Very low	PE	Markowitz (2015)	25	Yes	Yes	Yes	No	No
Very low	TF-CBT	Ehlers (2014)	3	Yes	Yes	Yes	No	No
Very low	Topiramate	Yen (2011)	26	Yes	Yes	Yes	No	No
Low	TF-CBT	Blanchard (2003), Blanchard (2003)	20	Yes	Uncertain	Yes	No	Yes
Low	TF-CBT	McDonaugh (2005)	23	Yes	Uncertain	Yes	No	Yes
Low	EMDR	Carlson (1598)	3	Yes	Uncertain	Yes	No	Yes
Low	EMDR, PE	Taylor (2003)	35	Yes	Uncertain	Yes	No	Yes
Low	Fluoxetine	Martenyi (2002), Martenyi (2002)	61	Yes	Yes	Yes	Yes	No
Low	Fluoxetine	Martenyi (2005)	67	No	Yes	Yes	No	Yes
Low	PE, SIT	Foa (1991)	18	Yes	Uncertain	Yes	No	Yes
Low	Prazosin	Raskind (2007)	18	Uncertain	Yes	Yes	No	Yes
Low	Divalproex	Davis (2008)	20	Uncertain	Yes	Yes	No	Yes
Moderate	Fluoxetine	van der Kolk (2007)	34	Uncertain	Uncertain	Yes	No	Yes
Moderate	Paroxetine	Schneier (2012)	41	Uncertain	Uncertain	Yes	No	Yes
Moderate	PE	Rauch (2014)	28	Uncertain	Uncertain	Yes	No	Yes
Moderate	Divalproex	Hamner(2009)	48	Yes	Uncertain	Yes	Yes	Yes
Moderate	Guanfacine	Neylan (2006)	10	Yes	Uncertain	Yes	No	Yes
High	Brofaromine	Baker (1995)	30	Uncertain	Uncertain	Uncertain	Yes	Yes
High	Brofaromine	Katz (1995)	27	Uncertain	Uncertain	Uncertain	Yes	Yes
High	Bupropion	Becker (2007)	23	Uncertain	Uncertain	Uncertain	Yes	Yes
High	Fluoxetine	Davidson (2005)	44	Yes	Uncertain	Uncertain	Yes	Yes
High	Mirtazapine	Davidson (2003)	31	Uncertain	Uncertain	Uncertain	No	Yes
High	Nefazodone	Davis (2004)	44	Uncertain	Uncertain	Yes	Yes	Yes
High	Paroxetine	Marshall (2007)	42	Uncertain	Uncertain	Yes	Yes	Yes
High	Prazosin	Raskind (2013)	39	Uncertain	Uncertain	Uncertain	No	Yes
High	Prazosin	Raskind (2003)	0	Uncertain	Uncertain	Uncertain	No	Yes
High	Sertraline	Brady (2000), Davidson (2001), Davidson (2001)	79	Yes	Uncertain	Uncertain	Yes	Yes
High	Sertraline	Friedman (2007)	24	Uncertain	Yes	Uncertain	Yes	Yes
High	Sertraline	Zohar (2002)	26	Yes	Uncertain	Uncertain	Yes	Yes
High	Olanzapine	Carey (2012)	29	Uncertain	Yes	Uncertain	Yes	Yes
High	Topiramate	Tucker (2007)	5	Uncertain	Yes	Uncertain	Yes	Yes
High	Aripiprazole	Naylor (2015)	25	Uncertain	Uncertain	Uncertain	No	Yes
High	Guanfacine	Davis (2008)	19	Uncertain	Uncertain	Uncertain	No	Yes
Very high	Fluoxetine	Martenyi (2007)	12	Uncertain	Uncertain	Uncertain	Yes	Yes
Very high	Paroxetine	GlaxoSmithKline (2001)	51	Uncertain	Uncertain	Uncertain	Yes	Yes
Very high	Paroxetine	Marshall (2001)	37	Uncertain	Uncertain	Uncertain	Yes	Yes
Very high	Paroxetine	Tucker (2000)	39	Uncertain	Uncertain	Uncertain	Yes	Yes
Very high	Sertraline, Citalopram	Tucker (2003)	24	Uncertain	Uncertain	Uncertain	Yes	Yes
Very high	Sertraline, Venlafaxine	Davidson (2006)	34	Uncertain	Uncertain	Uncertain	Yes	Yes
Very high	Venlafaxine	Davidson (2006)	32	Uncertain	Uncertain	Uncertain	Yes	Yes
Very high	Olanzapine	Butterfield (2001)	27	Uncertain	Uncertain	Uncertain	Yes	Yes
Very high	Tiagabine	Connor (2005)	50	Uncertain	Uncertain	Uncertain	Yes	Yes
Very high	Tiagabine	Davidson (2007)	61	Uncertain	Uncertain	Uncertain	Yes	Yes
Very high	Paroxetine	Fani (2009)	44	Uncertain	Uncertain	Uncertain	Yes	Yes
Very high	Paroxetine	Fani (2011)	0	Insufficient	Uncertain	Uncertain	Yes	Yes
Very high	Risperidone	Padala (2006)	0	Uncertain	Uncertain	Uncertain	Yes	Yes
Very high	Risperidone	Reich (2004)	0	Uncertain	Uncertain	Uncertain	Yes	Yes
Very high	Olanzapine	Stein (2002)	10	Uncertain	Uncertain	Uncertain	Yes	Yes
Very high	Risperidone	Bartzokis (2004)	26	Uncertain	Uncertain	Uncertain	Yes	Yes
Very high	Risperidone	Krystal (2011)	17	Uncertain	Uncertain	Uncertain	Yes	Yes
Very high	Risperidone	Rothbaum (2008)	44	Uncertain	Uncertain	Uncertain	Yes	Yes

