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Project Harmony: A Systematic Review and Network Meta-Analysis of Psychotherapy and Pharmacologic Trials for Comorbid Posttraumatic Stress, Alcohol, and Other Drug Use Disorders

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We conducted a systematic review and network meta-analyses (NMA) of psychotherapy and pharmacologic treatments for individuals with co-occurring posttraumatic stress disorder (PTSD) and alcohol or other drug use disorder (AOD). A comprehensive search spanning 1995–2019 yielded a pool of 39 studies for systematic review, including 24 randomized controlled trials for the NMA. Study interventions were grouped by target of treatment (PTSD + AOD, PTSD-only, and AOD-only) and approach (psychotherapy or medication). Standardized mean differences (SMD) from the NMA yielded evidence that at the end of treatment, integrated, trauma-focused therapy for PTSD + AOD was more effective at reducing PTSD symptoms than integrated, non-trauma-focused therapy (SMD = −0.30), AOD-focused psychotherapy (SMD = −0.29), and other control psychotherapies (SMD = −0.43). End-of-treatment alcohol use severity was less for AOD medication compared to placebo medication (SMD = −0.36) and trauma-focused therapy for PTSD + placebo medication (SMD = −0.67), and less for trauma-focused psychotherapy + AOD medication compared to PTSD medication (SMD = −0.53), placebo medication (SMD = −0.50), and trauma-focused psychotherapy + placebo medication (SMD = −0.81). Key limitations include the small number of studies in the NMA for pharmacologic treatments and the lack of demographic diversity apparent in the existing literature. Findings suggest room for new studies that can address limitations in study sample composition, sample sizes, retention, and apply new techniques for conducting comparative effectiveness in PTSD + AOD treatment.

Public Significance Statement

Roughly half of individuals with posttraumatic stress disorder (PTSD) also meet the criteria for an alcohol and other drug use disorder (AOD) with numerous and costly public health consequences. A systematic review and network meta-analysis characterized the evidence base of psychotherapy and pharmacological interventions for PTSD and AOD. Integrated, trauma-focused interventions targeting both PTSD and AOD were more effective at reducing PTSD symptoms than integrated non-trauma-focused, AOD-focused psychotherapy, and other control psychotherapies. AOD medications with and without trauma-focused therapies were more effective in reducing alcohol use severity than placebo controls. Few treatment studies reported adverse events for any intervention outcomes.

Keywords: alcohol and other drug use disorders, systematic review, network meta-analysis, clinical interventions, posttraumatic stress disorder comorbidity

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continued

Scope of the Problem

Roughly half of individuals with posttraumatic stress disorder (PTSD) also meet the criteria for an alcohol and other drug use disorder (AOD; Pietrzak et al., 2011) and national concerns regarding the growing societal costs of mental health and AOD care are rising. So too are questions regarding how to maximize the impact and reach of treatment research findings into clinical care for those most in need. Comorbidity with PTSD is common, difficult to treat, and represents a significant health care burden among those with AOD. Based on the most recent National Epidemiologic Survey on Alcohol and Related Conditions–III, individuals with *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* substance use disorder (SUD) were 1.6 times more likely to have a PTSD diagnosis than those without an SUD (Grant et al., 2016). The odds ratio for comorbidity in veterans with alcohol use disorder (AUD) and PTSD was 2.1 and for other SUD and PTSD was 3.1 (Goldstein et al., 2016; Grant et al., 2016).

Over 2 decades of research document the wide scope of problems associated with comorbid PTSD and AOD (PTSD + AOD), including poorer treatment prognosis (Najt et al., 2011), longer hospital stays for initial treatment and greater likelihood for readmission (Ouimette et al., 1997), lower treatment compliance (Bradizza et al., 2006), higher suicide rates (McCauley et al., 2012; Norman et al., 2018), and less social support for achieving and maintaining recovery goals than patients with AODs without PTSD (McCarthy & Petrakis, 2010). Among both civilian and military populations, PTSD + AODs are among the costliest of public health problems in the United States (Bouchery et al., 2011; Kessler et al., 2001; National Drug Intelligence Center, 2011). Health care costs related to excessive alcohol consumption and PTSD care are rising. In 2018, costs related to excessive consumption rose to $249 billion (Sacks et al., 2015) and health care costs related to PTSD care rose to $232.2 billion where the excess cost of AOD solely due to PTSD was $2.3 billion (Davis et al., 2022). Among veterans, the cost of PTSD care per year per person is $25,684 versus $18,640 per year for civilians (Davis et al., 2022). Despite the staggering health care burden, many questions regarding optimal treatment practices for PTSD + AOD across populations remain unanswered.

Treatment Frameworks

Knowledge in this area has been hampered by the exclusion of people with AOD from many PTSD treatment trials. For example, a recent review examined 156 studies of PTSD treatments and found that over three quarters excluded participants based on AOD (Leeman et al., 2017). However, PTSD and AOD are closely linked, and the mechanisms underlying that connection are likely multifaceted. One of the most prominent theories regarding the nature of the PTSD + AOD connection is the self-medication theory (Hawn et al., 2020; Khantzian, 1997), which postulates that individuals with PTSD use substances to alleviate distressing PTSD symptoms (e.g., to not remember nightmares, relieve negative mood or cognitions, reduce hyperarousal sensations). The self-medication theory is supported by patient perspectives, ecological momentary assessment studies examining the daily relationship between PTSD and AOD symptoms and behaviors, and the temporal order of onset, which most often involves the experience of trauma and onset of PTSD prior to substance use and onset of AOD (Back et al., 2014; Hawn et al., 2020; Simpson et al., 2014).

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Sequential Approach

Furthermore, there is a long-standing controversy and lack of consensus in the field of PTSD + AOD regarding whether it is best to treat one disorder first and then subsequently focus on treating the other disorder (sequential approach), treat only one disorder (single-disorder approach), or treat both co-occurring conditions conjointly in treatment (integrated approach). Early studies on PTSD + AOD treatments often used a sequential approach, where several sessions of AOD skills work were completed prior to initiating trauma work (e.g., Triffleman et al., 1999), likely in part because of limited evidence for offering PTSD treatment to participants still using substances or in early AOD treatment. Proponents of the sequential approach note concerns that addressing PTSD "too soon" in AOD treatment could increase the risk of relapse or excessive substance use (Nass et al., 2019), although this is unsupported by the data obtained over the past 2 decades (e.g., Hien et al., 2015; Norman et al., 2019; Ruglass et al., 2017). Instead, sequential approach proponents may offer single-disorder protocols for each disorder in sequence such as relapse prevention (RP) for AOD followed by Prolonged Exposure (PE) for PTSD. RP (Marlatt & Donovan, 2007) is a psychotherapy for AOD that focuses on preventing relapse in alcohol or substance use by identifying cues that increase risk of relapse and developing coping skills to manage cravings and reduce or avoid alcohol or substance use. Although RP does not target PTSD directly, it has been repeatedly studied in the treatment of PTSD and AOD (Back et al., 2019; Hien et al., 2004; Ruglass et al., 2017; Schäfer et al., 2019). On the other hand, PE exemplifies a single-disorder PTSD treatment that involves psychoeducation regarding PTSD (Foa et al., 2019), imaginal exposure to trauma memories, and in vivo exposure to trauma-related cues. Although PE does not focus on AOD, it has also been studied within PTSD + AOD samples (Foa et al., 2013).

Integrated Approach

Proponents of integrated approaches, such as Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure (COPE; Back et al., 2019) or Seeking Safety (Najavits, 2002), posit that failing to address PTSD and trauma-related symptoms may maintain problematic substance use because AOD and PTSD negatively impact one another. Trauma and substance use are functionally related for many patients (Back et al., 2014) as trauma-related symptoms may serve as potent triggers for substance use (e.g., using alcohol or drugs to forget nightmares or distressing memories). Moreover, proponents of integrated treatment note that it can be difficult for PTSD + AOD patients to effectively regulate their substance use in the face of untreated distressing and debilitating trauma-related symptoms (Back et al., 2009). In addition, by the time most patients engage in treatment, which is usually 5–10 years after symptom onset, both conditions need to be addressed to promote long-term recovery (Back et al., 2009).

Single-Disorder Approach

Recent literature raises the question of whether single-disorder treatments for AOD or PTSD may be sufficient (Simpson et al., 2017). Proponents of single-disorder approach note that in clinical trials investigating trauma-focused and non-trauma-focused integrated treatments compared to manualized AOD treatment, all treatments examined are associated with significant improvement in PTSD and AOD symptoms and suggest that using existing interventions has public health benefits. However, manualized AOD psychotherapies employed by well-trained and supervised clinicians in clinical trials are not the same as AOD psychotherapies applied in real-world clinical settings. Moreover, many patients prefer to address both PTSD and AOD together (Back et al., 2014).

Trauma-Focused Versus Non-Trauma-Focused Therapies

An additional point of historical debate has been whether trauma-focused (e.g., PE, Cognitive Processing Therapy, or eye movement desensitization and reprocessing) or non-trauma-focused (e.g., skills-based interventions such as Seeking Safety) therapies are optimal. Trauma-focused therapies encourage active engagement with and processing of trauma-related memories and meanings (Watkins et al., 2018). This contrasts with non-trauma-focused treatments where the interventions focus on coping skill building with limited processing of the trauma memories and their meanings (Watkins et al., 2018). For example, Seeking Safety (Najavits, 2002) and COPE (Back et al., 2019; Mills et al., 2012) are two frequently studied integrated interventions for PTSD + AOD. However, Seeking Safety focuses exclusively on the present by discussing a range of coping skills for PTSD and AOD symptoms using cognitive behavioral, interpersonal, and case management techniques (Najavits, 2002). Conversely, COPE focuses on the present and past by integrating RP strategies for AOD with PE strategies for PTSD symptoms including trauma memories (Mills et al., 2012). Anecdotal concerns claim that trauma-focused treatments that involve revisiting the trauma memory repeatedly in session (imaginal exposure) and approaching safe but anxiety-provoking situations in real life (in vivo exposure) may be intolerable for patients and increase substance use. Relatedly, some evidence of treatment dropout due to trauma processing has been found (Hoge & Chard, 2018; Najavits, 2015). Previously conducted meta-analyses (e.g., Roberts et al., 2015, 2022; Simpson et al., 2021), however, do not support these concerns and *have* demonstrated that integrated, trauma-focused treatments can be effective in reducing PTSD symptoms and appear to be more effective than non-trauma-focused integrated treatments on PTSD (Norman et al., 2019; Simpson et al., 2021) and alcohol use (Hien et al., 2022) outcomes. In the PTSD-only literature, in contrast to the PTSD–SUD literature on trauma-focused approaches like PE, some of the clients were excluded not only for their substance use but also were less severe cases (i.e., less likely to be diagnosed with complex trauma), which may explain why effect sizes for trauma-focused interventions are generally smaller among PTSD + AOD populations than PTSD-only populations (Forman-Hoffman et al., 2018).

Attrition has also been a factor in recovery outcomes for individuals with PTSD as well as those with PTSD + AOD. This is true for both trauma-focused and non-trauma-focused therapies with completion rates around 50%–75% depending on completion criteria (Roberts et al., 2015, 2022; Simpson et al., 2017). In a recent meta-analysis, Roberts et al. (2022) cited several factors that affect dropout including trauma type, AOD and/or PTSD symptoms severity, heavy use of alcohol or substances during treatment, employment, education, anxiety sensitivity, and early symptom improvement. While recognizing the efficacy of trauma-focused therapies, addressing retention remains a challenge for clinicians.

Hoge and Chard (2018) suggested some options for optimizing the delivery of these interventions such as compressing the time frame for the therapy (Foa et al., 2018), offering attendance incentives, using clinical judgment when using practice guidelines, and considering patient preferences.

However, concerns about potential dropout or relapse have dissuaded some clinicians from adopting and using effective, exposure-based, trauma-focused interventions. From a historical perspective, recognition of the high comorbidity between PTSD and AOD in the late 1990s—about 2 decades after PTSD was first added to the *DSM*—led to the first trials of how to treat this comorbidity. Most early studies were of integrated, non-trauma-focused approaches such as coping skills therapies (e.g., Seeking Safety) or of sequential approaches where AOD was treated first (e.g., Triffleman et al., 1999) because at the time it was widely believed that people using substances could not handle trauma processing (Herman, 2015). For example, Seeking Safety (Najavits, 2002) was published in the early 2000s and was widely adapted and studied, primarily in nonrandomized or very small studies initially (Litt et al., 2019). One of the earliest studies of exposure, trauma-focused therapy first had participants complete 12 weeks of non-trauma-focused work before introducing exposure (Triffleman et al., 1999). Studies of integrated, trauma-focused therapies for PTSD + AOD (where trauma processing and AOD treatment occur in the same time frame) began to emerge with greater frequency after 2010, as evidence countering the notion that focusing on trauma in AOD populations was unsafe (Roberts et al., 2015, 2022; Simpson et al., 2017). This was also a time that trauma-focused treatments in general came to be considered best practice treatments for PTSD (Institute of Medicine, Committee on the Assessment of Ongoing Effects in the Treatment of Posttraumatic Stress Disorder, 2012). By 2015, Roberts and colleagues published the first meta-analysis evaluating the efficacy of trauma-focused treatments relative to controls and non-trauma-focused treatments relative to controls that included eight randomized controlled trials (RCTs) of trauma-focused interventions and nine RCTs of non-trauma-focused interventions (primarily Seeking Safety). When they updated their meta-analysis in 2022, they were able to include 27 studies that were a mix of trauma-focused, non-trauma-focused and studies that evaluated both types of treatments. This increase in a number of trials shows the marked increase of work in this area.

Limits to the Existing Database of Randomized Clinical Trials for PTSD + AOD

Among AOD populations with co-occurring PTSD, findings across psychotherapy and pharmacotherapy trials have yielded some guidance for treatment (Bradizza et al., 2006; McCarthy & Petrakis, 2010; McCauley et al., 2012; Najt et al., 2011; Norman et al., 2018; Ouimette et al., 1997); however, over 50% of patients continue to report clinically impairing PTSD and AOD symptoms at the end of treatment (Bradley et al., 2005; Simpson et al., 2021). Thus, questions remain about the types of treatments that are most effective, who among patients benefit from which interventions, and who continue to struggle after treatment. Furthermore, individuals struggling with PTSD and AOD symptoms often may have longer histories of abuse (including childhood abuse) and be characterized as having complex PTSD (Hien et al., 2020), which can include emotional dysregulation, co-occurring depression, and other complicating factors.

RCT designs can pose challenges for research participation in populations with PTSD + AOD. Often in RCTs, short-term (up to 3 months on average) treatments are tested among individuals who normally have complicated clinical profiles often requiring years, not months of mental health care. Because of such clinical complexity, treatment attendance and attrition patterns (e.g., higher than in single diagnosis studies with patients who do not have AODs) may result in potential biases and lower ratings on internal validity metrics such as "risk of bias [ROB]" measures. To rigorously examine whether interventions can affect clinically significant change in PTSD, many trials have focused exclusively on those who meet the full criteria for PTSD. This decision, however, has excluded the population who meet subthreshold criteria from meta-analytic examination, despite the recognition that those with subthreshold PTSD suffer comparable functional impairments as those with full PTSD (Morgan-López et al., 2020; Norman et al., 2007).

Larger effectiveness trials, with more heterogeneous samples, such as those conducted within the National Institute on Drug Abuse Treatment Clinical Trials Network (https://www.drugabuse.gov/about-nida/organization/cctn/ctn) and more recently grants offered by the Patient-Centered Outcomes Research Institute (https://www.pcori.org/research-results/2019/comparing-two-ways-treat-people-ptsd-and-substance-use-disorder-compass-study) for large comparative effectiveness trials, may offer an important opportunity to address critical clinical questions regarding subgroup effects and possibly reveal limits to existing RCT designs. However, even in these examples, the number of large-scale trials is few due to cost and other barriers. The adoption of integrated treatments for PTSD + AOD has been slow and tends to be limited to approaches that are perceived by clinicians and patients to be more easily implemented and tolerated (e.g., non-trauma-focused treatment) but may have lower efficacy than interventions with larger effect sizes (e.g., trauma-focused treatments) that are perceived by providers to be more complex in terms of training requirements and implementation (e.g., Gielen et al., 2014; Institute of Medicine Committee on Community-Based Drug Treatment et al., 1998). For example, non-trauma-focused integrated treatments do not involve discussion of the traumatic event or processing the trauma memory, which can be "easier" for patients and providers, albeit potentially less effective than trauma-focused treatments (Cook et al., 2020; Nass et al., 2019; Simiola et al., 2019). In contrast, the implementation of trauma-focused interventions, in particular PE therapy, has been harder to adopt by patients who have difficulty discussing the trauma in detail, believe that avoidance is helpful, or do not fully believe the rationale for exposure (Hundt et al., 2015). Some providers are also less comfortable using PE and may not feel sufficiently trained to deliver PE (Simiola et al., 2019).

