Evidence Brief: Treatment of Comorbid Conditions

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AUTHORS

Author roles, affiliations, and contributions to the present report (using the CRediT taxonomy) are summarized in the table below.

Author	Role and Affiliation	Report Contribution
Erin H. Beech, MA	Senior Research Associate, Evidence Synthesis Program (ESP) Coordinating Center, Portland VA Health Care System Portland, OR	Methodology, Project Administration, Supervision, Investigation, Writing – original draft, Writing – review & editing,
Basmah Rahman, MPH	Research Associate, ESP Coordinating Center, Portland VA Health Care System Portland, OR	Investigation, Visualization, Writing – original draft, Writing – review & editing
Rachel Ward	Research Assistant, ESP Coordinating Center, Portland VA Health Care System Portland, OR	Visualization, Writing – review & editing
Johanna Anderson, MPH	Senior Research Associate, ESP Coordinating Center, Portland VA Health Care System Portland, OR	Methodology, Supervision, Writing – review & editing
Bradley E. Belsher, PhD	Clinician Investigator, ESP Coordinating Center, Portland VA Health Care System Portland, OR Clinical Psychologist, PTSD Clinical Team, Phoenix VA Health Care System Phoenix, AZ	Conceptualization, Writing – original draft, Writing – review & editing
Nicholas J. Parr, PhD, MPH	Research Scientist, ESP Coordinating Center, Portland VA Health Care System Portland, OR	Conceptualization, Methodology, Supervision, Writing – review & editing

This report was prepared by the Evidence Synthesis Program Coordinating Center located at the **VA Portland Health Care System**, directed by Mark Helfand, MD, MPH, MS and funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development.

PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policymakers as they work to improve the health and health care of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program comprises three ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, interface with stakeholders, and address urgent evidence needs. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

The present report was developed in response to a request from the Office of Mental Health and Suicide Prevention (OMHSP). The scope was further developed with input from Operational Partners (below) and the ESP Coordinating Center review team. Comments on this report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

ACKNOWLEDGMENTS

The ESP is grateful to the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

Christopher Loftis, PhD, PMP
National Director
VA/DoD Mental Health Collaboration

TABLE OF CONTENTS

FIGURES AND TABLES

EXECUTIVE SUMMARY

Key Findings

- Evidence from recent systematic reviews (SRs) on the treatment of comorbid conditions is inconsistent, and little evidence is available for most combinations of comorbidities.
- Based on data from a single study, 1 SR found that a baseline diagnosis of major depressive disorder (MDD) significantly predicted nonresponse to posttraumatic stress disorder (PTSD) treatment. However, these findings are limited to a single, imprecise study.
- Treatment with antidepressants may result in improvements in certain alcohol outcomes in individuals with comorbid depression and alcohol dependence, based on 1 well-conducted SR. The effect of treatment of a primary condition on a comorbid condition in 10 other SRs is unclear due to inconsistent, imprecise, and/or indirect findings.
- The evidence on the effectiveness of integrated treatment compared to nonintegrated treatment was inconsistent among 6 SRs but was most favorable for integrated treatment of PTSD and substance use disorder (SUD). The evidence was further limited by imprecise and/or indirect findings.

Psychiatric comorbidity in Veterans and military Service members with a mental health condition, substance use disorder (SUD), traumatic brain injury (TBI), or chronic pain is widespread and is generally associated with a more severe clinical profile, increased clinical complexity, and worse outcomes. Further, therapeutic efficacy may differ with the presence of a comorbid condition. The impact of comorbidity on treatment outcomes is not well understood, and there is debate about the optimal treatment course of these patients. Existing research evaluating the effectiveness of treatments for a primary condition alone often either excludes individuals with comorbid diagnoses or does not measure comorbidity.