CPT, cognitive processing therapy; EMDR, eye movement desensitization reprocessing therapy; IE, imaginal exposure; PE, prolonged exposure; PE/CR, prolonged exposure with cognitive restructuring; SIT, stress inoculation training; TF-CBT, trauma-focused cognitive behavioral therapy. All trials with ITT design. All therapy trials unblinded and all medication trials were blinded.

two studies[28,68] were particularly problematic; neither mean total CAPS nor baseline total CAPS were provided. Each required us to estimate CAPS and variance from a nonscaled graph. Several attempts to obtain data from Pfizer and Janssen were unsuccessful, forcing us to use our best estimate. Request for the second negative Pfizer study submitted to the FDA in support of a PTSD indication for sertraline was also unsuccessful. Psychotherapy data requests, in contrast, were returned promptly. Estimates based on FDFS suggested that 12,581 unpublished trials with no effect would be required to reduce controlled findings to statistical insignificance and 51,639 would be required to invalidate pre-/posttreatment findings.

EFFICACY TRENDS

Pre-/Posteffects for Monoagent Pharmacotherapy and Psychotherapy. Pre-/post comparisons across treatments demonstrated large effects for both medications and psychotherapy, which generally increased over time when follow-up data were included (Tables 3 and 4). Pre-/posteffect sizes for TFPs were larger than individual medications and medication groupings (i.e. SSRIs), and was particularly notable 9 months or more after psychotherapy was initiated. Most adjunctive pharmacotherapy studies failed to show benefit.

Efficacy of Monoagent Pharmacotherapy and Psychotherapy versus Controls. When compared with control, effect sizes were uniformly lower than those observed in pre-/postcomparisons. TFPs clearly outperformed individual and medication groupings and nontrauma-focused psychotherapies (non-TFPs) across the diverse group of psychotherapies including PE/IE, PE/CR, CPT, EMDR, and TF-CBT (Tables 3 and 4). PE/IE demonstrated the most consistent effects across time. Addition of cognitive techniques to PE appeared to make it less effective, although outcomes at final follow-up were consistent with PE alone. CPT and TF-CBT also demonstrated moderate-to-large effect sizes across time. EMDR demonstrated an effect size comparable to other trauma-focused therapies, but failed to reach significance at the final time-point, likely due to being underpowered. SIT demonstrated large initial effect with diminishing effects beyond 12 weeks. IPT never achieved significance versus active-control condition. Medications demonstrating large effects were sertraline, venlafaxine, and nefazodone.