Limits to the Existing Database of Systematic Reviews and Traditional Meta-Analyses for PTSD + AOD

One of the most widely cited Cochrane meta-analytic reviews conducted by Roberts et al. (2015) examined summary data (a traditional meta-analysis) from 14 published studies and concluded that trauma-focused therapies outperformed non-trauma-focused therapies. This was the first meta-analysis of which we are aware

that used systematic and stringent methods for examining PTSD + AOD treatments (e.g., conducted ROB ratings, including studies that required PTSD and AOD full or subthreshold diagnoses). Earlier reviews included studies that did not require PTSD diagnoses (e.g., Torchalla et al., 2012, which required only trauma history) or did not consider the ROB (e.g., van Dam et al., 2012).

In their traditional meta-analysis, Roberts et al. (2015) noted the low quality of evidence of several PTSD + AOD treatment studies at the time and suggested that questions remained regarding optimal treatment pathways. In a recent update to the 2015 meta-analysis, Roberts et al. (2022) examined data from 27 studies and similarly concluded that trauma-focused approaches outperformed non-trauma-focused approaches for PTSD and AOD but that even with trauma-focused approaches, gains were modest and dropout was high. Although the Cochrane Risk of Bias 2 (ROB2) assessment tool (Higgins et al., 2019) has been widely utilized to assess the ROB and evaluate the strength of the evidence for RCTs in general, its appropriateness for the assessment of psychotherapy RCTs has been called into question (Button & Munafò, 2015). For example, several of the domains assessed in the ROB2 are not feasible to accomplish in psychotherapy trials with this population. Examples include blinding of patients and clinicians to their assigned treatment interventions and achieving low attrition (i.e., complete outcome data) with highly distressed samples in lengthy interventions. This suggests the need to adapt ROB2 standards to more adequately evaluate the ROB differently in these types of trials, which the present review undertook.

One of the larger systematic reviews of 24 studies focused only on psychotherapy RCTs for PTSD + AOD, classifying interventions as exposure-based, addiction-focused, or coping-based (Simpson et al., 2017). The authors concluded that there may be "no wrong doors" for PTSD + AOD treatment suggesting that manualized interventions that target AOD-only might be equally effective as those that target PTSD-only or the disorders in combination. Several limitations with this review were noted, however, including that the available studies varied with regard to their assessment batteries, follow-up lengths, inclusion criteria, quality of the control group utilized, type of model applied (e.g., Norman & Hamblen, 2017), use of blind assessors, and whether clinically significant changes were reported (Simpson et al., 2017).

A more recent meta-analysis of PTSD + AOD treatment conducted by the same team (Simpson et al., 2021) included 28 psychotherapy studies and examined trauma-focused and non-trauma-focused PTSD interventions compared to all comparators and cognitive behavioral AOD treatments. There were small-to-large within-group effect sizes for all active treatments. Only trauma-focused treatments outperformed all other comparators for PTSD outcomes at posttreatment. In that meta-analysis, manualized SUD treatments reduced substance use more than trauma-focused treatments. The authors concluded that trauma-focused, non-trauma-focused, and AOD-only were all sound treatment options.

The most recent systematic review of nine RCTs examining pharmacotherapy for concurrent PTSD and AUD was published in 2017 (Petrakis & Simpson, 2017). Results across studies were contradictory and thus inconclusive. PTSD-only medications were most helpful for PTSD symptoms, and alcohol-only medications were most helpful to reduce alcohol use. The authors concluded that AUD and PTSD medications can safely be prescribed in comorbid populations but that there was no one agent that effectively treated both conditions.

Supplemental Material A summarizes the past 7 years of systematic reviews and traditional meta-analyses. Taken as a whole, the most recent existing systematic reviews and traditional meta-analyses pooling different categories of interventions provide some indication that trauma-focused psychotherapies were superior to non-trauma-focused comparators, as well as AOD-targeted psychotherapies. However, these most recent systematic reviews and meta-analyses did not include all available treatment types (psychotherapeutic and pharmacologic) in a single review and did not include a broader representation of study types, treatment classes, broader diagnostic inclusion criteria, or updated ROB analyses to characterize the existing data to inform the next generation of clinical trials for the field.

Rationale for the Present Systematic Review and Network Meta-Analysis

Thus, an important next step in moving the field forward to identify which treatments seem to be most effective for addressing which domain of symptoms (PTSD or AOD) in a population that has both is a revised and updated systematic review and network meta-analysis (NMA) of extant studies with both psychotherapies and pharmacologic interventions that broaden the inclusion criteria to allow for a fuller range of intervention types and study designs. Our systematic review expands search and study inclusion criteria to allow for (a) agnostic selection of treatment types and symptom targets including psychotherapies *and* psychopharmacologic interventions and their primary outcomes; (b) inclusion of full and subthreshold PTSD allowing for a more ecologically valid participant sample; (c) rigor as established by emphasis on *DSM*-established diagnosis of participants (diagnostic criteria varied in studies based on whether *DSM-IV* or *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* criteria were used), as well as adherence and fidelity monitoring to the treatment protocol; (d) use of the ROB2 that accommodates some of the challenges unique to psychotherapy trials with complex comorbid populations; and (e) trial designs in which a quasi-experimental design or single group pre–post analyses were conducted that increase heterogeneity of the pool of studies by capturing interventions that are in earlier phases of testing (e.g., acceptance and commitment therapy for PTSD + AOD; Meyer et al., 2018) and populations that may not meet all RCT inclusion criteria (e.g., having elevations in suicidal ideation) but nonetheless reflect the population of interest (e.g., chart review of Cognitive Processing Therapy in a Veteran's Hospital; Kaysen et al., 2014).

Our systematic review includes RCTs and open trials with established fidelity, using a narrative synthesis approach to describe important characteristics of the empirical literature base, along with adverse events to inform the field. The NMA conducted with the subgroup of RCTs provides direct and indirect comparative effectiveness estimates of outcomes by important treatment categories; these comparisons provide us with the gaps in the types of available comparators, signals for future RCTs, and other indications to advance our field.

Method

The protocol for this systematic review, narrative synthesis, and NMA was published via PROSPERO (PROSPERO: International

Prospective Register of Systematic Reviews, 2019. CRD42019146678. Available from https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019146678; Hien et al., 2019).

Search Strategy

We conducted an electronic search on May 23, 2019, and August 15, 2019, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews, using the following seven electronic databases from 1995 to the present: Cochrane Depression, Anxiety and Neurosis Group, Clinical Trials Registers Database, MEDLINE, EMBASE, Pubmed, Web of Science, APA PsycInfo, and PTSDpubs. We replicated and combined the search terms, criteria, and parameters of past meta-analyses and systematic reviews (Roberts et al., 2015; Simpson et al., 2017; van Dam et al., 2012). The initial search produced 1,397 results, which were reduced to 776 after duplicates were removed (Figure 1). Supplemental Material B lists all the search terms utilized.

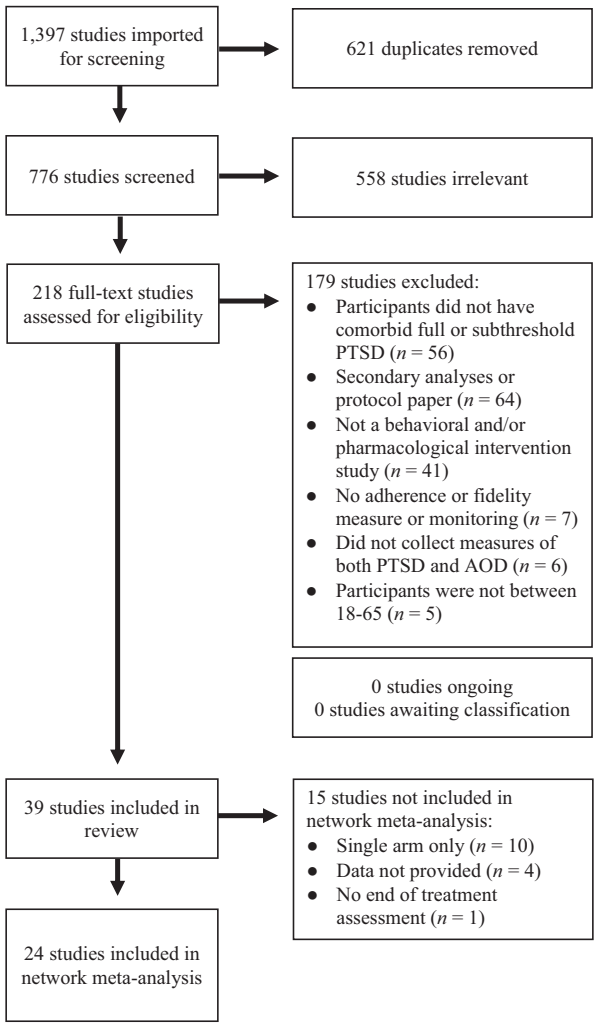
Eligibility Criteria

Eligible studies met the following inclusion criteria:

1. A primary study analysis of a psychotherapy or pharmacological intervention.
2. The study sample had comorbid full or subthreshold PTSD and full AOD. Supplemental Material C provides the definitions of subthreshold PTSD applied by each study.
3. The sample was between 18 and 75 years old.
4. One of the interventions in the study targeted PTSD symptoms (PTSD-only), AOD symptoms (AOD-only), or both.
5. The study collected measures of both PTSD and AOD symptoms, even if the treatment only explicitly targeted one of them.
6. The intervention was monitored for fidelity or adherence.

Studies were selected for inclusion via a two-stage review process. In the first phase, two independent coders conducted title and abstract screening for each initial article to determine eligibility using the aforementioned inclusion criteria. *Covidence*, a web-based software platform, was used as the primary tool to manage and streamline the systematic review process. All levels of screening were conducted on *Covidence*. Articles were not included if they were not empirical treatment studies, studies that did not involve humans, case studies, studies that only provided baseline data drawn from a larger clinical trial, reviews, or secondary data analyses. Coders were instructed to err on the side of overinclusion at this stage, and discrepancies were resolved by consensus. In the second phase, studies eligible for full-text review were assessed for eligibility independently by at least two review authors. Disagreements were solved by group discussion among all experienced raters.

Figure 1
PRISMA Flow Diagram



Note. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PTSD = posttraumatic stress disorder; AOD = alcohol and other drug use.

Data Extraction (Coding)

Data extraction and coding were done by two independent extensively trained coders. We were able to leverage our proximity to the UNC-Chapel Hill/Research Triangle Institute International's Evidence-Based Practice (EPC) center to ensure we carried about best practices around coding. This involved including an independent experienced EPC analyst (Robyn Fortman, who has overseen over 15 systematic reviews for the EPC) to oversee the reliability process for two coders from Rutgers University (a different institution from the EPC). Coders participated in a 2-week training. Mrs. Fortman trained and oversaw all coding activities and served as an independent arbiter for individual reliability and consensus coding. Initial reliability estimates were the desired 80%. Additional training took place by Mrs. Fortman until individual coders were above 80%. Consensus

coding reliability was over 80%. Extracted data for included studies were inserted into a preformatted Excel table and included *study details* (e.g., design/methodology, setting, inclusion/exclusion criteria, recruitment and study completion rates, sample size, PTSD, and AOD measures used); *study population and participant demographics and baseline characteristics* (e.g., race/ethnicity, gender, socioeconomic status, trauma type, substance type), *intervention and control condition* details (intervention name and type, adherence/fidelity, and differential session attendance); *outcomes* (e.g., PTSD and AOD constructs measured, measurement time points; improvement/worsening/no change in PTSD and AOD symptoms, statistically significant differences between the intervention and control/comparator groups, study-related adverse events); and *information for assessment of the ROB*. Discrepancies were identified and resolved through discussion (with a third rater where necessary).

Systematic Review and Narrative Synthesis

In alignment with this study's goals to identify and characterize the existing literature on psychotherapy and medication-based PTSD + AOD interventions, a narrative synthesis was conducted. Study intervention characteristics (e.g., age range, predominant gender and racial/ethnic groups, treatment type) were tabulated across the set of included studies. Study interventions were further grouped according to the treatment target (i.e., PTSD + AOD, PTSD-only, AOD-only) and approach (i.e., psychotherapy, medication) in order to further qualitatively compare the populations, interventions, and comparators across studies.

ROB

The Cochrane ROB 2.0 was used to assess for bias in the included studies. All nine coders were also trained by Dr. Leila Kahwati, consultant from Research Triangle Institute International-University of North Carolina at Chapel Hill's EPC. Before the ROB coding, the team reached a consensus on how each domain was to be judged. The team adapted criteria to better standardize the ratings with input from Dr. Kahwati. We considered how and whether the investigator accounted for missing data in their analyses to determine whether this category was coded as low or high ROB (Dziura et al., 2013). Finally, the ROB domain for blinding/concealment was rated as low if there was evidence of independent assessor evaluation of study outcomes regardless of whether the clinicians or participants were blind to intervention condition. Each study was assessed by two independent reviewers, and any differences in ratings were resolved through discussion. Bias was assessed as judgment (low, some concerns, or high) for each fixed set of individual domains. The five domains assessed were as follows: (a) randomization and allocation concealment, (b) masking and deviations from intended intervention, (c) missing outcome data, (d) measurement of the outcome, and (e) reporting bias. A series of content-driven prompts (e.g., use of unvalidated and/or unreliable scales; selective outcome reporting of only statistically significant results and omitting nonsignificant results) guided coders to judge elements of the clinical trials that are relevant to ROB. Each domain has between three and seven signaling questions to help you think through the ROB for that domain. The overall domain bias rating was determined based on answers to the level of concerns on these domains. For example, ratings of medium or high ROB within individual domains raise the level of concern for overall ROB.

NMA

Standard pairwise meta-analyses are limited in the context of PTSD + AOD because a large variety of interventions exist, many of which have not been directly compared in randomized clinical trials. NMA overcomes this limitation by synthesizing both direct and indirect evidence from a network of connected interventions (Caldwell et al., 2005; Lu & Ades, 2004). Direct evidence is estimated from trials in which common intervention pairs have been compared (e.g., A vs. B), and indirect evidence is estimated from trials that have at least one intervention in common (e.g., A vs. C and B vs. C allows for indirect comparison of A vs. B). An initial step in NMA is assessment of network connectivity; when a common comparator does not exist between some interventions, these may be examined in fully connected subnetworks. In addition to considering the ROB and cross-study heterogeneity in populations, interventions, and/or outcome measurement among studies included in the NMA, assessing the validity of results includes tests of effect size heterogeneity, effect size inconsistency, small study effects, indirectness, and imprecision (each discussed in greater detail below; Nikolakopoulou et al., 2020). For readers who wish to learn more about NMA, we recommend a freely available primer (Mavridis et al., 2015) as well as several published reviews; tutorials; and discussions of the methodology, application, and interpretation of NMA (Caldwell, 2014; Cipriani et al., 2013; Nikolakopoulou et al., 2014; Salanti, 2012; Sullivan et al., 2014).

Studies from the systematic review were included in the NMA if they used a randomized design with at least two arms. Of the 39 studies included in the systematic review, 24 RCTs were eligible for inclusion in the NMA (Figure 1). Continuous or discrete PTSD outcomes based on assessment of the frequency and/or severity of PTSD symptoms were selected. Most of the studies (83.3%) had clinician-assessed PTSD outcomes (20 total: 16 Clinician-Administered PTSD Scale, Weathers et al., 1999; three PTSD Symptom Scale–Interview for *Diagnostic and Statistical Manual of Mental Disorders, fifth edition*, Foa et al., 1993; one Posttraumatic Diagnostic Scale, Foa et al., 2016) and the remainder (16.7%) had self-reported PTSD outcomes (four total: three PTSD Checklist, Weathers et al., 2013; one PTSD Scale–Self-Report, Foa et al., 1993). Alcohol use outcomes were selected because they were available for all studies, whereas drug or drug and alcohol combined outcomes were only available for a minority of studies. For each study, a single continuous or discrete outcome indicating alcohol use severity was selected; when more than one was available, the primary or first reported outcome was selected. Most of the studies (83.3%) had self-reported alcohol outcomes. The most common self-reported alcohol outcome selected across studies was days of use (10), followed by percent days of use (four), drinks per drinking day (two), alcohol problems (one; e.g., feeling unhappy because of one's drinking or not eating well because of one's drinking; Pearson et al., 2019), days of heavy use (one), percent days of heavy use (one), and standard drinks per week (one). A clinician-assessed alcohol outcome (e.g., the Addiction Severity Index composite score for alcohol) was available for four studies. Effect sizes for PTSD and alcohol use outcomes were calculated as SMD by extracting means, standard deviations, and sample sizes from the publications. Each outcome was extracted by two independent raters, and disagreements were resolved by

consensus. When the necessary statistics were not present in the study publication, we used data provided by the study authors. Although trials varied in the number and timing of follow-up assessments, all trials included an assessment at the end of treatment; therefore, this time point was selected for the NMA to reduce heterogeneity.