The purpose of this review is to identify and synthesize evidence related to the treatment of comorbid conditions, focusing on evidence reported in existing systematic reviews (SRs) that examines whether treatment of a primary condition is impacted by the presence or severity of comorbidities, whether treatment of patients' primary condition leads to clinical improvement of comorbidities, and the effectiveness of integrated treatment compared to nonintegrated treatment. This review included the following combinations of conditions: adults with PTSD comorbid with anxiety, depression, bipolar disorder, TBI, SUD, or chronic pain; adults with TBI comorbid with anxiety, depression, bipolar disorder, PTSD,

Background

The Evidence Synthesis Program Coordinating Center is responding to a request from the Office of Mental Health and Suicide Prevention (OMHSP) for an Evidence Brief on treatment of comorbid mental health conditions, or mental health conditions comorbid with a traumatic brain injury, substance use disorder, or chronic pain, among Veterans and military Service members. Findings from this Evidence Brief will be used to inform development of a clinical provider toolkit, as required by the Commander John Scott Hannon Veterans Mental Health Care Improvement Act (S.785 2019).[1]

Methods

To identify systematic reviews, we searched Ovid MEDLINE, Cochrane Database of Systematic Reviews, and other sources from 2014 to August 2021. We used prespecified criteria for study selection, data abstraction, and rating internal validity and strength of the evidence. See the Methods section and our PROSPERO protocol for full details of our methodology.

SUD, or chronic pain; or adults with anxiety, depression, or bipolar disorder comorbid with SUD or chronic pain.

Due to the complexity and large volume of literature, we prioritized our inclusion to recent SRs. Among 26 prioritized SRs, most were well-conducted but primary studies within the SRs often had methodological limitations, including small sample sizes and moderate-to-high risk of bias. The eligibility criteria of the included SRs did not always line up entirely with our criteria and several of the SRs included studies with populations, comparators, and outcomes not relevant to our review. We focused our synthesis on SRs reporting a synthesis of studies relevant to our criteria (Table ES-1).

Among 6 SRs examining whether response to treatment of a primary condition is impacted by the presence or severity of a comorbid condition, only 1 concluded that the presence of a comorbid condition had a negative impact on treatment outcomes. Based on data from a single study, this SR conducted a trajectory analysis and found that a baseline diagnosis of major depressive disorder (MDD) was a significant predictor of nonresponse to PTSD treatment. The remaining 5 SRs either found that the presence of a comorbid condition had no effect or that the evidence was inconsistent.

Among 11 SRs examining whether treatment of a primary condition results in improvements in a comorbid condition, 1 well-conducted SR reported that treatment with antidepressants may result in improvements in certain alcohol outcomes in individuals with comorbid depression and alcohol dependence. Evidence on other comorbid combinations was limited by inconsistent, imprecise, and/or indirect findings.

Six SRs evaluated the effectiveness of integrated treatment of 4 comorbid conditions (PTSD and SUD, PTSD and anxiety/depression, SUD and depression, and SUD and bipolar disorder). Our findings suggest that integrated cognitive-behavioral treatments for PTSD and SUD may be more effective than usual care or treatments for either condition alone. Evidence from 2 SRs on Seeking Safety was limited by inconsistent findings across time points and outcomes. Results on treatments that target the other comorbid conditions were mixed or did not indicate benefit of integrated treatments compared to usual care interventions.

Although comorbidity is widespread and may be associated with worsened outcomes, evidence captured in recent SRs on the treatment of comorbid conditions is sparse and inconsistent. Inconsistent findings across the included SRs may reflect different ways of defining and measuring comorbidity, heterogeneous study samples, and methodological variation across the SRs and their included studies. Given the absence of strong evidence from recent SRs to guide treatment of comorbid conditions, clinicians and policymakers may look to a general pattern of research findings and clinical practice guideline recommendations indicating that: 1) comorbidity should be taken into consideration in the treatment of mental health conditions, substance use, TBI, and chronic pain; and 2) concurrent treatment of comorbid conditions appears to be effective, in particular for the treatment of comorbid PTSD and SUD. There is a need for better-conducted studies on the treatment of comorbid conditions that: 1) appropriately define and measure comorbidity; 2) incorporate appropriate methodology to allow conclusions to be made about the impact of comorbidity on treatment outcomes; and 3) specifically aim to examine the treatment of comorbid conditions. Future systematic reviews of primary literature on individual condition combinations could also benefit the field.