Brofaromine, bupropion, citalopram, monoagent and adjunctive divalproex, mirtazapine, risperidone, tiagabine, topiramate, adjunctive aripiprazole, adjunctive guanfacine, and adjunctive olanzapine never achieved significance against control. Paroxetine and fluoxetine both performed poorly against control. Antiepileptics as a class failed to achieve significance. Antipsychotics as a class demonstrated small effects, but this conclusion is limited by the myriad of side effects and high risk of study bias.

Adjunctive Pharmacotherapy. Prazosin was the only medication to demonstrate large effect and only at 14–27 weeks.

Comparison of Guidelines. When studies were grouped by guideline recommendations for first and second-line interventions, guidelines considering psychotherapy superior to medications (Australian, WHO, NICE) outperformed guidelines considering psychotherapy and medications equivalent (ISTSS, APA, VA/DoD) (Table 4). Guidelines recommending both demonstrated lower effects than those restricting first-line interventions to TFPs. ISTSS, APA, and VA/DoD guideline recommendations performed similarly, with the exception of ISTSS recommendations showing larger effects at 14–27 weeks due to inclusion of prazosin as a first-line intervention. Second-line interventions performed poorly across all guidelines.

DISCUSSION

This is the most comprehensive set of meta-analyses comparing psychotherapy and medication efficacy for PTSD, and determining which specific treatments warrant first-line recommendations. Only psychotherapy trials involving active-control conditions were included, mirroring as closely as possible placebo-control conditions used in medication trials.

By every measure considered in this study, TFPs were superior to medications. In general, large reductions in gold-standard outcomes persisted long after psychotherapy completion, whereas continued use of medication was necessary for long-term benefits. These findings are further strengthened considering the requirement for active-control conditions and many advantages medication studies had in participant enrollment, industry involvement and funding, and likelihood of bias toward more positive outcomes in medication trials (e.g. methodological bias or prioritizing recruitment of patients with lower comorbidities or less prior treatment). Our findings suggest that medications largely act by blunting expression of symptoms of PTSD, rather than acting on critical neurobiological mechanisms underlying, for example, extinction of conditioned fear responses, which is a primary target of exposure and cognitive-based TFPs.

Concerning guideline recommendations, our findings suggest PTSD treatment guidelines need revision. Clinicians should be educated on the priority of TFPs, and many changes are required in medication recommendations. For example, our findings suggest patients who experience partial responses to medication treatment should be referred for TFP rather than being prescribed a second medication. Superiority of the broad class of TFPs over SIT or IPT suggests working directly with trauma in some form leads to better outcomes, although this conclusion is limited by the fact that only two studies directly compared non-TFPs with another active-control condition. For individuals too avoidant or autonomically activated to engage in TFP, SIT, sertraline, or

TABLE 3. Comparative table of effect sizes (95% CIs) calculated using CAPS/SPRINT/PSS-I grouped by time