Treatments were grouped into categories based on treatment target (PTSD, AOD, or PTSD and AOD), psychotherapy treatment type (integrated or nonintegrated; trauma-focused or non-trauma-focused), and approach (psychotherapy, medication, or combination; Hien, Fitzpatrick, et al., 2021; Roberts et al., 2015). Petrakis et al. (2006) included three arms with different AOD medications; in order to include all data in the NMA, these three arms were pooled together within the study and compared to the placebo arm. We excluded two arms in Petrakis et al. (2012) that administered the antidepressant desipramine because it did not meet our criteria for PTSD or AOD medication; however, the other two arms (paroxetine + naltrexone and paroxetine + placebo) were included in the NMA.

Analyses were conducted in R, Version 4.0.2 (R Core Team, 2020) using the *netmeta* package (Version 2.0; Rücker et al., 2015). The *pairwise* function was used to transform extracted data to contrasts between treatment categories. Random-effects models were estimated that incorporated both direct evidence from pairwise comparisons between treatment categories and indirect evidence from the complete network of treatment categories. For each pairwise comparison between treatment categories, two estimates were derived: one that integrated direct and indirect evidence from all studies in the network, and another based only on the direct evidence from studies that included comparisons between treatment categories. We refer to these estimates as NMA and direct, respectively, but note that both types of estimates used the between-study variance from the NMA. To evaluate study heterogeneity, we calculated τ^2 (the between-study variance, where 0.04, 0.09, and 0.16 can be interpreted as low, moderate, and high heterogeneity, respectively), and to evaluate inconsistency, we calculated I^2 (the amount of cross-study variation attributable to heterogeneity, where 25%, 50%, and 75% can be interpreted as low, moderate, and high, respectively; Higgins et al., 2003). We also tested differences within- and between designs with Cochran's Q statistic (nonsignificant results indicate a lack of evidence of heterogeneity and inconsistency, respectively; Borenstein et al., 2021). Small study effects were assessed using comparison-adjusted funnel plots and Egger's linear regression test of funnel plot asymmetry (Egger et al., 1997). In addition to reporting significant results, we reported comparisons in which imprecision was reflected in the estimates. Specifically, we considered imprecision to be a concern when an estimated effect had confidence intervals that included −0.50 and 0.50 because this range suggests that there may be a medium effect size difference favoring either treatment category in the comparison. We considered indirectness, or the relevance of studies included in the network, and conducted sensitivity analyses to examine the impact of results when studies and/or treatment arms that may have been indirectly relevant were removed from the NMA. In addition to the NMA, we conducted pairwise meta-analyses of all direct comparisons; in contrast to the direct estimates from the NMA, these were based on unadjusted standard errors, and the variance of between-study heterogeneity was allowed to be different across comparisons.

Transparency and Openness

The systematic review was registered with PROSPERO 2019 CRD42019146678. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols checklist when preparing the protocol, and we followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines for the final report. The meta-analytic data and code to reproduce the NMA and supporting analyses are available on the Open Science Framework repository (https://osf.io/qh4ew/).

Results

Systematic Review

Thirty-nine studies were included in the systematic review, including 28 RCTs, 10 pilot studies, and one chart review (Figure 1). Tables 1–3 summarize the information extracted from the 39 studies included in the systematic review. Supplemental Material D provides a narrative description of study characteristics and outcomes. Supplemental Material E summarizes our review of the exclusion criteria across 33 of the 39 studies (exclusion data were missing for six studies). Most of the studies ($k = 23$) excluded participants because of psychosis or severe mental illness or psychiatric hospitalization or suicide/violence risk. Seventeen studies ruled out cognitive or brain impairment. Fourteen studies excluded participants who were either on an unstable medication regimen and/or were taking medications or participating in psychotherapies that were targeting the symptoms being treated by the approach being tested. Medical problems ($k = 15$ studies) and alcohol or other substance use or dependence ($k = 4$ PTSD-only studies) were also exclusion criteria. Another category we labeled *other* captured exclusion criteria such as limited English proficiency ($k = 5$) and pregnancy/lactation/childbearing age but not on contraceptive ($k = 6$). Most studies required meeting full diagnostic criteria for PTSD for inclusion ($k = 26$). However, 13 studies had inclusion criteria that involved meeting full or subthreshold diagnostic criteria for PTSD, and the definition of subthreshold varied across studies (Supplemental Material C). All included studies had study participants that met full diagnostic criteria for an AOD.

Interventions and Comparators

Most studies ($k = 30$, 77%) had elements to actively target both PTSD and AOD, and the majority of reviewed studies consisted of psychotherapy-only interventions ($k = 27$, 69%; Table 1). Psychotherapy interventions included trauma-focused and non-trauma-focused, and integrated (targeting both PTSD + AOD) or nonintegrated (targeting PTSD-only or AOD-only) treatment models. Trauma-focused models commonly included COPE (integrated; $k = 5$) and PE (nonintegrated; $k = 4$). Non-trauma-focused models commonly included Seeking Safety (integrated; $k = 11$). Some interventions were cognitive behavioral and utilized both exposure and coping skills-based elements (e.g., substance dependence posttraumatic stress disorder therapy). Studies assessed three combined medication-only interventions: desipramine and naltrexone, paroxetine and naltrexone, and aprepitant (Kwako et al., 2015; Petrakis et al., 2012). Four studies assessed a combination of medication and therapy, varenicline with PE, Seeking Safety with sertraline, and PE with naltrexone (Foa et al., 2013, 2017; Hien et al., 2015).

Table 1
Description of the 39 Studies Included in Systematic Review

Descriptor	*N*	%
Study design		
RCTs	28	71.79
Pilot studies	10	25.64
Other	1	2.56
Sample characteristics		
Gender		
Female only	8	20.51
Male only	2	5.13
Mixed gender	29	74.36
Predominantly male	19	48.72
Race/ethnicity		
Predominately White	24	61.54
Predominately Black/African American	6	15.38
Mixed sample	2	5.13
Other	2	5.13
Not reported	5	12.82
Military status		
Veteran only	11	28.21
Civilian/mixed	5	12.82
Not reported	25	64.10
Primary intervention type		
Combination medication + therapy	4	10.26
Therapy only	27	69.23
Medication only	8	20.51
Medication type		
Aprepitant	1	2.56
Desipramine	1	2.56
Disulfiram	1	2.56
Naltrexone	4	10.26
N-Acetylcysteine (NAC)	1	2.56
Paroxetine	1	2.56
Prazosin	2	5.13
Sertraline	3	7.69
Topiramate	1	2.56
Varenicline	1	2.56
Integrated treatments		
Acceptance and commitment therapy (ACT)	1	2.56
Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure (COPE)	5	12.82
Cognitive behavioral therapy (CBT) for PTSD/AOD (integrated CBT)	3	7.69
Creating Change (CC)	2	5.13
Seeking Safety (SS)	12	30.77
Substance dependence posttraumatic stress disorder therapy (SDPT)	1	2.56
PTSD-only treatments		
CBT for PTSD	1	2.56
Cognitive Processing Therapy (CPT)	2	5.13
Prolonged Exposure (PE) and modified PE (mPE)	3	7.69
Structured writing therapy (SWT)	1	2.56
Trauma Adaptive Recovery Group Education and Therapy (TARGET)	1	2.56
AOD-only treatments		
CBT for AOD	2	5.13
Individual Addiction Counseling (IAC)	1	2.56
Relapse prevention (RP)	3	7.69
Treatment developer as study author		
No	21	53.85
Yes	18	46.15
Training for study providers		
Master's-level clinicians	2	5.13
Doctoral-level clinicians	4	10.26
Mixed levels of training	30	76.92
Not reported	3	7.69
The study described training needed for the delivery of intervention		
No		
Yes	11	28.21
Not reported	3	7.69
Treatment dropout ≥ 50		
No	31	79.49
Yes	5	12.82
Not reported	3	7.69
Study-related adverse events		
Reported yes	7	17.95
One event	1	2.56
Three events	1	2.56
Five events	2	5.13
Seven events	1	2.56
Eight or more events	2	5.13
None/not reported	32	82.05

Note. PTSD = posttraumatic stress disorder; AOD = alcohol or other drug use disorder.

Nine studies were of interventions that targeted PTSD, and PTSD-only interventions were either behavioral therapy only ($k = 5$) or medication only ($k = 4$). Studies included RCTs on structured writing therapy for PTSD and culturally adapted Cognitive Processing Therapy among Native American/Indigenous women (Coffey et al., 2016; Pearson et al., 2019; van Dam et al., 2013). Other designs were a pilot study on cognitive behavioral therapy for PTSD and a Department of Veterans Affairs-based chart review of Cognitive Processing Therapy (Kaysen et al., 2014; McGovern et al., 2009). Trauma-focused medication trials were on prazosin and sertraline (Brady et al., 1995, 2005; Petrakis et al., 2016; Simpson et al., 2015).

One study had an active intervention that targeted AOD with naltrexone and disulfiram (Petrakis et al., 2006). Medications targeted for AOD included N-acetylcysteine, varenicline, naltrexone, disulfiram, and topiramate. Nearly, all studies ($k = 32$, 82%) included a comparator arm, including behavioral control conditions (e.g., Healthy Lifestyle Sessions, Women's Health Education). AOD-focused treatment arms included RP ($k = 4$), supportive counseling or addiction counseling ($k = 2$), cognitive behavioral therapy for AUD ($k = 1$), and placebo medication ($k = 10$). Finally, nine studies included nonspecific treatment as usual (control) conditions, which ranged broadly within and across studies. Active comparison conditions were typically an active treatment, which could be psychosocial or pharmacological or both. Placebo refers to all pill placebos. In the studies with pill placebos (e.g., Back et al., 2019; Batki et al., 2014; Petrakis et al., 2012, 2016; Simpson et al., 2015), each was paired against medications that were frontline medications for AOD (e.g., prazosin, naltrexone, N-acetylcysteine). For instance, a community-based study reported that participants in the control condition attended self-help meetings; engaged in psychotherapy outpatient treatment for psychological, drug, or alcohol problems; or received medication (Hien et al., 2004). Other studies also described control participants engaging in intensive outpatient services (McGovern et al., 2015) and individual or group therapy for PTSD or AUD (Capone et al., 2018; Schäfer et al., 2019). Five studies combined treatment as usual with the active intervention being tested, including a broad range of psychotherapy

Table 2
PICOTS Summary and Description of Studies Included in the Systematic Review (K = 39)

	Population				Planned outcomes		Timing			
Citation	*N*	Demographics (overall sample)	Intervention	Comparison	PTSD	AOD	Duration	Sessions and/or dose	Setting	Focus
Randomized clinical trials										
Back et al. (2019)[a]	81	Gender: 90% M Race: 60% W, 37% B, 3% H Age: 40.4 (10.7) Veterans: 100% Trauma: Mixed	COPE	RP	CAPS severity and subscale scores, PCL-M, PTSD diagnostic remission	TLFB, ASI, breathalyzer, UDS	12 weeks	12	Outpatient	Int.
Batki et al. (2014)[a]	30	Gender: 93% M Race: 53% W, 23% B, 10% O Age: NR Veterans: 100% Trauma: Combat	Topiramate	Placebo	PCL	TLFB (PDD, PHDD, DDD, drinks per week)	12 weeks	300 mg/day	Outpatient	Int.
Brady et al. (2005)[a]	94	Gender: 54% M Race: NR Age: 18–65 Veterans: NR Trauma: Mixed, noncombat	Sertraline + CBT for alcohol use	Placebo + CBT for alcohol use	NR	TLFB (PDD, drinks per day, DDD, HDD), ASI, OCDS	12 weeks	150 mg/day, 12 sessions	NR	Int.
Capone et al. (2018)	44	Gender: 95% M Race: 85% W, 14% H, 7% B Age: NR Veterans: 100% Trauma: Combat, sexual assault	ICBT	TAU	CAPS severity and subscale scores	TLFB (PDD, PDU, PDA), ASI, toxicology	12 weeks	12	Outpatient	Int.
Coffey et al. (2016)	126	Gender: 54% M Race: 79% W, 19% B Age: 34 (NR) Veterans: NR Trauma: Civilian, mixed	mPE alone or mPE + MET	Healthy lifestyle sessions	IES	TLFB (PDA), the Alcohol Craving Questionnaire–Now (ACQ-Now)	8 weeks	10–16	Residential treatment facility	PTSD
Foa et al. (2013)[a]	165	Gender: 66% M Race: 64% B, 30% W, 4% H Age: NR Veterans: NR Trauma: Mixed	PE + naltrexone, PE + placebo, naltrexone + supportive counseling	Placebo + supportive counseling (BRENDA)	PSS-I	TLFB (PDD), PACS	18 weeks	100 mg/day; 12 weeks weekly sessions, 6 weeks biweekly sessions	Outpatient	Int., AOD, PTSD
Foa et al. (2017)	142	Gender: 61% M Race: 74% B, 23% W, 7% H Age: 42.7 (9.9) Veterans: NR Trauma: Mixed	VARCC + PE	VARCC only	PSS-I	TLFB smoking status, toxicology, 7-day PPA	12 weeks	1 mg/day, 12 sessions	Outpatient	Int.

(*table continues*)

Table 2 (*continued*)

Citation	Population		Intervention	Comparison	Planned outcomes		Timing		Setting	Focus
	N	Demographics (overall sample)			PTSD	AOD	Duration	Sessions and/or dose		
Frisman et al. (2008)	234	Gender: 61% F Race: 56% W, 24% B, 10% H Age: 38 (NR) Veterans: NR Trauma: NR	TARGET + trauma-sensitive usual care	Trauma-sensitive usual care	PTCI	GAIN (substance use frequency, % drinking to intoxication, % using any drug, % abusing drugs/ alcohol)	12 months	34–49	Outpatient	PTSD
Hien et al. (2004)[a]	115	Gender: 100% F Race: 42% B, 37% W, 20% H Age: NR Veterans: NR Trauma: NR	SS or RP	Community care	CAPS, IES, clinical global impression (CGI)	SUI composite score, CGI	12 weeks	24	NR	Int., AOD
Hien et al. (2009)[a]	353	Gender: 100% F Race: 46% W, 34% B, 13% O Age: 39.2 (9.3) Veterans: NR Trauma: Mixed	SS	WHE	PSS-SR, CAPS	7-day abstinence from drug or alcohol use; days using drugs/ alcohol	6 weeks	12	Outpatient, multi-site, community	Int.
Hien et al. (2015)	69	Gender: 81% F Race: 59% B, 23% W, 10% H Age: 18–65 Veterans: NR Trauma: Mixed	SS + Sertraline	SS + placebo	CAPS	TLFB (DDD, HDD), abstinence, breathalyzer	12 weeks	200 mg/day, 12 sessions	Outpatient, community	Int.
Kwako et al. (2015)	60	Gender: 45% F Race: 43% W Age: 40.8 (NR) Veterans: NR Trauma: Mixed, combat/civilian	Aprepitant	Placebo	CAPS, PSS-I	Alcohol Urge Questionnaire	3 weeks	125 mg/day	Inpatient	Int.
McGovern et al. (2015)[a]	221	Gender: 60% F Race: 96% W Age: 35.30 (10.42) Veterans: NR Trauma: Assault	ICBT or IAC	Standard care	CAPS	ASI, TLFB, toxicology	8–12 weeks	8–12	Outpatient	Int., AOD
Mills et al. (2012)[a]	103	Gender: 64% F Race: 87% O (Australian) Age: 33.7 (7.9) Veterans: NR Trauma: Mixed	COPE + TAU	TAU	CAPS	CIDI	13 weeks	13	Outpatient	Int.
Myers et al. (2015)[a]	40	Gender: 100% F Race: 60% W, 25% H, 12% B Age: 42.2 (10.5) Veterans: None Trauma: NR	SS	TSF	CAPS	TLFB (PDD)	12 weeks	25	Outpatient	Int.