Table ES-1. Summary of Findings

Key Question	Evidence	Summary of Findings
KQ1: PTSD & depression	2 SRs	**Low SOE**: A diagnosis of comorbid depression may have a negative impact on PTSD treatment outcome based on indirect, inconsistent, and imprecise information from 2 SRs.
KQ1: PTSD & TBI	2 SRs	**Low SOE**: It is unclear whether a history of TBI has a negative impact on PTSD treatment outcome based on indirect, inconsistent, and imprecise information from 2 SRs.
KQ1: Chronic pain & depression	2 SRs	**Low SOE**: A diagnosis of comorbid depression may not have an impact on chronic pain outcomes based on direct, but inconsistent and imprecise evidence from 2 SRs.
KQ2: PTSD & anxiety	1 SR	**Low SOE:** Treatment of PTSD may not be associated with improvements in comorbid anxiety based on indirect, imprecise information from 1 SR with unclear risk of bias.
KQ2: PTSD & depression	1 SR	**Low SOE:** Treatment of PTSD may lead to an improvement in comorbid depression based on indirect, imprecise information from 1 SR with unclear risk of bias.
KQ2: PTSD & SUD	3 SRs	**Low SOE:** Treatment of PTSD may not be associated with improvement in comorbid substance use disorder based on direct and consistent, but imprecise information from 2 SRs with low risk of bias.
KQ2: Chronic pain & TBI	1 SR	**Insufficient SOE:** One SR reported headache-related outcomes and it is unclear if this can be considered an outcome of the secondary condition (TBI).
KQ2: Anxiety & SUD	1 SR	**Insufficient SOE:** It is unclear whether treatment of anxiety may impact alcohol use outcomes based on 1 SR with low risk of bias, but low-quality evidence.
KQ2: Depression & SUD	5 SRs	**Moderate SOE:** Treatment with antidepressants may result in improvements in some alcohol outcomes based on moderate-quality evidence from 1 SR with low risk of bias. **Low SOE:** Treatment with interpersonal therapy or behavioral activation may not be associated with improvements in comorbid SUD, based on low- to very low-quality evidence from 2 SRs.
KQ2: Chronic pain & depression	1 SR	**Low SOE:** Treatment with acupuncture may result in improvements in depression outcomes, based on 1 SR with unclear risk of bias.
KQ3: PTSD & SUD	3 SRs	**Low SOE:** Integrated treatments may be more effective than usual care or treatments for either condition alone, based on inconsistent findings from 3 SRs with low risk of bias.
KQ3: SUD & anxiety/depression	1 SR	**Low SOE:** Integrated cognitive-behavioral interventions for individuals with alcohol or drug use and co-occurring anxiety or depression may not be associated with improvements in substance use outcomes, compared to usual care only or a single-disorder intervention, based on indirect but precise information from 1 SR with low risk of bias.
KQ3: SUD & depression	2 SRs	**Low SOE:** Evidence is mixed on the effectiveness of integrated treatments for comorbid SUD and depression compared to usual care or interventions for SUD or depression alone based on indirect, consistent information from 2 SRs with low risk of bias.
KQ3: SUD & bipolar disorder	1 SR	**Insufficient SOE:** It is unclear whether integrated CBT-based interventions for SUD and bipolar disorder are more effective than interventions for SUD alone based on 1 SR with unclear risk of bias.

Abbreviations. CBT=cognitive behavioral therapy; KQ=key question; PTSD=posttraumatic stress disorder; SOE=strength of evidence; SR=systematic review; SUD=substance use disorder; TBI=traumatic brain injury.

EVIDENCE BRIEF

INTRODUCTION

PURPOSE

The Evidence Synthesis Program (ESP) Coordinating Center is responding to a request from the Office of Mental Health and Suicide Prevention (OMHSP) for an Evidence Brief on treatment of comorbid mental health conditions, or mental health conditions comorbid with a traumatic brain injury, substance use disorder, or chronic pain among Veterans and military Service members. Findings from this Evidence Brief will be used to inform the development of a clinical provider toolkit, as required by the Commander John Scott Hannon Veterans Mental Health Care Improvement Act (S.785 2019).[1] The toolkit is intended to enhance clinical provider training in delivery of comprehensive care for Veterans and military Service members with comorbid conditions.