	Monoagent pharmacotherapy					
	8-12 wk pre/post	14–27 wk pre/post	34+ Wk pre/post	8–12 wk vs. control	14–27 wk vs. control	34+ wk vs. Control
Brofaromine	−1.30 (−1.62 to −0.98)		−1.53 (−2.14 to −0.92)	−0.07 (−0.37 to 0.22)		−0.60 (−1.20 to 0.00)
Bupropion	−1.11 (−1.88 to −0.34)			−0.22 (−1.12 to 0.68)		
Citalopram	−1.54 (−2.17 to −0.91)			0.18 (−0.56 to 0.91)		
Divalproex	−0.69 (−1.14 to −0.25)			−0.03 (−0.46 to 0.41)		
Fluoxetine	−1.46 (−1.57 to −1.34)		−2.60 (−2.88 to −2.32)	−0.23 (0.39 to −0.07)		−0.10 (−0.35 to 0.15)
Mirtazapine	−1.23 (−1.97 to −0.50)			−0.81 (−1.65 to 0.02)		
Nefazodone	−0.86 (−1.43 to −0.30)			−1.32 (−2.02 to −0.63)		
Olanzapine	−2.00 (−2.69 to −1.31)			−0.72 (−1.36 to −0.09)		
Paroxetine	−1.35 (−1.49 to −1.22)	−1.67 (−2.47 to −0.86)	Missing data	−0.36 (−0.49 to −0.28)	0.09 (−0.67 to 0.86)	−0.08 (−0.38 to 0.21)
Risperidone	−1.35 (−2.00 to −0.71)			−0.48 (−1.1 to 0.14)		
Sertraline	−1.49 (−1.64 to −1.34)		−2.34 (−2.73 to −1.96)	−0.51 (−0.64 to −0.38)		−1.46 (−1.91 to −1.01)
Tiagabine	−2.47 (−2.81 to −2.12)	−3.28 (−4.33 to −2.23)		0.02 (−0.24 to 0.28)	0.11 (−0.82 to 1.04)	
Topiramate	−2.12 (−2.70 to −1.54)			−0.34 (−0.82 to 0.14)		
Venlafaxine	−3.78 (−4.12 to −3.43)	−2.45 (−2.74 to −2.16)		−1.78 (−2.01 to −1.52)	−0.32 (−0.54 to −0.10)	
			Psychotherapy			
CPT	−6.71 (−7.70 to −5.72)	−7.20 (−8.25 to −6.15)	−8.61 (−9.84 to −7.38)	−1.08 0 (−1.54 to −0.62)	−1.22 (−1.69 to −0.75)	−0.57 (−1.01 to −0.13)
EMDR	−2.06 (−2.72 to −1.41)		−2.12 (−3.28 to −0.96)	−0.87 (−1.42 to −0.32)		−1.12 (−2.41 to 0.16)
IPT	−0.95 (−1.42 to −0.48)	−1.42 (−1.93 to −0.92)		−0.15 (−0.67 to 0.37)	−0.25 (0.77 to 0.27)	
PE/IE	−2.57 (−2.83 to −2.31)	−3.72 (−4.09 to −3.35)	−4.38 (−4.80 to −3.96)	−1.01 (−1.20 to −0.83)	−1.03 (−1.24 to −0.82)	−0.80 (−1.03 to −0.57)
PE/CR	−1.54 (−2.05 to −1.03)	−2.37 (−3.27 to −1.47)	−2.49 (−3.12 to −1.85)	−0.41 (−0.88 to 0.06)	−0.38 (−1.14 to 0.38)	−1.50 (−2.22 to −0.78)
SIT	−2.75 (−4.04 to −1.46)	−1.49 (−2.53 to −0.45)		−1.26 (−2.12 to −0.40)	−0.40 (−1.33 to 0.53)	
TF−CBT	−1.37 (−1.7 to −1.03)	−2.08 (−2.53 to −1.63)	−1.94 (−2.38 to −1.50)	−0.39 (−0.70 to −0.08)	−0.83 (−1.21 to −0.45)	−0.69 (−1.07 to −0.31)
			Adjunctive pharmacotherapy (used with an antldepressant)			
Aripiprazole	−0.97 (−2.08 to 0.13)			−0.03 (−1.08 to 1.02)		
Divalproex	0.08 (−0.63 to 0.8)			0.38 (−0.36 to 1.12)		
Guanfacine	−0.37 (−0.78 to 0.04)			−0.11 (−0.51 to 0.29)		
Olanzapine	−0.8 (−1.71 to 0.11)			−0.8 (−1.73 to 0.14)		
Prazosin	−0.62 (−1.31 to 0.07)	−2.19 (−2.76 to −1.63)		−0.38 (−1.06 to 0.30)	−1.01 (−1.46 to −0.56)	
Risperidone	−1.16 (−1.96 to −0.36)	−1.22 (−1.46 to −0.97)		−0.19 (−0.98 to 0.6)	−0.49 (−0.71 to −0.28)	

Wk, weeks; pre/post, pre-/post-treatment; TF-CBT, trauma-focused cognitive behavioral therapy; CPT, cognitive processing therapy; EMDR, eye movement desensitization reprocessing; IE, imaginal exposure; IPT, interpersonal therapy; PE/CR, prolonged exposure with cognitive restructuring; PE, prolonged exposure; SIT, stress inoculation training.
All pre-/post-treatment changes calculated using initial baseline for treatment group. Red highlighting signifies nonsignificance. Green highlighting signifies a large effect. Nonhighlighted boxes signify small or moderate effect.