(*table continues*)

Table 2 (*continued*)

Citation	Population		Intervention	Comparison	Planned outcomes		Timing		Setting	Focus
	N	Demographics (overall sample)			PTSD	AOD	Duration	Sessions and/or dose		
Najavits et al. (2018)	88	Gender: 73% M Race: 60% W, 30% B, 4% H Age: 48.8 (10.7) Veterans: 100% Trauma: Mixed	CC	SS	PTSD diagnosis, PCL, WAS, Trauma-Related Guilt Inventory	ASI, BSAS	17 weeks	17	Outpatient	Int.
Norman et al. (2019)[a]	186	Gender: 90% M Race: 78% W, 16% B, 6% O Age: 41.6 (12.6) Veterans: 100% Trauma: Mixed	Cope (I-PE)	SS (I-CS)	CAPS	TLFB (PHDD)	12–16 weeks	12–16	Outpatient	Int.
Pearson et al. (2019)	73	Gender: 100% F Race: 100% Native American Age: 18–60 Veterans: NR Trauma: NR	Adapted CPT	Wait-list	PSS-SR	SIP, alcohol use frequency, AOD diagnosis	6 weeks	NR	Outpatient	PTSD
Petrakis et al. (2006)	254	Gender: 97% M Race: 90% W, 17% B, 5% H Age: NR Veterans: 100% Trauma: NR	Naltrexone and disulfiram (alone or combined)	Placebo	CAPS	TLFB, GGT, OCDS	12 weeks	250 mg/day disulfiram, 50 mg/day naltrexone	Outpatient	AOD
Petrakis et al. (2012)[a]	88	Gender: 90% M Race: 75% W, 21% B, 3% O Age: 47.1 (8.9) Veterans: 92% Trauma: Combat	Paroxetine + naltrexone or desipramine + naltrexone	Paroxetine + placebo or desipramine + placebo	CAPS	TLFB (DDD, PHDD, drinks per week), abstinence	12 weeks	40 mg/day paroxetine, 200 mg/day desipramine, 50 mg/day naltrexone	Outpatient	Int.
Petrakis et al. (2016)[a]	96	Gender: 93% M Race: 81% W, 15% B, 3% O Age: 21–65 Veterans: 100% Trauma: NR	Prazosin	Placebo	CAPS	TLFB (HDD, DDD), GGT, abstinence, OCDS	13 weeks	16 mg/day	Outpatient	PTSD
Ruglass et al. (2017)	110	Gender: 63% M Race: 59% B, 19% H, 19% W Age: 44.8 (NR) Veterans: NR Trauma: Mixed	COPE or RP	Active monitoring	CAPS, MPSS-SR	ASI, SUI	12 weeks	12	Community	Int., AOD
Sannibale et al. (2013)	62	Gender: 53% F Race: NR Age: 41.2 (11.9) Veterans: NR Trauma: Mixed	Integrated therapy	Alcohol support	CAPS severity and change (reduction $\geq$ 30 points), PDS, PTSD diagnosis	TLFB (DDD, PDA), SDS, SIP, AUD diagnosis	12 weeks	12	Outpatient	Int.

(*table continues*)

Table 2 (*continued*)

Citation	Population		Intervention	Comparison	Planned outcomes		Timing		Setting	Focus
	N	Demographics (overall sample)			PTSD	AOD	Duration	Sessions and/or dose		
Schäfer et al. (2019)	343	Gender: 100% F Race: NR Age: 40.9 (11.4) Veterans: N/A Trauma: Mixed	SS + TAU or RP + TAU	TAU	PSS-I, PDS	ASI	16 weeks	14	Outpatient	Int., AOD
Simpson et al. (2015)[a]	54	Gender: 37% F Race: 40% W, 40% B, 20% O Age: 43.3 (NR) Veterans: 30% Trauma: Mixed	Prazosin	Matched placebo	PSS-I	Change in PDD, PHDD (Form-42)	6 weeks	4 mg each morning and afternoon and 8 mg before bed	Outpatient	PTSD
Triffleman (2000)	19	Gender: 53% F Race: 63% W, 32% B, 5% H Age: 34.6 (5.6) Veterans: NR Trauma: NR	SDPT	TSF	CAPS severity and number of symptoms, PTSD diagnosis	ASI drug composite scores, number of days using substances	20 weeks	40	Outpatient	Int.
van Dam et al. (2013)[a]	36	Gender: 68% M Race: 68% W, 11% B, 12% O Age: 42.3 (9.0) Veterans: NR Trauma: NR	SWT + TAU	TAU	PDS, PTSD diagnosis	TLFB, AOD diagnosis	12 weeks	SWT + TAU: 10 weekly sessions	Outpatient	PTSD
Zlotnick et al. (2009)	49	Gender: 100% F Race: 47% W, 33% B, 14% H Age: 34.6 (7.4) Veterans: NR Trauma: Mixed	SS + TAU	TAU	CAPS, Trauma Symptom Checklist, PTSD diagnosis	ASI, abstinence	SS: 6–8 weeks	25 SS group sessions; 12 individual booster sessions	Prison	Int.
Pilot studies										
Back et al. (2016)[a]	35	Gender: 96% M Race: 70% B, 30% W Age: 49.0 (8.2) Veterans: 100% Trauma: Mixed, combat/civilian	N-acetylcysteine (NAC) + CBT for AOD	Placebo + CBT for AOD	CAPS, PCL-M	TLFB, craving (visual analog scale)	8 weeks	2,400 mg/day, group sessions 5 days/ week	Outpatient	Int.
Brady et al. (1995)	9	Gender: 54% F Race: NR Age: 36.7 (NR) Veterans: NR Trauma: Abuse, accident	Sertraline	None	IES, MPSS-SR	TLFB	12 weeks	200 mg/day	Outpatient	Int.
McGovern et al. (2009)	23	Gender: 91% F Race: 100% W Age: 34 (8.8) Veterans: NR Trauma: Mixed	CBT for PTSD	None	CAPS	TLFB, ASI, urine toxicology, breathalyzer	NR	10.5	Outpatient	PTSD

(*table continues*)

Table 2 (*continued*)

Citation	Population		Intervention	Comparison	Planned outcomes		Timing		Setting	Focus
	N	Demographics (overall sample)			PTSD	AOD	Duration	Sessions and/or dose		
Meyer et al. (2018)	43	Gender: 88% M Race: 57% B, 31% W, 21% H Age: 45.26 (8.6) Veterans: 100% Trauma: Mixed, civilian/combat	Acceptance and Commitment Therapy	None	CAPS, PCL-5	SCID-5 (AUD symptom count), TLFB, DAST	12 weeks	12	Outpatient	Int.
Najavits et al. (1998)	27	Gender: 100% F Race: 88% W, 12% B Age: 35.9 (8.5) Veterans: NR Trauma: Mixed	SS	None	MPSS-SR, TSC-40	Weekly SUI, ASI, urinalysis, breath alcohol	12 weeks	24	Outpatient	Int,
Najavits et al. (2005)	5	Gender: 100% M Race: 100% W Age: 37.6 (5.6) Veterans: NR Trauma: Mixed	SS + exposure therapy-revised	None	TSC-40, WAS	ASI	20 weeks	30	Outpatient	Int.
Najavits and Johnson (2014)	9	Gender: 57% M Race: 29% B, 29% W, 29% O, 14% H Age: 45.1 (10.5) Veterans: NR Trauma: Mixed	CC	None	PCL-C, TSC-40, WAS	ASI, BSAS	17–24 weeks	17	Outpatient	Int.
Norman et al. (2010)	14	Gender: 100% M Race: NR Age: NR Veterans: 100% Trauma: Combat	SS	None	PCL-M	AUDIT, DAST	10 weeks	10	Outpatient	Int.
Persson et al. (2017)	22	Gender: 100% F Race: 67% W, 22% B, 11% O Age: 45.5 (10.4) Veterans: N/A Trauma: Mixed	COPE	None	CAPS, PCL-C	TLFB (PHDD), AUDIT, PACS	12 weeks	12	Outpatient	Int.
Zlotnick et al. (2003)	18	Gender: 100% F Race: 67% W, 17% O, 11% B Age: 32 (NR) Veterans: NR Trauma: Physical and sexual abuse	SS + TAU	None	CAPS	ASI, SCID, urinalysis	12 weeks	24	Prison	Int.
Other design (chart review)										
Kaysen et al. (2014)	536	Gender: 90% M Race: 82% W	CPT	None	CAPS, PCL-S	None	12 weeks	12	Outpatient	PTSD

(*table continues*)

Table 2 (*continued*)

Citation	Population		Intervention	Comparison	Planned outcomes		Timing		Setting	Focus
	N	Demographics (overall sample)			PTSD	AOD	Duration	Sessions and/or dose		
		15% B, 3% O Age: 44.6 (14.5) Veterans: 100% Trauma: Mixed, civilian/combat								

Note. Age is reported as *M* (*SD*) or range. PICOTS = Patient Population, Intervention, Comparator, Outcome, Timing, and Setting; W = White or European American; B = Black or African American; H = Hispanic/Latino; O = other; F = female; M = male; N/A = not applicable; NR = not reported; BRENDA = Biopsychosocial evaluation, Report to the patient on assessment, Empathic understanding of the patient's situation, Needs collaboratively identified by the patient and treatment provider, Direct advice to the patient on how to meet those needs, Assess reaction of the patient to advice and adjust as necessary for best care; CBT = cognitive behavioral therapy; CPT = Cognitive Processing Therapy; COPE = Concurrent Treatment of PTSD and AODs using Prolonged Exposure; CC = Creating Change; IAC = Individual Addiction Counseling; ICBT = integrated cognitive behavioral therapy; I-PE = integrated Prolonged Exposure (i.e., COPE); I-CS = Integrated Coping Skills (i.e., Seeking Safety); MET = motivational enhancement therapy; mPE = modified Prolonged Exposure; RP = relapse prevention; SDPT = Substance Dependency Posttraumatic Stress Disorder Therapy; SS = Seeking Safety; SWT = Structural Writing Therapy; TARGET = Trauma Adaptive Recovery Group Education and Therapy; TAU = treatment as usual; TSF = 12-Step Facilitation; VARCC = concurrent varenicline; WHE = Women's Health Education; ASI = Addiction Severity Index; AUD = alcohol use disorder; AUDIT = Alcohol Use Disorders Identification Test; BSAS = Beliefs about Substance Abuse Scale; CAPS = Clinician-Administered PTSD Scale; CIDI = Composite International Diagnostic Interview; DDD = Drinks per drinking day; GAIN = Global Appraisal of Individual Needs; GGT = gamma-glutamyl transferase; HDD = heavy drinking days; IES = Impact of Events Scale; MPSS-R = Modified PTSD Symptom Scale; OCDS = Obsessive Compulsive Drinking Scale; PACS = Penn Alcohol Craving Scale; PCL-C = PTSD Checklist–Civilian; PCL-M = PTSD Checklist–Military; PCL-S = PTSD Checklist–Specific; PTCI = Posttraumatic Cognitions Inventory; PDA = percent days abstinent; PDD = percent days drinking; PDS = Posttraumatic Stress Diagnostic Scale; PDU = percent days using drugs; PHDD = percentage heavy drinking days; PPA = point prevalence abstinence; PSS-I = The PTSD Symptom Scale–Interview; PSS-SR = PTSD Symptom Scale–Self-Report; PTSD = posttraumatic stress disorder; SCID-5 = Structured Clinical Interview for *DSM-5*; DAST = Drug Abuse Screening Test; SDS = Severity of Dependence Questionnaire; SIP = Short Inventory of Problems (Alcohol); SUI = Substance Use Inventory; TLFB = Timeline Followback; UDS = urine drug screen; WAS = World Assumptions Scale; TSC-40 = Trauma Symptom Checklist–40; Int. = integrated (PTSD + AOD), PTSD = PTSD-only, AOD = AOD-only; AOD = alcohol or other drug use disorder; MPSS-SR = Modified PTSD Symptom Scale–Self-Report; PCL-5 = PTSD Checklist for *DSM-5*; N/A = not applicable; PE = Prolonged Exposure; *DSM-5* = *Diagnostic and Statistical Manual of Mental Disorders, fifth edition*.

[a] Data necessary for conducting the meta-analyses that was not included in the original publication were provided by study authors.

and medication-based treatments paired with COPE (Mills et al., 2012), Seeking Safety (Zlotnick et al., 2003, 2009), structured writing therapy (van Dam et al., 2013), and Trauma Adaptive Recovery Group Education and Therapy (Frisman et al., 2008).

ROB

Figure 2 shows a summary of the ROB ratings for all included trials. Overall, RCTs were rated as the lowest ROB, especially in the "missing outcome data" domain, as data were collected for each randomized participant and/or the study had a prespecified analysis plan. Sixty percent (17/28) of the RCT studies were rated as low ROB overall, all other 39% (11/28) were coded with some concerns overall. None were coded as high ROB. The RCTs that were coded as some concerns overall were all coded as "some concerns" on "randomization and allocation concealment." As displayed in Figure 2, 100% of RCTs had low ROB in the domain of missing outcome data," and most (71.4%, 20/28) had low ROB on "randomization and allocation concealment." In contrast, other study designs such as pilot studies and chart reviews were rated with the highest ROB across most domains. Sixty percent (6/10) of the pilot studies were rated as high ROB overall, 30% were rated as "some concerns" overall, and only one study (10%) was rated as low ROB overall. The chart review study was rated as high ROB overall. Almost all (90%) pilot studies were rated as high ROB on "randomization and allocated concealment": The one chart review was rated as "some concerns." Among the 11 total pilot and chart review studies, four were rated as high ROB on "reporting bias."

NMA Results

Among the 24 trials included in the NMA, treatments were grouped into 12 categories based on their approach and putative targets (Table 4), resulting in 37 pairwise comparisons spanning two subnetworks for each outcome (Supplemental Material F). Throughout the tables and figures, treatment categories that are integrated and/or trauma-focused are labeled as such. If a category does *not* have the label "integrated," then it is nonintegrated; similarly, if a category does *not* have the label "trauma-focused," then it is non-trauma-focused. For example, the category "psychotherapy" only includes nonintegrated, non-trauma-focused treatments.

Figure 3A shows the subnetwork of 16 studies that included 1,240 participants with PTSD outcomes (1,207 with alcohol outcomes) and 24 pairwise comparisons between six treatment categories, and Figure 3B shows the subnetwork of eight studies that included 426 participants with PTSD outcomes (489 with alcohol outcomes) and 13 pairwise comparisons between the remaining six treatment categories. Subnetworks exist when there are groups of treatment categories that share no direct or indirect comparisons. In the first subnetwork, treatment categories were linked through direct or indirect comparisons with a psychotherapy control, whereas in the second subnetwork, treatment categories were linked through direct or indirect comparisons with a placebo control; henceforth, we refer to these subnetworks as the psychotherapy control NMA and placebo control NMA. Results from each subnetwork (NMA and direct estimates) are summarized by outcome below.