BACKGROUND

Comorbidity refers to an *additional co-occurring condition* in patients with a specific index (*ie*, primary) condition.[2] Psychiatric comorbidity in Veterans and military Service members with a mental health condition, substance use disorder (SUD), traumatic brain injury (TBI), or chronic pain is widespread,[3-8 9] and individual studies have found that these comorbidities are generally associated with a more severe clinical profile and worse outcomes compared to patients without comorbidities.[10-14] Specifically, people with comorbidities often have more severe symptomatology, higher rates of psychological problems, poorer physical health, and greater functional impairment and disability.[15-21] Comorbidity is also associated with a more chronic course of impairment,[22] poorer treatment outcomes,[23] increased treatment dropout,[24] and higher treatment utilization and costs.[15,11,12,25,26] Despite these trends, evidence is sometimes conflicting; for example, while some studies have found greater symptom severity in individuals with comorbid post-traumatic stress disorder (PTSD) and SUD compared to those with 1 disorder,[20,27] others have found no difference in symptom severity.[18,28]

Studies in Veterans demonstrate that psychiatric comorbidity in patients with a mental health condition, SUD, TBI, or chronic pain is associated with negative outcomes.[10-14] In a study using national Veterans Health Administration (VHA) data from fiscal year 2012, Veterans with PTSD with higher levels of psychiatric multimorbidity had a greater likelihood of recent homelessness, SUD, and a range of medical diagnoses, as well as greater psychotropic medication use.[11] In an analysis of data from the National Health and Resilience in Veterans Study, Veterans with probable comorbid PTSD and major depressive disorder (MDD) were more likely to screen positive for current suicidal ideation, lifetime suicide attempts, and probable generalized anxiety and social anxiety disorders, and scored lower on measures of mental health functioning, cognitive functioning, and quality of life compared to Veterans with probable MDD or probable PTSD alone.[12] Comorbidity may be a barrier to care in Veteran populations. For example, Veterans with comorbid PTSD and SUD who are required to abstain from alcohol and other substances to receive treatment in certain settings may be reluctant to do so and may not initiate treatment.[9] Additionally, Veterans with comorbidities have increased service use and higher healthcare costs.[11,12,25,26]

Comorbidity increases clinical complexity, and therapeutic efficacy may differ with the presence of a comorbid condition.[23] The presence of comorbidities can affect treatment priorities, the selection of interventions, and treatment setting.[29] In treatment planning, clinicians must consider the focus of the treatment as well as the sequencing of treatment components.[30] The impact of comorbidity on treatment outcomes is not well understood and there is debate about the optimal treatment course of these patients.[31-33] Overlapping symptomology between conditions may lead to uncertainty over which symptoms to address, when to address them, and which intervention is most appropriate. For example, clinicians may be hesitant to begin trauma-focused treatment for patients with comorbidities because they believe that a comorbid condition may worsen, or inhibit the patients' ability to benefit from the treatment.[34,35] Therefore, the presence of a comorbid condition may require the use of novel approaches or adjustments to existing treatment protocols.[36]

The clinical complexity present in "real-world" populations may not be reflected in clinical trials that exclude participants with comorbidity.[37] For example, randomized controlled trials investigating treatments for PTSD tend to exclude individuals with concurrent SUDs and the trials that do include individuals with comorbid conditions often do not specifically examine this subgroup.[18] Inconsistent definitions, inappropriate comparators, and challenges in outcome measurement also hamper research in this area.[38]

In recent years, increasing effort has been made to test the effects of psychological and pharmacological interventions in comorbid patients. Although most studies do not examine comorbidity as the primary aim, subgroup analyses in trials where a subset of participants have a comorbid condition can tell us whether treatment outcomes were different in those with the comorbid condition versus those without. Additionally, some studies may measure the effect of an intervention that is designed to treat a 'primary' condition in a comorbid sample, while reporting the effects of this intervention on a comorbid, or 'secondary' condition. More recently, 'combined' or 'integrated' treatments (*ie*, those developed specifically for simultaneous treatment of comorbid conditions) have been examined and compared to treatment of comorbid conditions individually. For example, Concurrent Treatment of PTSD and Substance Use Disorder Using Prolonged Exposure (COPE) integrates prolonged exposure, an evidence-based trauma-focused intervention for PTSD, with relapse prevention principles.[35]

Though there has been increased effort in recent years to test interventions in comorbid samples, uncertainty remains regarding the effect of the presence of a comorbid condition on treatment outcomes,[33] the effect of treating a primary condition on a comorbid condition, and the effectiveness of integrated treatments designed to treat both conditions in comorbid populations. The purpose of the review was to identify and synthesize evidence reported in existing SRs related to these questions among adults with PTSD comorbid with anxiety, depression, bipolar disorder, TBI, SUD, or chronic pain; adults with TBI comorbid with anxiety, depression, bipolar disorder, PTSD, SUD, or chronic pain; or adults with anxiety, depression, or bipolar disorder comorbid with SUD or chronic pain.