TABLE 4. Comparative table of effect sizes (95% CIs) of various groupings

	Sub meta-analyses					
	8–12 wk pre/post	14–27 wk pre/post	34+ wk pre/post	8–12 wk vs. control	14–27 wk vs. control	34+wk vs. control
SSRIs Only	−1.43 (−1.51 to −1.36)	−1.67 (−2.47 to −0.86)	−2.51 (−2.14 to −2.82)	−0.37 (−0.45 to −0.29)	0.90 (−0.67 to 0.86)	−0.30 (−0.47 to −0.12)
SSRIs + SNRIs	−1.54 (−1.61 to −1.46)	−2.36 (−2.63 to −2.09)	−2.51 (−2.14 to −2.82)	−0.50 (−0.58 to −0.43)	−0.29 (−0.50 to −0.08)	−0.30 (−0.47 to −0.12)
All Antiepileptics	−1.65 (−1.89 to −1.42)	−3.28 (−4.33 to −2.23)		−0.03 (−0.22 to 0.17)	0.11 (−0.82 to 1.04)	
All Antipsydiotics	−1.36 (−1.71 to −1.01)	−1.22 (−1.46 to −0.97)		−0.49 (−0.83 to −0.15)	−0.49 (−0.71 to −0.28)	
EMDR+PE/IE + CPT	−2.74 (−2.97 to −2.50)	−4.10 (−4.45 to −3.75)	−4.54 (−4.91 to −4.16)	−1.01 (−1.20 to −0.83)	−1.03 (−1.24 to −0.82)	−0.80 (−1.03 to −0.57)
EMDR + PE/IE + CPT+SIT	−2.74 (−2.97 to −2.51)	−3.84 (−4.17 to −3.51)	−4.54 (−4.91 to −4.16)	−1.02 (−1.18 to −0.85)	−1.03 (−1.22 to −0.84)	−0.80 (−1.03 to −0.57)
All trauma-focused therapies	−2.19 (−2.37 to −2.01)	−3.26 (−3.52 to −3.00)	−3.28 (−3.54 to −3.02)	−0.83 (−0.97 to −0.69)	−0.96 (−1.13 to −0.80)	−0.75 (−0.92 to −0.57)
All nontrauma-focused therapies	−1.16 (−1.60 to −0.72)	−1.43 (−1.89 to −0.98)		−0.45 (−0.89 to −0.01)	−0.29 (−0.74 to 0.17)	
All therapies	−2.04 (−2.21 to −1.88)	−2.80 (−3.03 to −2.58)	−3.28 (−3.54 to −3.02)	−0.79 (−0.93 to −0.66)	−0.90 (−1.06 to −0.74)	−0.79 (−0.96 to −0.62)
All medications	−1.50 (−1.56 to −1.43)	−2.36 (−2.59 to −2.13)	−2.39 (−2.60 to −2.18)	−0.43 (−0.49 to −0.36)	−0.44 (−0.58 to −0.30)	−0.32 (−0.49 to −0.15)
All interventions	−1.54 (−1.60 to −1.48)	−2.17 (−2.30 to −2.03)	−2.75 (−2.91 to −2.58)	−0.50 (−0.56 to −0.44)	−0.64 (−0.75 to −0.54)	−0.55 (−0.67 to −0.43)
	First-line interventions					
APA	−1.54 (−1.61 to −1.47)	−3.11 (−3.36 to −2.86)	−2.84 (−3.01 to −2.67)	−0.48 (−0.55 to −0.41)	−0.91 (−1.08 to −0.75)	−0.52 (−0.65 to −0.40)
Australian, NICE, and WHO	−2.19 (−2.37 to −2.01)	−3.26 (−3.52 to −3.00)	−3.28 (−3.54 to −3.02)	−0.83 (−0.97 to −0.69)	−0.96 (−1.13 to −0.80)	−0.75 (−0.92 to −0.57)
ISTSS	−1.63 (−1.70 to −1.55)	−3.23 (−3.50 to −2.96)	−3.06 (−3.26 to −2.87)	−0.51 (−0.59 to −0.44)	−1.24 (−1.38 to −1.10)	−0.44 (−0.55 to −0.32)
VA/DoD	−1.65 (−1.73 to −1.58)	−2.95 (−3.16 to −2.74)	−3.48 (−3.75 to −3.22)	−0.59 (−0.66 to −0.52)	−0.70 (−0.84 to −0.56)	−0.48 (−0.62 to −0.34)
	Second-line interventions					
APA	−3.32 (−3.63 to −3.01)	−2.45 (−2.74 to −2.16)		−0.51 (−1.16 to 0.15)	−0.32 (−0.54 to −0.10)	
Australian and WHO	−1.43 (−1.51 to −1.36)	−1.67 (−2.47 to −0.86)	−2.51 (−2.14 to −2.82)	−0.37 (−0.45 to −0.29)	0.90 (−0.67 to 0.86)	−0.30 (−0.47 to −0.12)
ISTSS	−1.11 (−1.88 to −0.34)			−0.22 (−1.12 to 0.68)		
NICE	−1.35 (−1.48 to −1.22)	−1.67 (−2.47 to −0.86)		−0.37 (−0.49 to −0.24)	0.09 (−0.67 to 0.86)	−0.08 (−0.38 to 0.21)
VA/DoD	−1.12 (−1.37 to −0.88)	−2.19 (−2.76 to −1.63)	−1.53 (−2.14 to −0.92)	−0.33 (−0.57 to −0.08)	−1.03 (−1.54 to −0.52)	−0.60 (−1.20 to 0.00)