Table 3

Attendance, Adverse Events, and Impacts on PTSD + AOD Clinical Outcomes Among Studies in the Systematic Review (K = 39)

Citation	Intervention	Comparison	Significant improvement in outcomes[a]		Treatment dropout (50% or greater)[b]	Study-related adverse events
			PTSD	AOD		
Randomized clinical trials						
Back et al. (2019)[c]	COPE	RP	Improvement in PTSD symptom severity (int., $d = 2.68$; comp., $d = 1.60$)	Improvement in alcohol and substance use (int., $d = .046$; comp., $d = .20$)	No	None
Batki et al. (2014)[c]	Topiramate	Placebo	Improvement in PTSD symptom severity ($d = .90$)	Improvement in PDD, PHDD, DDD, alcohol craving, and drinks per week ($d = 1.57$)	No	Four medical events and one psychiatric event (all comp. group)
Brady et al. (2005)[c]	Sertraline + CBT for alcohol use	Placebo + CBT for alcohol use	No	Improvement in alcohol use (int., $d = 1.44$; comp., $d = 1.63$)	No	NR
Capone et al. (2018)[c]	ICBT	TAU	No	No	Yes	NR
Coffey et al. (2016)	mPE alone or mPE + MET	Healthy lifestyle sessions	Improvement in PTSD symptoms (int. groups compared to control)	No	No	NR
Foa et al. (2013)[c]	PE + naltrexone, PE + placebo, naltrexone + supportive counseling	Placebo + supportive counseling (BRENDA)	No	Improvement in PDD ($d = .82$)	No	None
Foa et al. (2017)	VARCC + PE	VARCC only	Improvement in PTSD symptom severity	No	No	Five psychiatric events (groups not specified)
Frisman et al. (2008)	TARGET + trauma-sensitive usual care	Trauma-sensitive usual care	No	No	Yes	NR
Hien et al. (2004)[c]	SS or RP	Community care	Improvement in PTSD symptom severity (SS group, $d = .71$; RP group, $d = .89$)	Improvement in substance use severity (SS group, $d = .28$; RP group, $d = .67$)	No	NR
Hien et al. (2009)[c]	SS	WHE	Improvement in PTSD symptom severity (int., $d = 1.39$; comp., $d = 1.46$)	No	No	NR
Hien et al. (2015)[c]	SS + sertraline	SS + placebo	Improvement in PTSD symptom frequency and intensity ($d = 1.20$)	No	No	None
Kwako et al. (2015)	Aprepitant	Placebo	No	No	No	None
McGovern et al. (2015)[c]	ICBT or IAC	Standard care	No	Improvement in drug use and toxicology reports (ICBT group, $d = .30$)	No	None
Mills et al. (2012)[c]	COPE + TAU	TAU	Improvement in PTSD symptom severity (int., $d = 1.14$; comp., $d = .87$)	Improvement in number of drug classes used and severity of dependence (int., $d = .23$; comp., $d = .26$)	No	None
Myers et al. (2015)[c]	SS	TSF	NR	NR	Yes	NR

(*table continues*)

Table 3 (*continued*)

Citation	Intervention	Comparison	Significant improvement in outcomes[a]		Treatment dropout (50% or greater)[b]	Study-related adverse events
			PTSD	AOD		
Najavits et al. (2018)[c]	CC	SS	Improvement in PTSD severity and remission (int., $d = .30$; comp., $d = .27$)	Improvement in ASI alcohol and drug composite scores (int., $d = .23$; comp. = 1.10)	NR	None
Norman et al. (2019)[c]	Cope (I-PE)	SS (I-CS)	Improvement in PTSD symptom severity ($d = 1.39$)	Improvement in PHDD (int., $d = .70$; comp., $d = .70$)	No	None
Pearson et al. (2019)[c]	Adapted CPT	Wait-list	Improvement in PTSD symptom severity ($d = 1.28$)	Improvement in alcohol use ($d = 1.42$)	Yes	NR
Petrakis et al. (2006)[c]	Naltrexone and disulfiram (alone or combined)	Placebo	Improvement in PTSD symptom severity (for participants with PTSD and/or no alcohol use and for disulfiram group compared to naltrexone group)	Improvement in alcohol use (entire sample), improvement in drinking days per week and consecutive days abstinent (int. groups)	NR	Three medical events (two int. and one comp.) and one psychiatric event (comp. group)
Petrakis et al. (2012)[c]	Paroxetine + naltrexone or desipramine + naltrexone	Paroxetine + placebo or desipramine + placebo	PTSD symptom severity and clusters (int. [paroxetine + naltrexone], $d = .27$; comp. [paroxetine + placebo], $d = 1.84$)	Improvement in PHDD, DDD, drinks per week (desipramine groups); craving (naltrexone groups)	No	Five medical events (two int. and three comp.) and three psychiatric events (one int. and two comp.)
Petrakis et al. (2016)[c]	Prazosin	Placebo	No	No	No	None
Ruglass et al. (2017)[c]	COPE or RP	Active monitoring	Improvement in PTSD severity (COPE group, $d = .87$; RP group, $d = 1.10$)	Improvement in days of primary substance used (int. RP group, $d = 1.38$)	No	None
Sannibale et al. (2013)[c]	Integrated therapy	Alcohol support	Improvement in PTSD symptom severity ($d = 1.00$)	No	No	NR
Schäfer et al. (2019)[c]	SS + TAU or RP + TAU	TAU	Improvement in PTSD symptom severity (int., SS group, $d = .22$; RP group, $d = .29$; comp., $d = .28$)	No	No	Four psychiatric events (group not specified)
Simpson et al. (2015)[c]	Prazosin	Matched placebo	No	Improvement in PDD and PHDD ($d = 1.34$)	No	Not specified
Triffleman (2000)	SDPT	TSF	No	No	Yes	NR
van Dam et al. (2013)[c]	SWT + TAU	TAU	Improvement in PTSD severity ($d = 1.15$) and remission	Improvement in abstinence (int., $d = 1.38$; comp., $d = .54$)	No	NR
Zlotnick et al. (2009)[c]	SS + TAU	TAU	Improvement in PTSD symptom severity (int., $d = .72$; comp., $d = .56$)	Improvement in ASI drug composite score (int., $d = .47$; comp., $d = .52$)	No	NR

(*table continues*)

Table 3 (*continued*)

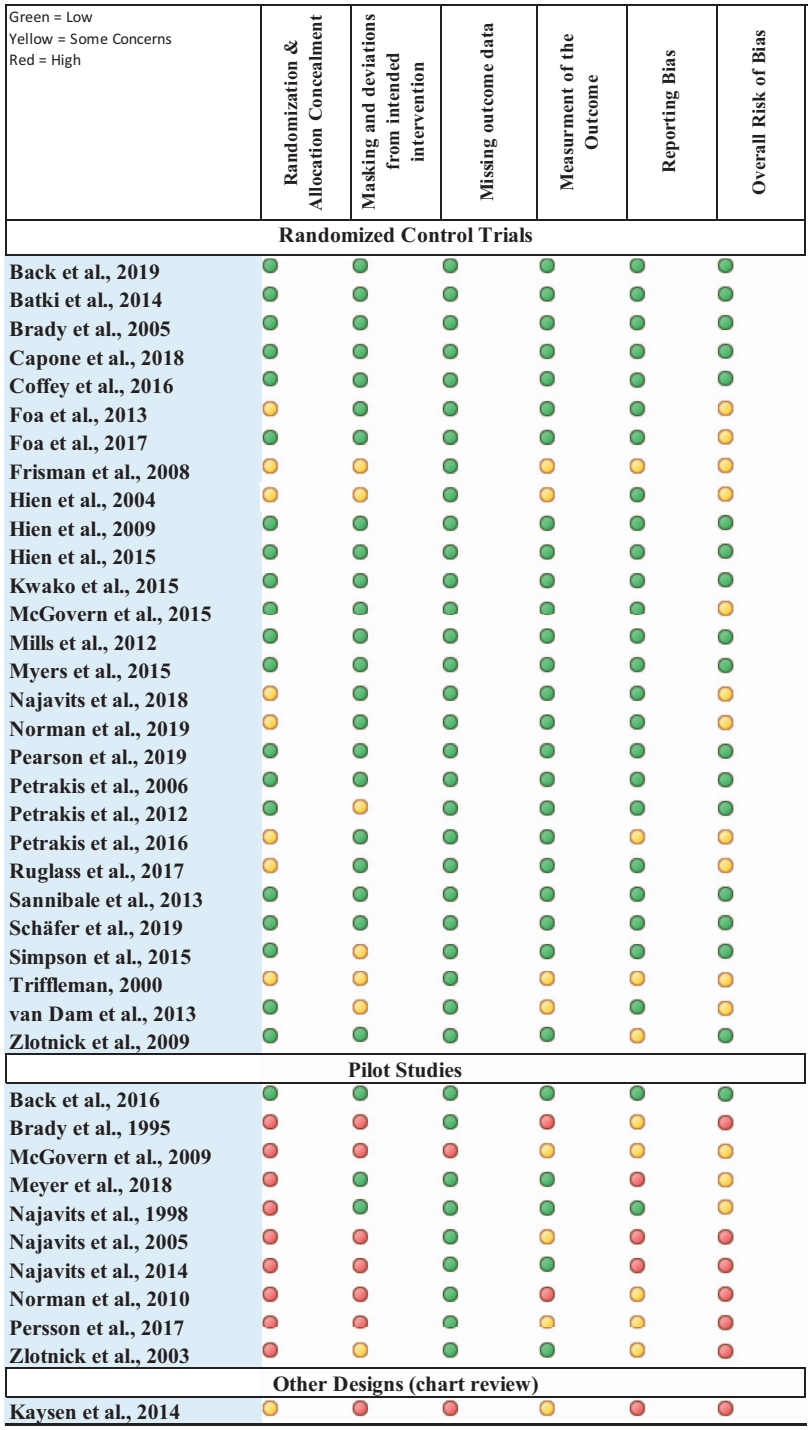
Citation	Intervention	Comparison	Significant improvement in outcomes[a]		Treatment dropout (50% or greater)[b]	Study-related adverse events
			PTSD	AOD		
Pilot studies						
Back et al. (2016)[c]	NAC + CBT for AOD	Placebo + CBT for AOD	Improvement in PTSD symptoms (d = 1.20)	No	No	One medical event (group not specified)
Brady et al. (1995)	Sertraline	None	No	No	NR	NR
McGovern et al. (2009)	CBT for PTSD	None	Improvement in PTSD symptom severity, symptom clusters, and PTSD diagnosis	No	No	NR
Meyer et al. (2018)	Acceptance and commitment therapy	None	No	No	No	None
Najavits et al. (1998)	SS	None	Improvement in PTSD trauma-related symptoms and beliefs	Improvement in abstinence	No	None
Najavits et al. (2005)	SS + exposure therapy-revised	None	Improvement in trauma-related symptoms and beliefs	Improvement in drug use	No	NR
Najavits and Johnson (2014)	CC	None	Improvement in trauma-related symptoms and beliefs	Improvement in substance use beliefs	No	None
Norman et al. (2010)	SS	None	Improvement in PTSD symptom severity (for four of nine participants)	No	No	None
Persson et al. (2017)	COPE	None	Improvement in PTSD symptom severity	Improvement in alcohol use, PHDD, alcohol craving, and severity of alcohol dependence	No	None
Zlotnick et al. (2003)	SS + TAU	None	Improvement in PTSD symptom severity	Improvement in drug and alcohol use (6-weeks postrelease is first reported follow-up time point)	No	NR
Other design (chart review)						
Kaysen et al. (2014)	CPT	None	Improvement in PTSD symptom severity	No	No	NR

Note. Int. = intervention arm; comp. = comparison arm; N/A = not applicable; NR = not reported; ASI = Addiction Severity Index; DDD = drinks per drinking day; PTSD = posttraumatic stress disorder; ICBT = integrated cognitive behavioral therapy; PDD = percent drinking days; PHDD = percent heavy drinking days; RP = relapse prevention; AOD = alcohol or other drug use disorder; COPE = Concurrent Treatment of PTSD and AODs using Prolonged Exposure; CBT = cognitive behavioral therapy; TAU = treatment as usual; MET = motivational enhancement therapy; mPE = modified Prolonged Exposure; PE = Prolonged Exposure; BRENDA = Biopsychosocial evaluation, Report to the patient on assessment, Empathic understanding of the patient's situation, Needs collaboratively identified by the patient and treatment provider, Direct advice to the patient on how to meet those needs, Assess reaction of the patient to advice and adjust as necessary for best care; VARCC = concurrent varenicline; TARGET = Trauma Adaptive Recovery Group Education and Therapy; SS = Seeking Safety; WHE = Women's Health Education; IAC = Individual Addiction Counseling; TSF = 12-Step Facilitation; CC = Creating Change; I-PE = integrated Prolonged Exposure (i.e., COPE); I-CS = Integrated Coping Skills (i.e., Seeking Safety); CPT = Cognitive Processing Therapy; SDPT = Substance Dependency Posttraumatic Stress Disorder Therapy; SWT = Structural Writing Therapy.

[a] Significant outcomes represent pre–post comparisons for the intervention group(s), unless otherwise noted. [b] Less than 50% of sessions attended across all treatment arms. Table 3 lists the total number of sessions available. [c] Indicates studies included in the network meta-analysis.

Figure 2

Risk of Bias (ROB) Ratings



PTSD Outcomes

Figure 4A shows results from the psychotherapy control NMA of PTSD outcomes at the end of treatment. Among the NMA estimates, PTSD severity was significantly less for integrated and trauma-focused (PTSD + AOD) interventions compared to (a) psychotherapy (AOD), SMD = −0.29, 95% CI [−0.56, −0.03], $z = -2.16$, $p = .031$; (b) psychotherapy (control), SMD = −0.43, 95% CI [−0.68, −0.18], $z = -3.34$, $p < .001$; and (c) integrated (PTSD + AOD), SMD = −0.30, 95% CI [−0.56, −0.04], $z = -2.29$, $p = .022$. Although the direct estimates for these three comparisons were not statistically significant, the effect sizes of the direct estimates were comparable to (and fell

Table 4
Treatment Categories for Studies Included in the Network Meta-Analyses (K = 24)

Treatment category (target)	Included treatments (first author, year)	Intervention description
Psychotherapy (AOD)	1. Addiction counseling (McGovern et al., 2015)	8–12 weekly manualized sessions that focus on initiating AOD treatment, attaining and maintaining abstinence, and recovering from AOD. Derived from individual drug counseling from NIDA Cocaine Collaborative Study and 12-Step Facilitation from NIAAA Project MATCH (Mercer & Woody, 1999; Nowinski et al., 1994).
	2. CBT for alcohol use disorder (Sannibale et al., 2013)	12 weekly manualized sessions focusing on AOD based on Project MATCH CBT manual and motivational interventions for AOD (Kadden et al., 1994; Miller et al., 2004). Early sessions target motivation using motivational interviewing strategies as well as goal setting and treatment rationale. Interventions also focus on identifying situations, thoughts, and feelings that increase risk for alcohol or substance use; identifying coping plans to prevent and respond to lapses in abstinence; and targeting negative moods. Relapse prevention is emphasized throughout.
	3. Relapse prevention (Back et al., 2019; Hien et al., 2004; Ruglass et al., 2017; Schäfer et al., 2019)	Manualized AOD intervention (number of sessions varies depending on study) focused on preventing relapses in substance or alcohol use. Interventions focus on identifying situations, thoughts, and feelings that increase risk for alcohol or substance use; identifying skills that help manage cravings and reduce substance use in risky situations; and identifying coping plans to prevent and respond to lapses in abstinence (Marlatt & Donovan, 2007).
Psychotherapy (control)	1. Active monitoring (Ruglass et al., 2017)	Weekly meetings with research assistants over intervention period that involves completing self-report measures, urine toxicology, alcohol breathalyzers, and broad assessments of health and safety.
	2. Facilitated 12-step (Myers et al., 2015)	Twice weekly sessions for 12 weeks of therapist-guided support group that is derived from 12-Step Facilitation from NIAAA Project MATCH (Mercer & Woody, 1999; Nowinski et al., 1994) and focuses on promoting abstinence. Groups cover four core topics from 12-Step Facilitation (introductions, acceptance, surrender, and getting active), as well as six elective topics (e.g., enabling). Sessions involve reviewing readings, didactic material, and discussing behaviors that promote recovery.
	3. Standard care or treatment as usual (Capone et al., 2018; Hien et al., 2004; McGovern et al., 2015; Mills et al., 2012; Schäfer et al., 2019; van Dam et al., 2013; Zlotnick et al., 2009)	Allowing participants to access any interventions they would typically access (e.g., community AOD treatment) or continuing in the usual care they receive in the treatment setting that the study occurs in (e.g., in the Veterans Administration Hospital or an AOD inpatient unit). Number of sessions varies depending on study.
	4. Wait-list (Pearson et al., 2019)	Waiting for intervention and completing study measurements.
	5. Women's Health Education (Hien et al., 2009)	Twice per week manualized group psychoeducational health curriculum occurring for 6 weeks. Focuses on topics such as the female body and sexual health and pregnancy. Groups involved review of homework exercises, introducing new topics, exercises to facilitate discussion regarding group topics, and setting homework goals.
Integrated non-trauma-focused (PTSD and AOD)	1. Integrated CBT (Capone et al., 2018; McGovern et al., 2015)	8–12 weekly manualized sessions focusing on both PTSD and AOD reduction with three core components: Psychoeducation; mindfulness-based relaxation for negative mood and cravings; and cognitive restructuring.
	2. Seeking Safety (Hien et al., 2004, 2009, 2015; Myers et al., 2015; Najavits et al., 2018; Norman et al., 2019; Schäfer et al., 2019; Zlotnick et al., 2009)	Typically, 25 weekly manualized sessions focusing on PTSD and AOD through a range of topics that focus on teaching a range of coping skills using cognitive behavioral, interpersonal, and case management

(*table continues*)

Table 4 (*continued*)