CPT, cognitive processing therapy; EMDR, eye movement desensitization reprocessing; IE, imaginal exposure; PE, prolonged exposure; SIT, stress inoculation training; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; APA, American Psychiatric Association; ISTSS, International Society for Traumatic Stress Studies; NICE, National Institutes for Clinical Excellence; VA/DoD, Veteran's Association/Department of Defence; WHO, World Health Organization.

All pre-/posttreatment changes calculated using initial baseline for treatment group. Red highlighting signifies nonsignificance. Green highlighting signifies a large effect. Nonhighlighted boxes signify small or moderate effect.

venlafaxine appeared to be the most viable alternatives, with caveats noted below.

Our findings contradict conventional wisdom and prescribing patterns, particularly in the United States. Our analysis demonstrated psychotherapy and medication are not equivalent, and not all SSRIs or SNRIs are alike. Our study provides strong evidence against the theory that PTSD involves a seizure-like kindling phenomenon; antiepileptics were noneffective. Our study also provides evidence against common U.S. practice of utilizing antipsychotics in PTSD treatment.

Concerning second-line interventions, our finding that sertraline, venlafaxine, and nefazodone outperformed other medication treatments comes with important caveats. Although sertraline appeared to gain efficacy compared with control over time, this finding was driven by a single industry sponsored trial with selectively reported data and high risk of bias.[28] Pfizer did not provide data from a second sertraline trial that was negative. Although venlafaxine demonstrated a large initial effect, this appeared to diminish beyond 12 weeks. Nefazodone performed strongly in the short term, but incurs the risk of liver failure.

Adjunctive medication treatment showed lack of efficacy, with the exception of prazosin. However, this finding is driven by studies from a single research group with irregular study endpoints (15 and 20 weeks).[63,64] Furthermore, a recent large multicenter trial of prazosin failed to differentiate from placebo in the primary global change score outcome, and PTSD-specific outcomes have still not been published 3 years since completion of recruitment.[78] Most adjunctive trials, including the prazosin studies, involved treatment-resistant PTSD, which is a population on which little research has been done. It is possible that individuals with treatment-resistant PTSD fundamentally differ from those participating in most of our included research studies, although this is currently unclear.