Treatment category (target)	Included treatments (first author, year)	Intervention description
		techniques. Sessions involve an assessment of use of coping skills and unhealthy behavior, presentation of an inspirational quote, relating didactic material to participant's experience, and check out/homework assignment (Najavits, 2002).
Integrated + PTSD medication (PTSD and AOD)	1. Seeking Safety + sertraline (Hien et al., 2015)	A selective serotonin reuptake inhibitor + Seeking Safety. Participants started on 50 mg daily and increased dosage up to 200 mg daily over 2 weeks.
Integrated trauma-focused (PTSD and AOD)	1. CBT for PTSD and alcohol use disorder (Sannibale et al., 2013)	12 weekly manualized sessions that combine CBT for alcohol use disorder with an exposure-based CBT for PTSD and cognitive restructuring for PTSD-related cognitions. Sessions involve CBT for alcohol use disorder elements (e.g., increasing motivation, identifying high-risk situations for alcohol use) as well as psychoeducation on PTSD and its interaction with AUD; imaginal and in vivo trauma-related exposure; and identifying and challenging trauma-related cognitions.
	2. COPE (Back et al., 2019; Mills et al., 2012; Norman et al., 2019; Ruglass et al., 2017)	12–13 weekly manualized sessions that involve increasing motivation for AOD reduction; CBT strategies for AOD (including relapse prevention strategies); psychoeducation regarding PTSD and its interaction with AOD; in vivo and imaginal trauma-related exposure; and identifying and challenging trauma-related cognitions.
	3. Creating Change (Najavits et al., 2018)	17 weekly manualized sessions that introduce new topics which simultaneously address PTSD and AOD. Format is similar to Seeking Safety, but trauma and AOD memories may be actively addressed and participants are given the choice regarding whether to focus on their past (Creating Change) or present (Seeking Safety). Sessions involve an assessment of use of coping skills and unhealthy behavior, presentation of an inspirational quote, relating didactic material to participant's experience, and check out/homework assignment (Najavits, 2014).
	4. Structured writing therapy for PTSD (van Dam et al., 2013)	10 weekly manualized sessions added onto treatment as usual that involve psychoeducation regarding the intersection between PTSD and AOD, written trauma exposure, and cognitive restructuring of trauma-related beliefs. Two "flexible sessions" wherein the therapist and participant could decide what therapy content to revisit also occur (van Dam et al., 2013).
Medication (AOD)	1. N-acetylcysteine (Back et al., 2016)	Antioxidant medication thought to stabilize synaptic transmission of glutamate. Starting dose was 1,200 mg twice per day.
	2. Naltrexone (Foa et al., 2013)	Opiate antagonist with starting dose of 50 mg per day and a target dose of 100 mg per day.
	3. Topiramate (Batki et al., 2014)	GABA agonist and inhibitor of a subtype of glutamate. Starting dose was 25 mg nightly, with 100 mg in the morning and 200 mg in the evening as the target dose.
	4. Naltrexone, disulfiram, or both (Petrakis et al., 2006)	See above for naltrexone description. Disulfram target dose was 250 mg/day.
Medication (PTSD)	1. Paroxetine + placebo (Petrakis et al., 2012)	Paroxetine is a selective serotonin reuptake inhibitor. Target dose was 40 mg per day. Placebo is a sham medication with no active therapeutic ingredients.
	2. Prazosin (Petrakis et al., 2016; Simpson et al., 2015)	α-1 adrenergic receptor antagonist. Starting dose was 1 mg every evening. Target dose was 4 mg every morning, 4 mg every evening, and 8 mg every night.
	3. Sertraline (Brady et al., 2005)	Selective serotonin reuptake inhibitor. Participants started on 50 mg daily and increased dosage up to 150 mg daily.
Medication (PTSD and AOD)	1. Paroxetine + naltrexone (Petrakis et al., 2012)	See above for description.
Placebo (control)		See above for description.

(*table continues*)

Table 4 (*continued*)

Treatment category (target)	Included treatments (first author, year)	Intervention description
	2. Placebo (Back et al., 2016; Batki et al., 2014; Brady et al., 2005; Foa et al., 2013; Petrakis et al., 2006, 2016; Simpson et al., 2015)	
Trauma-focused (PTSD)	1. Cognitive Processing Therapy (Pearson et al., 2019)	Cognitive Processing Therapy is a manualized PTSD intervention that utilizes cognitive restructuring to systematically target unhelpful beliefs that maintain PTSD over time. Some versions of Cognitive Processing Therapy involve writing and rereading a written account of the traumatic event (Resick et al., 2016). In Pearson et al. (2019), it was adapted for use in the American Indian and Alaska Native community and was 13 sessions over 6 weeks, with added content on relationships, safe sex practices, and substance use.
Trauma-focused + AOD medication (PTSD and AOD)	1. Prolonged Exposure + naltrexone (Foa et al., 2013)	12 weekly manualized sessions followed by 6 biweekly sessions that focus on psychoeducation regarding PTSD, imaginal exposure to trauma memories, discussing reactions to exposure practices, and in vivo exposure to safe trauma-related cues. See above for naltrexone.
Trauma-focused + placebo (PTSD)	1. Prolonged Exposure + placebo (Foa et al., 2013)	See above for descriptions.
Studies excluded from network meta-analyses	1. Single-arm studies (Brady et al., 1995; Kaysen et al., 2014; McGovern et al., 2009; Meyer et al., 2018; Najavits et al., 1998, 2005, 2014; Norman et al., 2010; Persson et al., 2017; Zlotnick et al., 2003) 2. Did not have an end of treatment assessment (Frisman et al., 2008) 3. Data needed for analyses not available (Coffey et al., 2016; Foa et al., 2017; Kwako et al., 2015; Triffleman, 2000)	

Note. AOD = alcohol or other drug use disorder; NIDA = National Institute on Drug Abuse; NIAAA = National Institute on Alcohol Abuse and Alcoholism; MATCH = Matching Alcoholism Treatments to Client Heterogeneity; CBT = cognitive behavioral therapy; PTSD = posttraumatic stress disorder; AUD = alcohol use disorder; COPE = Concurrent Treatment of PTSD and AODs using Prolonged Exposure; GABA = gamma-aminobutyric acid.

within the 95% CI of) the NMA estimates (Figure 4A). No other NMA or direct estimates reached statistical significance. There was no significant evidence of heterogeneity within designs ($Q = 12.72$, $df = 10$, $p = .240$) or inconsistency between designs ($Q = 6.19$, $df = 5$, $p = .288$). Between-study heterogeneity was low ($\tau^2 = 0.015$), and inconsistency was low ($I^2 = 20.7\%$, 95% CI [0.0%, 56.2%]). There was no significant evidence of small study effects (Supplemental Figure S1A). Imprecision met the criterion of concern (i.e., 95% CI that overlapped with −0.50 and 0.50) in the estimates for integrated (PTSD + AOD) versus trauma-focused (PTSD); integrated + PTSD medication (PTSD + AOD) versus integrated and trauma-focused (PTSD + AOD); integrated + PTSD medication (PTSD + AOD) versus trauma-focused (PTSD); integrated and trauma-focused (PTSD + AOD) versus trauma-focused (PTSD); and psychotherapy (AOD) versus trauma-focused (PTSD); see Figure 4A. Figure 5A summarizes results from the pairwise meta-analyses of studies included in the psychotherapy control NMA of PTSD outcomes.

Figure 4B shows results from the placebo control NMA of PTSD outcomes at the end of treatment. No NMA or direct estimates reached statistical significance. There was no significant evidence of heterogeneity within designs ($Q = 3.13$, $df = 4$, $p = .536$) or inconsistency between designs ($Q = 0.00$, $df = 1$, $p = .959$). Between-study heterogeneity was low ($\tau^2 = 0$), and inconsistency was low ($I^2 = 0\%$, 95% CI [0.0%, 74.6%]). There was no significant evidence of small study effects (Supplemental Figure S1B). Imprecision did not meet the criterion of concern in any of the comparisons (Figure 4B). Figure 5B summarizes results from the pairwise meta-analyses of studies included in the placebo control NMA of PTSD outcomes.

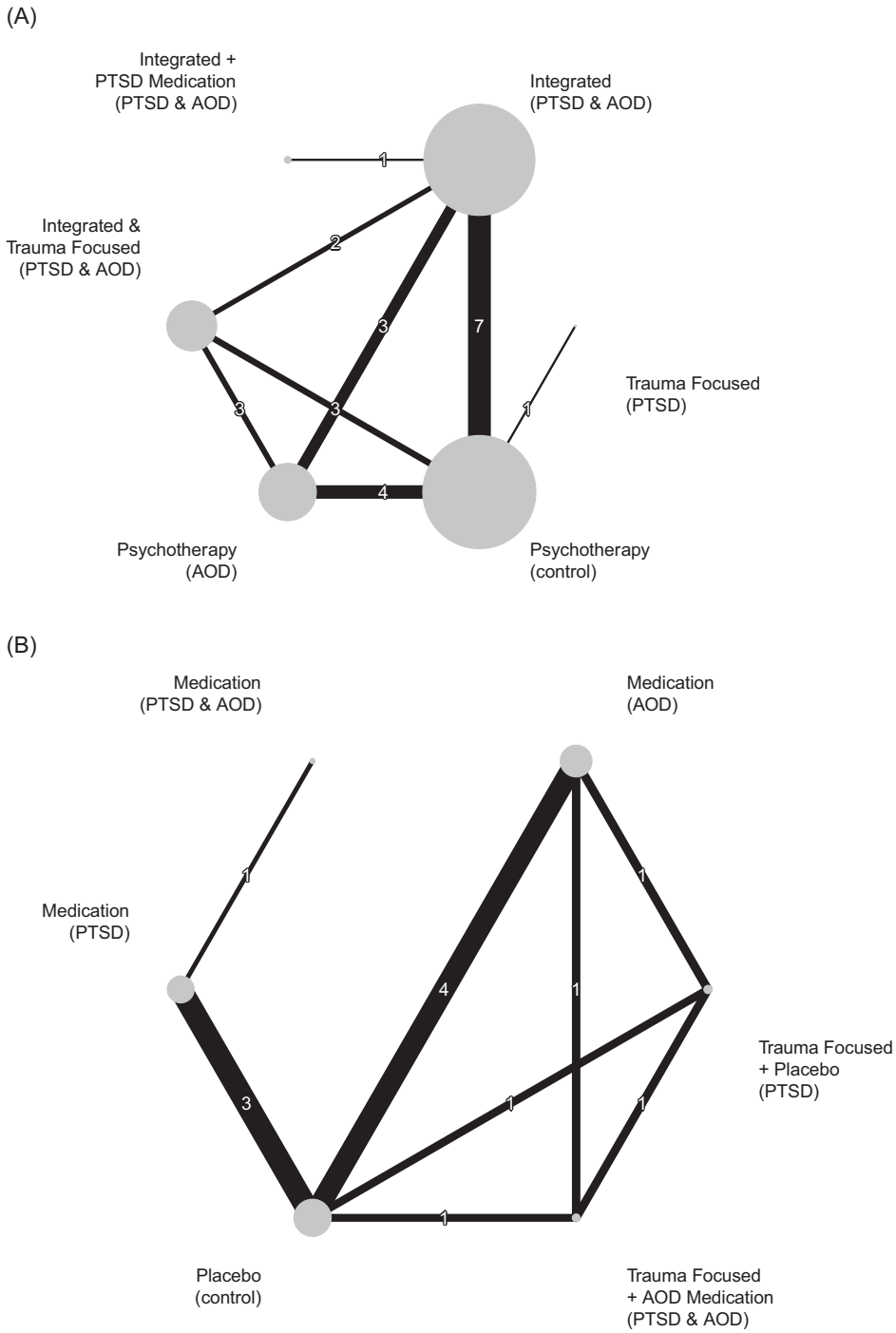
Alcohol Outcomes

Figure 4C shows results from the psychotherapy control NMA of alcohol outcomes at the end of treatment. No NMA or direct estimates that reached statistical significance. There was significant evidence of heterogeneity within designs ($Q = 18.93$, $df = 10$, $p = .041$), but no evidence of inconsistency between designs ($Q = 2.96$, $df = 5$, $p = .707$). Between-study heterogeneity was low to moderate ($\tau^2 = 0.028$), and inconsistency was low to moderate ($I^2 = 31.5\%$, 95% CI [0.0%, 62.4%]). There was no significant evidence of small study effects (Supplemental Figure S1C). Imprecision met the criterion concern in all comparisons with trauma-focused (PTSD) and in integrated + PTSD medication (PTSD + AOD) versus integrated and trauma-focused (PTSD + AOD); see Figure 4C. Figure 5C summarizes results from the pairwise meta-analyses of studies included in the psychotherapy control NMA of alcohol outcomes.

Figure 4D shows results from the placebo control NMA of alcohol outcomes at the end of treatment. Among the NMA estimates, alcohol severity was significantly less for medication

Figure 3

Networks of Comparisons at End of Treatment



Note. (A) Subnetwork included direct or indirect comparisons with psychotherapy control (16 studies, N = 1,240 with PTSD outcomes, N = 1,207 with alcohol outcomes). (B) Subnetwork included direct or indirect comparisons with placebo control (eight studies, N = 426 with PTSD outcomes, N = 489 with alcohol outcomes). The size of each node is proportional to the number of participants within each treatment category. The thickness of each edge is proportional to the number of comparisons between two categories, which is indicated by the numeral on each edge. PTSD = posttraumatic stress disorder; AOD = alcohol and other drug use.

Figure 4
End-of-Treatment Outcomes for Each Treatment Category

(A)

Psychotherapy (AOD)	-0.21 [-0.46, 0.04] N = 4	0.06 [-0.22, 0.33] N = 3	NA	0.26 [-0.12, 0.65] N = 3	NA
-0.14 [-0.36, 0.09] N = 16	**Psychotherapy (control)**	0.14 [-0.05, 0.34] N = 7	NA	0.32 [-0.04, 0.69] N = 3	0.61 [-0.42, 1.64] N = 1
-0.01 [-0.23, 0.22] N = 16	0.13 [-0.05, 0.31] N = 16	**Integrated (PTSD+AOD)**	0.20 [-0.42, 0.81] N = 1	0.37 [-0.04, 0.77] N = 2	NA
0.19 [-0.46, 0.84] N = 16	0.33 [-0.31, 0.96] N = 16	0.20 [-0.42, 0.81] N = 16	**Integrated + PTSD Medication (PTSD+AOD)**	NA	NA
0.29 [0.03, 0.56] N = 16	**0.43 [0.18, 0.68]** N = 16	**0.30 [0.04, 0.56]** N = 16	0.11 [-0.56, 0.77] N = 16	**Integrated & Trauma Focused (PTSD+AOD)**	NA
0.47 [-0.58, 1.52] N = 16	0.61 [-0.42, 1.64] N = 16	0.48 [-0.57, 1.52] N = 16	0.28 [-0.93, 1.49] N = 16	0.18 [-0.88, 1.24] N = 16	**Trauma Focused (PTSD)**

(B)

Medication (Alcohol)	NA	NA	-0.10 [-0.43, 0.23] N = 4	0.23 [-0.28, 0.75] N = 1	0.12 [-0.39, 0.62] N = 1
-0.39 [-1.21, 0.44] N = 8	**Medication (PTSD & Alcohol)**	0.29 [-0.40, 0.98] N = 1	NA	NA	NA
-0.10 [-0.55, 0.36] N = 8	0.29 [-0.40, 0.98] N = 8	**Medication (PTSD)**	-0.00 [-0.32, 0.31] N = 3	NA	NA
-0.10 [-0.43, 0.23] N = 8	0.29 [-0.47, 1.04] N = 8	-0.00 [-0.32, 0.31] N = 8	**Placebo (control)**	0.34 [-0.19, 0.88] N = 1	0.23 [-0.30, 0.75] N = 1
0.24 [-0.24, 0.72] N = 8	0.63 [-0.28, 1.53] N = 8	0.33 [-0.25, 0.91] N = 8	0.34 [-0.15, 0.83] N = 8	**Trauma Focused + AOD Medication (PTSD & AOD)**	-0.12 [-0.63, 0.40] N = 1
0.12 [-0.35, 0.59] N = 8	0.51 [-0.39, 1.40] N = 8	0.22 [-0.36, 0.79] N = 8	0.22 [-0.26, 0.70] N = 8	-0.12 [-0.63, 0.40] N = 8	**Trauma Focused + Placebo (PTSD)**

(C)

Psychotherapy (AOD)	-0.11 [-0.40, 0.17] N = 4	0.00 [-0.30, 0.31] N = 3	NA	-0.14 [-0.57, 0.28] N = 3	NA
-0.12 [-0.37, 0.13] N = 16	**Psychotherapy (control)**	0.15 [-0.06, 0.37] N = 7	NA	-0.12 [-0.53, 0.29] N = 3	0.37 [-0.67, 1.41] N = 1
0.02 [-0.23, 0.28] N = 16	0.14 [-0.06, 0.34] N = 16	**Integrated (PTSD+AOD)**	-0.38 [-1.05, 0.28] N = 1	-0.16 [-0.59, 0.27] N = 2	NA
-0.36 [-1.07, 0.35] N = 16	-0.24 [-0.94, 0.45] N = 16	-0.38 [-1.05, 0.28] N = 16	**Integrated + PTSD Medication (PTSD+ Alcohol)**	NA	NA
-0.15 [-0.44, 0.15] N = 16	-0.03 [-0.31, 0.25] N = 16	-0.17 [-0.45, 0.11] N = 16	0.21 [-0.51, 0.93] N = 16	**Integrated & Trauma Focused (PTSD+AOD)**	NA
0.25 [-0.82, 1.32] N = 16	0.37 [-0.67, 1.41] N = 16	0.23 [-0.83, 1.29] N = 16	0.61 [-0.64, 1.86] N = 16	0.40 [-0.68, 1.48] N = 16	**Trauma Focused (PTSD)**