STRENGTHS AND LIMITATIONS

Strengths of this study include the methodological rigor in data abstraction and analyses and presentation of data simultaneously for controlled and pre-/posttreatment effects. We believe excluding medication trials without placebo-controls and psychotherapy studies relying on waitlist or treatment-as-usual controls was critically important in addressing our primary scientific question, although this reduced analyzable studies. Limitations included relatively few medication studies extending beyond 12 weeks (reducing analyzable long-term data), few psychotherapy studies running eight or more sessions using active-control conditions and gold-standard outcome measurements (many studies were excluded), small sample sizes in many studies (widening confidence intervals), differing study designs (increasing heterogeneity), and fundamental differences in bias between medication and psychotherapy studies.

Other limitations included concomitant use of psychotropics in some medication and psychotherapy studies, and incomplete or misleading reporting of data. Concomitant psychotropics could not be controlled for as they were present in nearly every study analyzed. There are also limitations in generalizing clinical trials data to normative clinical populations, in part because selection of study participants is unable to fully account the stepped manner in which PTSD treatments are often utilized.[79] The high rate of prior psychotropic treatment in many clinical trials, for example, could reflect a select subset of the PTSD population that has already received some degree of medical stabilization that has prepared them for engagement in trauma-focused psychotherapy.[79] However, since disease chronicity is lower and proportion of treatment naïve patients higher in industry-sponsored pharmacotherapy trials compared with psychotherapy trials, one would expect biases in the direction favoring medications, rather than the results we observed. Although not systematically analyzed, psychotherapy interventions appeared to outperform medications overall for both treatment naïve samples as well as samples with high rates of prior or current psychotropic treatment.

Our decision to group studies by time may have introduced bias into our analysis, although this is unlikely. A small correlation effect was introduced by using the same control group twice for the multiarmed studies; this method did not impact results as overall data remained unchanged when individual arms or the entire study was excluded. Each study demonstrated its own idiosyncratic inclusion and exclusion criteria, which resulted in unavoidable differences in study populations. Comorbidities, previous treatment, and rates of substance abuse varied. Analyzing these studies as a group presumably minimizes the impact of individual differences. PTSD symptom duration was not reported by most studies and could not be analyzed. Outcome measure standardization resulted in different treatment conclusions for some studies than reported by their authors.

Although these analyses represent the highest level of evidence available for medications, they should not be used to compare effect sizes between different TFPs due to exclusion of psychotherapy trials without active-control conditions, including several important trials that compared different TFPs head-to-head. The very large pre-/posteffects for CPT in this meta-analysis were driven by a single study,[36] and the mildly inferior performance of TF-CBT and EMDR compared with other TFPs is likely an artifact of inclusion/exclusion criteria and small samples. Individual TFPs have generally been found equivalent in head-to-head trials. Due to our study design, we cannot make recommendations for individual TFPs or comment on individual versus group TFP; these remain areas for further study. Additionally, these analyses standardized comparisons across studies using mean effects, and recommendations do not fully address heterogeneity of underlying pathophysiological mechanisms contributing to differences

in individual risk, severity, chronicity, or response to treatment.

CONCLUSIONS

For future research, greater rigor and consistency in design and reporting of outcomes is necessary across studies to prevent biases. Medication trials, in particular, would benefit from rigorous head-to-head comparisons against FDA-indicated medications such as sertraline or paroxetine, or TFPs, in addition to placebo comparisons. Reduction in the influence of industry sponsorship is critical. Well-controlled head-to-head studies of TFPs versus medication are needed, as are studies of combinations of TFP with sertraline or venlafaxine or other medications that could potentially facilitate efficacy of TFPs in relatively refractory patients.

Our findings contradict several aspects of VA/DoD, NICE, ISTSS, WHO, Australian, and APA CPGs for treatment of PTSD, and suggest a need for reconsideration of current guideline recommendations. Guidelines could be improved by focusing on TFPs as the preferred first-line intervention, with sertraline and venlafaxine taking an adjunctive or secondary role. Guidelines should also begin discouraging use of polypharmacy for PTSD. Future research should focus on ways of tailoring treatment to individual patients to improve response and retention rates.

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