(*figure continues*)

Figure 4 (*continued*)

(D)

Medication (Alcohol)	NA	NA	**-0.36 [-0.68, -0.05] N = 4**	0.06 [-0.42, 0.53] N = 1	**-0.75 [-1.24, -0.27] N = 1**
-0.12 [-0.93, 0.68] N = 8	**Medication (PTSD & Alcohol)**	-0.26 [-0.95, 0.42] N = 1	NA	NA	NA
-0.39 [-0.81, 0.03] N = 8	-0.26 [-0.95, 0.42] N = 8	**Medication (PTSD)**	0.02 [-0.26, 0.31] N = 3	NA	NA
-0.36 [-0.68, -0.05] N = 8	-0.24 [-0.98, 0.50] N = 8	0.02 [-0.26, 0.31] N = 8	**Placebo (control)**	**0.59 [0.11, 1.06] N = 1**	-0.22 [-0.69, 0.25] N = 1
0.14 [-0.30, 0.58] N = 8	0.27 [-0.60, 1.13] N = 8	**0.53 [0.01, 1.05]** N = 8	**0.50 [0.06, 0.94]** N = 8	**Trauma Focused + AOD Medication (PTSD & AOD)**	**-0.81 [-1.30, -0.33] N = 1**
-0.67 [-1.11, -0.22] N = 8	-0.54 [-1.40, 0.32] N = 8	-0.28 [-0.80, 0.24] N = 8	-0.30 [-0.74, 0.14] N = 8	**-0.81 [-1.29, -0.32]** N = 8	**Trauma Focused + Placebo (PTSD)**

Note. (A) PTSD outcomes in the subnetwork included psychotherapy control. (B) PTSD outcomes in the subnetwork included placebo control. (C) Alcohol outcomes in the subnetwork included psychotherapy control. (D) Alcohol outcomes in the subnetwork included placebo control. Standardized mean differences (SMDs) [95% CI] from the network meta-analyses. Estimates in the lower triangle (green) integrate direct and indirect evidence from all studies in the network, and estimates in the upper triangle (blue) are based on direct evidence from studies that included comparisons between treatment categories. Statistically significant differences are indicated in bold. Negative SMDs with 95% CIs that do not overlap with 0 indicate the superiority of the category in the column versus row for the network meta-analysis and row versus column for the pairwise meta-analysis (positive SMDs indicate the reverse). AOD = alcohol and other drug use; integrated = non-trauma-focused psychotherapy targeting both PTSD and AOD; PTSD = posttraumatic stress disorder; *N* = the number of studies used to estimate the effect; NA = not applicable because the two treatment categories were not directly compared in any studies; CI = confidence interval.

(AOD) compared to (a) placebo (control), SMD = −0.36, 95% CI [−0.68, −0.05], $z = -2.27$, $p = .023$ and (b) trauma-focused + placebo (PTSD), SMD = −0.67, 95% CI [−1.11, −0.22], $z = -2.92$, $p = .003$. Trauma-focused + AOD medication (PTSD and AOD) was superior to (a) medication (PTSD), SMD = −0.53, 95% CI [−1.05, −0.01], $z = -1.99$, $p = .047$; (b) placebo (control), SMD = −0.50, 95% CI [−0.94, −0.06], $z = -2.25$, $p = .025$; and (c) trauma-focused + placebo (PTSD), SMD = −0.81, 95% CI [−1.29, −0.32], $z = -3.26$, $p = .001$. Results from direct evidence for these comparisons (where available) were also significant (Figure 4D). Specifically, alcohol severity was significantly reduced for medication (AOD) compared to (a) placebo (control), SMD = −0.36, 95% CI [−0.68, −0.05], $z = -2.27$, $p = .023$ and (b) trauma-focused + placebo (PTSD), SMD = −0.75, 95% CI [−1.24, −0.27], $z = -3.06$, $p = .002$. Trauma-focused + AOD medication (PTSD and AOD) was superior to (a) placebo (control), SMD = −0.59, 95% CI [−1.06, −0.11], $z = -2.43$, $p = .015$ and (b) trauma-focused + placebo (PTSD), SMD = −0.81, 95% CI [−1.30, −0.33], $z = -3.28$, $p = .001$. There was no significant evidence of heterogeneity within designs ($Q = 2.95$, $df = 4$, $p = .567$) or of inconsistency between designs ($Q = 0.86$, $df = 1$, $p = .354$). Between-study heterogeneity was low ($\tau^2 = 0$), and inconsistency was low ($I^2 = 0\%$, 95% CI [0.0%, 74.6%]). There was no significant evidence of small study effects (Supplemental Figure S1D). Imprecision met the criterion of concern in the comparison of medication (AOD) versus medication (PTSD + AOD); medication (PTSD + AOD) versus placebo (control); and medication (PTSD + AOD) versus trauma-focused + AOD medication (PTSD + AOD); see (Figure 4D). Figure 5D summarizes results from the pairwise meta-analyses of studies included in the placebo control NMA of alcohol outcomes.

Sensitivity Analyses

To assess the robustness of the findings, we conducted several sensitivity analyses. We reestimated the psychotherapy control NMA after the removal of one study that included medication (Hien et al., 2015) and two studies that did not use an active treatment as behavioral control (Pearson et al., 2019; Ruglass et al., 2017). Results for the PTSD outcomes suggesting superiority of integrated, trauma-focused (PTSD + AOD) compared to (a) psychotherapy (AOD), (b) psychotherapy (control), and (c) integrated (PTSD + AOD) remained statistically significant; alcohol outcomes remained nonsignificant, but heterogeneity and inconsistency were reduced (Supplemental Material H).

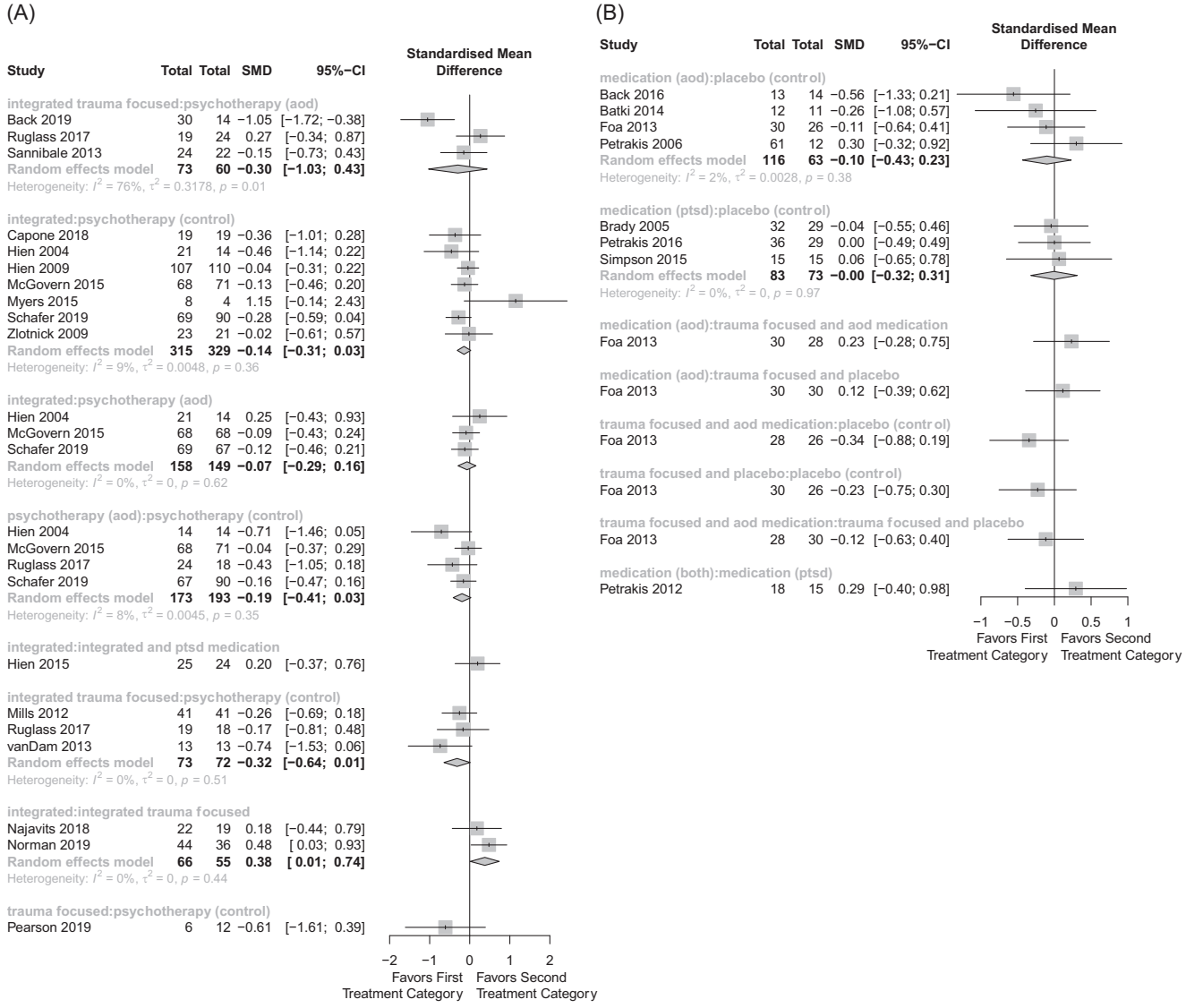
We also reestimated the placebo control NMA after the removal of one study (Back et al., 2016) that targeted alcohol or substance use (all other studies in this NMA specifically targeted alcohol). Results for the PTSD outcomes remained nonsignificant (Supplemental Material I). Results for the alcohol outcomes suggesting superiority of medication (AOD) compared to (a) placebo (control) and (b) trauma-focused + placebo (PTSD) and suggesting superiority of trauma-focused + AOD medication (PTSD and AOD) compared to (a)

medication (PTSD), (b) placebo (control), and (c) trauma-focused + placebo (PTSD) remained statistically significant; moreover, medication (AOD) reached statistical superiority over medication (PTSD) in this analysis (Supplemental Material I).

A review of the studies included in the systematic literature review that were excluded from the NMA ($k = 12$) identified two reasons for study exclusion from the NMA: either because it was a single-armed pilot study or because the data needed to conduct the NMA were not available (Table 4). Single-arm studies could not be included in the NMA because they lacked a comparator arm. Six of the excluded single-armed pilot studies employed integrated, non-trauma-focused psychotherapies (PTSD + AOD; either Seeking Safety or cognitive behavioral therapy for PTSD, see Najavits et al., 1998, 2005; Najavits, 2014; McGovern et al., 2009; Norman et al., 2010; Zlotnick et al., 2003). All reported significant pre- to posttreatment improvements in PTSD symptom severity. Five of these integrated, non-trauma-focused (PTSD + AOD) psychotherapies also reported some significant impacts on substance use beliefs, abstinence, alcohol, or drug use with the exception of Norman et al. (2010). One excluded integrated trauma-focused study (Persson et al., 2017) reported significant impacts on both PTSD and alcohol outcomes. The one single-armed pilot study (Meyer et al., 2018) using nonintegrated, trauma-focused treatment showed no significant findings in either outcome domain.

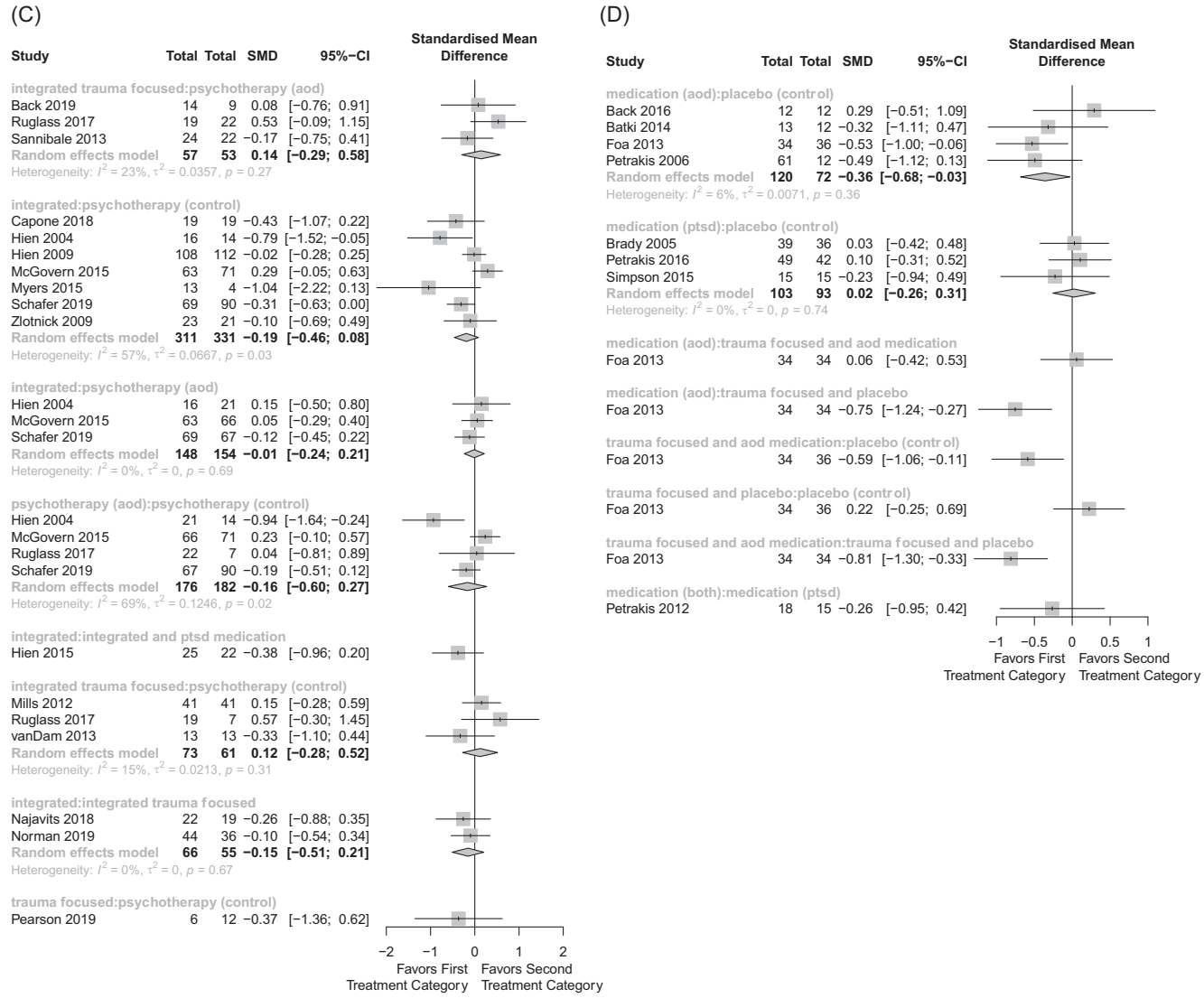
Of the three RCTs that were excluded from the NMA due to unavailability of data, one (Triffleman, 2000) was an integrated,

Figure 5
Forest Plots for Pairwise Meta-Analyses



(*figure continues*)

Figure 5 (*continued*)



Note. (A) Forest plot for the pairwise meta-analyses of PTSD outcome across treatment categories included in the psychotherapy control NMA. (B) Forest plot for the pairwise meta-analyses of PTSD outcome across treatment categories included in the placebo control NMA. (C) Forest plot for the pairwise meta-analyses of alcohol outcome across treatment categories included in the psychotherapy control NMA. (D) Forest plot for the pairwise meta-analyses of alcohol outcome across treatment categories included in the placebo control NMA. PTSD = posttraumatic stress disorder; AOD = alcohol and other drug use; NMA = network meta-analysis; CI = confidence interval; SMD = standardized mean difference

non-trauma focused treatment compared to twelve steps facilitation reported no differences between treatments for either PTSD or alcohol outcomes, consistent with the NMA comparison between integrated psychotherapy and psychotherapy controls. Another excluded RCT (Coffey et al., 2016) tested a non-integrated trauma-focused therapy compared with healthy lifestyle sessions (a psychotherapy control) and found that the trauma-focused therapy was superior on the PTSD outcome (inconsistent with the NMA), but not on the alcohol outcome (consistent with the NMA). Finally, a medication trial (Kwako et al., 2015) of aprepitant (an alcohol targeting medication) versus placebo medication showed no impact on PTSD (consistent with the NMA) or on alcohol outcomes (inconsistent with the NMA where the alcohol targeting medications were superior to placebo medications on alcohol outcomes).

Discussion

This systematic review and NMA characterized and compared the extant literature on treatments for PTSD + AOD, with a specific focus on identifying the range of populations, intervention types, comparators, along with safety indicators and outcomes. The present review aimed to cast a broad net to include an assessment of the quality of the existing empirical evidence base of all kinds of study designs, treatments (psychotherapeutic and pharmacologic), and

targets (PTSD, AOD, or both), in order to provide the field with guidelines for treatment development and future research that critically examines impacts for a heterogeneous pool of patients.

Applying an NMA to the subset of 24 RCTs yielded some statistically significant differences across treatment categories on PTSD and alcohol use outcomes. In the intervention subnetwork with the psychotherapeutic comparator, there was evidence of superiority of integrated, trauma-focused treatment for PTSD outcomes across three comparators: (a) integrated, non-trauma-focused treatment, (b) AOD-only targeted psychotherapy controls, and (c) psychotherapy control including treatment as usual. There were, however, no significant differences across any of the interventions in the psychotherapy intervention subnetwork for the alcohol outcomes. These findings are largely in line with mounting evidence from the most recent traditional meta-analyses of psychotherapy interventions (e.g., Roberts et al., 2022; Simpson et al., 2021), which continue to provide support for the integrated, trauma-focused interventions over treatment as usual for the treatment of PTSD.

Although each of the two cited traditional meta-analyses (representing the most updated findings for the field) used different meta-analytic methods and treatment groupings, we found similarities regarding the findings favoring trauma-focused treatments. For end-of-treatment PTSD outcomes, Roberts et al. (2022) found that trauma-focused treatments that included treatment as usual for AOD outperformed treatment as usual for AUD-only interventions; this effect size estimate overlaps with our NMA results comparing interventions that were both integrated and trauma-focused to psychotherapy controls that included treatment as usual for AUD. Similarly, Simpson et al. (2021) reported their effect size estimates using Hedge's *g* and found that trauma-focused treatments outperformed nonspecific comparators (e.g., treatment as usual, manualized AOD treatment, no-treatment control) on PTSD outcomes. Taking the previous findings one step further, the present NMA provided evidence of the superiority of the integrated, trauma-focused treatments compared to integrated, non-trauma-focused psychotherapy, manualized AOD treatment, and treatment as usual on PTSD outcomes.

However, Simpson et al. (2021) did find that substance outcomes, which included alcohol and other drugs, were favorably impacted by manualized AOD treatment over either trauma-focused or non-trauma-focused approaches, whereas our NMA, which was restricted to alcohol outcomes, did not find significant differences among the psychotherapy treatment categories. Our analysis differs from a traditional meta-analysis such as Simpson et al.'s (2021) in that network meta-analyses produce estimates of the relative effects between any pair of interventions in the network by incorporating indirect evidence from trials with a common comparator. Differences in outcome measurement may also have led to the discrepancy between our findings and Simpson et al.'s (2021), leaving room for future research to ascertain which treatments or techniques can directly impact AOD outcomes best.

Overall, our findings generally support the observation that comorbidity treatments for PTSD and SUD demonstrate more efficacy on PTSD symptoms, whereas substance use may require strategies that extend beyond trauma-focused interventions. Findings are consistent with emotional processing (Rauch & Foa, 2006) and social cognitive (Chard et al., 2020) theories in that treatments that allow for activation and processing of trauma-related memories and encourage exposure to safe yet avoided trauma-related reminders are key to fear reduction/habituation as well as shifting negative/maladaptive beliefs around the trauma experience and associated consequences. All of which, in turn, contribute to greater reductions in PTSD symptoms than non-trauma-focused coping therapies.

It is worth pointing out that clinician concerns about implementing trauma-focused models with those who use substances have not been borne out by research with more severe populations like those with complex trauma. De Jongh et al. (2016) noted that for those with complex trauma, guidelines that recommend delaying trauma-focused treatment could demoralize clients, by suggesting that they are incapable of dealing with their traumatic memories and diminishing client confidence in and motivation for trauma work. Jerud et al. (2016) have demonstrated that emotion dysregulation, a sequela of early traumatization and a common feature also among those with substance use disorders, is improved following trauma-focused treatment. And cross-lagged findings from a trial of COPE (an integrated, trauma-focused treatment) compared to relapse prevention found that the heaviest users benefited significantly more from the trauma-focused approach in reducing their substance use *through* diminishing PTSD symptoms (Hien et al., 2018). These latter findings support the self-medication hypothesis (Khantzian, 1997) and argue for an integrative treatment framework, which target the core neurofunctional domains that connect PTSD + SUD (Hien, López-Castro, et al., 2021).

In contrast to the findings for the psychotherapy network reported above, for the medication comparator subnetwork, there was no clear evidence that the pharmacologic treatments significantly impacted PTSD severity compared with medication placebo, but some evidence that AOD medication (on its own or in combination with trauma-focused therapy) had superior outcomes for alcohol when compared to a medication placebo. However, because of the small number of studies, these findings may reflect inconclusive evidence. Nonetheless, unlike the most recent systematic review of medications for PTSD and AUD outcomes (Petrakis & Simpson, 2017) that revealed no superiority of any treatment, our network analysis did support the benefits of the alcohol targeted medications, such as naltrexone or topiramate for alcohol symptoms compared with placebo medications alone. Given the costs and complexities of conducting combination psychotherapy and pharmacotherapy trials, our findings provide a strong indication for researchers to continue to investigate the benefits of combined therapies. The synergy between psychotherapeutic techniques involving trauma processing with a targeted medication also supports anecdotal clinical evidence (e.g., Hien et al., 2020).

Studies included in the broader systematic review of the literature that were excluded from the NMA differed by design (i.e., single-armed pilot trials without comparators could not be included) or lacked the necessary data. The excluded trials generally were consistent with the NMA findings. Although the integrated, non-trauma-focused single-armed pilot studies reported at least one significant pre–post treatment outcome on PTSD severity, as well as on a substance use measure, the lack of a control group in these studies makes it difficult to rule out confounds, or to assess the treatment's relative efficacy.

Overall, the sample sizes were small. The majority were RCTs with samples of less than 100 participants. However, more than three fourths of the included studies had study retention of 50% or

greater across all treatment arms. The largest trial ($N = 353$) was a multisite study that tested Seeking Safety among diverse women in community settings. Another large trial by Frisman et al. (2008) enrolled 239 participants but had more than 50% treatment dropout. Only one study that tested medications (i.e., naltrexone and disulfiram) found significant improvements in both PTSD and AOD outcomes among a large sample (more than 100 participants) while maintaining 50% or greater retention by end of treatment (Petrakis et al., 2006).

In terms of inclusion and exclusion criteria (Supplemental Table S3), it should be noted historically that, for the majority of trauma-focused trials for PTSD-only, individuals with severe and major AODs were excluded because they were viewed as too fragile to receive PTSD treatment that involved direct trauma processing (Leeman et al., 2017), although this has improved recently based upon newer trials published in the past 5 years. Trauma-focused trials for PTSD-only also appeared to exclude suicidal ideation (77%) more often than other trials (63%). However, PTSD + AOD trials that have included current suicidal ideation suggest that trauma-focused treatments do not increase risk more than non-trauma-focused interventions. For example, Tripp et al. (2021) evaluated whether participants randomized to COPE were more likely to show exacerbations in suicidal ideation than participants randomized to Seeking Safety in a trial that compared the two treatments (Norman et al., 2019) and found that they were not more likely to show exacerbations. Further evidence of this is that trials have not shown a greater number of adverse events for trauma-focused than other treatment conditions (Lancaster et al., 2020; Mills et al., 2012; Roberts et al., 2022). Given clinician concerns about the safety of trauma-focused interventions in the PTSD + AOD population, it is important that future trials, whenever possible, continue to include participants with suicidal ideation as more work examining suicidal ideation is warranted.

The findings from our NMA have clinical implications. For example, integrated trauma-focused interventions demonstrated better results than several other types of psychotherapies for treating PTSD among those with alcohol or substance use disorders, which suggest that when feasible, integrated trauma-focused treatments should be made available to patients with PTSD + AOD. However, these treatments require resources that may not be available in all settings (e.g., to train staff, to have adequate staff to schedule individual psychotherapy sessions that are sometimes as long as 90 min). Also, trauma-focused techniques may require more training and expense and may not readily be conducted in AOD treatment settings where individual therapy is rarer, and group models are the norm (day programs, residential). In contrast, AOD-only and non-trauma-focused achieve smaller effects for PTSD than trauma-focused treatments, but may be less complex, less costly, and can be delivered in a group format, which are likely more appealing and feasible for the general workforce. Moreover, not all patients are good candidates for trauma-focused treatment, such as those with no or insufficient memory of the trauma due to serious injury or loss of consciousness during the event or the early age of the trauma. Other treatment options such as AOD-only or non-trauma-focused psychotherapies, which may produce less change in PTSD symptoms than trauma-focused treatments but still lead to clinical improvement, are viable options for clients who do not want trauma-focused treatments or are not able to access them. Moreover, trauma-focused treatments and other types of AOD treatments appear to be comparable, and in some cases superior (Simpson et al., 2021), on substance use outcomes. These recommendations will evolve as we learn more about how to improve attendance (which will likely improve outcomes) and about how to implement precision medicine strategies to inform what works best for whom.

To further inform clinical practice and treatment recommendations, additional studies are needed with larger samples that can provide a foundational understanding of treatment effectiveness across diverse populations. Furthermore, larger trials should make targeted efforts to promote treatment retention among these clients, given the likelihood that individuals with PTSD + AOD may leave treatment early or attend sessions sporadically due to numerous barriers to treatment access (e.g., lower socioeconomic resources, multiple life stressors; Belleau et al., 2017; Jarnecke et al., 2019).

Intervention Safety

Forty-four percent of the studies in this review ($k = 17$) did not report any information on study-related adverse events. Of those that did report study-related adverse events s ($k = 22$; ~56%), few studies ($k = 6$; ~18%) had study-related adverse events. The studies that reported adverse events were primarily medication-only (Batki et al., 2014; Petrakis et al., 2006, 2012; Simpson et al., 2015) or combination studies with medications and psychotherapy interventions (Back et al., 2016; Foa et al., 2017). Only one behavioral study (Schäfer et al., 2019) reported adverse events—with a low rate of occurrence across the length of the study and no significant differences between treatment groups. Interventions in the therapy-only trial (Schäfer et al., 2019) were relapse prevention and Seeking Safety, which in other trials were associated with no adverse events. See Table 3 for more information. Researchers and clinicians have previously expressed concern about risk of inducing or exacerbating symptoms of either PTSD or AOD during concurrent treatment (McCauley et al., 2012). However, our findings support the notion that PTSD and AOD can be treated concurrently and that even relatively intensive treatments can be delivered safely and without increased risk of adverse events compared to other treatments for interventions for other mental health disorders, including PTSD and AOD separately.

Strengths and Limitations

Risk of Bias Assessments for Study Populations Like PTSD + AOD

Our findings revealed that concealment and study attrition are two dimensions of ROB ratings that require careful consideration to most accurately review the quality of PTSD + AOD studies. One limit of the traditional systematic review methodology for PTSD + AOD studies involves the mismatch between the current "gold standard" for rating the quality of a study and trials that are behavioral and which target a population where diagnostic complexities may result in barriers to the clinical trial design (e.g., such as allocation blinding and high study attrition rates). While double blinding is feasible in medication trials (i.e., neither the participant nor the investigator knows if they are in the active medication or placebo condition), it is often not possible or even appropriate for psychotherapy trials. Other internal validity factors such as whether or not there were independent assessors conducting

study outcomes, assessments of how much data were missing and accounted for, and whether clients dropped out of treatment or just did not receive their assessments, were all considered in our evaluation of ROB for all included studies.

Our analysis of internal validity revealed overall that the body of existing studies has low ROB, particularly those with RCT designs where none received a high ROB based on the ROB2 criteria. By definition, some of the pilot studies, where randomization, independent assessors for outcome assessment, and study preregistration did not occur, were considerably more likely to have some concerns or high ROB ratings overall.

Other Limitations

Data extraction and ROB2 coding were completed in a consensus model where differences in rating were resolved through discussion. Single, independent ratings could have been conducted, but a consensus model ensures greater interrater reliability among the team. Although consensus coding is susceptible to groupthink and hierarchical influence, we attended to this possibility by ensuring oversight of this process by an independent experienced analyst from an Evidence-Based Practice Center (https://www.rti.org/impact/rti-unc-evidence-based-practice-center-epc). Single, independent ratings could have been conducted, but a consensus model overseen by independent investigators trained in evidence synthesis methodology provided greater assurance that information from individual studies was not inadvertently omitted.

The potential for investigator bias is a known endemic factor in clinical trials, especially in PTSD + AOD trials as this is a relatively young field. In this NMA, seven of the 24 trials had treatment developers as investigators, five of which included trauma-focused interventions. Although it is possible there is bias, given that 20% of the included studies involved treatment developers, NMA may reduce the potential for an "allegiance effect" by incorporating more studies that do not include treatment developers in its indirect estimates of effect size differences across treatment categories. Future analyses like meta-analysis with individual patient data can help combat this limitation.

We note several limitations of the NMA approach. SMDs were calculated from the group means and standard deviations at the outcome time point. This means that baseline severity was not directly incorporated nor were individuals whose data were excluded from the reported means and standard deviations; however, the SMDs are based on treatment arms within the same studies that had the same inclusion/exclusion criteria. Due to the relatively lower number of studies that reported drug use outcomes, our NMA focused on alcohol use outcomes that were reported by all studies; future meta-analyses can examine whether drug use outcomes are differentially impacted by interventions that target AOD and/or PTSD. Although our analyses did not find evidence of effect size heterogeneity and inconsistency, this does not preclude the possibility of treatment effect moderators. Future research that is adequately powered to test focalized hypotheses about specific moderators is needed. Finally, direct comparisons between all treatment types were not always possible to estimate (especially in the medication subnetwork); indirect estimates of these comparisons should be cautiously interpreted.

Future Directions

It has been demonstrated that social determinants are associated with higher rates of traumatic stress exposures and PTSD + AOD among populations from racial, ethnic and other minoritized backgrounds (e.g., gender and sexual groups; Alegría et al., 2013; Galvan & Caetano, 2003). Future research would benefit from increased diversity, and greater incorporation of measures of social determinants. Most studies examined treatments ranging from 12 to 25 sessions. Whether there is an ideal length or dose of treatment that would lead to larger effects is also a question for future research.

Any given RCT or single-armed trial will be overly narrow with regard to its particular inclusion and exclusion criteria and population, thereby limiting the generalizability of any particular study to PTSD + AOD treatment seekers as a whole. Systematic reviews, conventional and network meta-analyses are both tried-and-true methods of synthesizing findings and data, but there are also very specific limitations to each of these synthesis approaches. These limitations suggest the potential to consider conducting meta-analysis with individual patient data (MIPD), which could have significant advantages over conventional meta-analysis and NMA, especially when a smaller number of studies are available. The practical implications for PTSD + AOD treatment can be seen with the potential findings of an MIPD, as contrasted against a conventional meta-analysis or NMA, with MIPD being a more nuanced examination of variation in treatment efficacy across patient types (e.g., Saavedra et al., 2021). And, a future program of research syntheses could also capitalize upon a number of other new methods and generated findings, including second-order meta-analyses of previous meta-analytic studies ("metas of metas"), meta-syntheses of qualitative studies, and meta-analyses of quantitative single-case studies in order to cast a broad net on this public mental health problem.

Other future directions include matching individual characteristics (i.e., the severity of AOD/PTSD symptoms, trauma type, substance type, PTSD symptom development prior to AOD, other comorbidities) with treatment approaches and more comparative effectiveness studies of integrated treatments in real-world AOD treatment programs (delivery methods, group/individual, adapting interventions for delivery feasibility and patient tolerability, training and supervision ability, resources available to a treatment program, long-term outcomes).

Conclusion

Our systematic review revealed a wide set of therapeutic approaches (12 discrete category types) for PTSD + AOD. Narrative synthesis ($k = 39$) suggests that PTSD and AOD can be treated concurrently without increased risk of adverse events. Consistent with prior meta-analytic findings, the NMA ($k = 24$) found that integrated, trauma-focused interventions were more effective at reducing PTSD symptoms than three types of comparator interventions (integrated, non-trauma-focused; AOD-focused; other controls). AOD medications with and without trauma-focused interventions were also found to be superior to placebo for alcohol severity. Collectively, these findings support the theoretical framing of optimal PTSD + AOD care as attentive to the multifaceted and mutually reinforcing nature of the comorbidity. The current results are limited by the pool of studies' relative lack of demographic

diversity and the small number of pharmacological interventions available for inclusion in the NMA. In addition to more sophisticated comparative effectiveness analyses, research should focus on increasing demographic representation in trials, improving treatment retention, and exploring the novel blending of psychotherapy and pharmacotherapy approaches.

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