METHODS

PROTOCOL

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number #CRD42021273109).

KEY QUESTIONS

The following key questions (KQs) were the focus of this review:

KQ1: Among adults with comorbid conditions, is response to treatment of a primary condition (*eg*, PTSD or TBI) impacted by the presence or severity of comorbidities (*eg*, anxiety, depression, bipolar disorder, SUD, or chronic pain)?

KQ2: Among adults with comorbid conditions, does treatment of patients' primary condition (*eg*, PTSD or TBI) lead to clinical improvement of comorbidities (*eg*, anxiety, depression, bipolar disorder, SUD, or chronic pain)?

KQ3: Among adults with comorbid conditions, what is the effectiveness of integrated treatment of patients' primary condition and comorbidity compared to nonintegrated treatment?

ELIGIBILITY CRITERIA

The ESP included studies that met the following criteria:

***P**opulation*	Adults with PTSD comorbid with anxiety, depression, bipolar disorder, TBI, SUD, or chronic pain; adults with TBI comorbid with anxiety, depression, bipolar disorder, PTSD, SUD, or chronic pain; or adults with anxiety, depression, or bipolar disorder comorbid with SUD or chronic pain
***I**ntervention*	• KQ1, KQ2: Treatment of primary condition (*eg*, PTSD or TBI); treatments with demonstrated efficacy for the primary condition may be prioritized over developmental treatments with limited evidence of efficacy • KQ3: Integrated treatment of primary condition and comorbidity
***C**omparator*	• KQ1: Treatment of primary condition in patients without comorbidity • KQ2: Any (*eg*, alternative treatment, placebo, treatment referral), or no comparator • KQ3: Nonintegrated treatment
***O**utcomes*	Clinical outcomes (*eg*, patient-reported symptoms, diagnostic status)
***T**iming*	Any
***S**etting*	Any

***S**tudy Design* Using a best-evidence approach, we will prioritize evidence from systematic reviews and randomized controlled trials. Inferior study designs will only be accepted to fill gaps in higher-level evidence.

DATA SOURCES AND SEARCHES

Preliminary scoping searches identified a very large quantity of primary literature relevant to the KQs, and additional exploratory searches identified a number of recent systematic reviews (SRs) on the topic of treatment of comorbid conditions. As a result, the current review was limited to SRs published in the last 7 years. To identify SRs relevant to the KQs, a research librarian searched Ovid MEDLINE and Cochrane Database of Systematic Reviews (CDSR), as well as the Agency for Healthcare Research and Quality (AHRQ), Canadian Agency for Drugs and Technologies in Health (CADTH), and the Department of Veteran Affairs' Health Services Research and Development Service (HSR&D) for systematic reviews published from 2014 through August 2021, using terms for the conditions of interest (*ie*, PTSD, anxiety, depression, bipolar disorder, SUD, TBI, or chronic pain) and comorbidity (see Appendix A in the Supplemental Materials for complete search strategies). We limited the search to published and indexed articles available in the English language.

Study selection was based on the eligibility criteria described above (see Appendix B in the Supplemental Materials for full inclusion/exclusion criteria). SRs had to meet 4 criteria established by the AHRQ Evidence-based Practice Program[39] to merit inclusion: 1) have an explicit and adequate search; 2) apply predefined eligibility criteria to select studies; 3) conduct risk of bias assessment for included studies; and 4) present a synthesis of results. All titles, abstracts, and full-text articles were reviewed by 1 investigator and checked by another. All disagreements were resolved by consensus or discussion with a third reviewer.

DATA ABSTRACTION AND ASSESSMENT

Information on population, intervention, and comparator characteristics and results for each KQ were abstracted from all included studies. As the eligibility criteria of the included SRs was often broader than the criteria for this review, we only abstracted data that met our criteria, when possible. The internal validity (risk of bias) of each included SR was rated using predefined criteria from the ROBIS tool.[40] All data abstraction and internal validity ratings were first completed by 1 reviewer and then checked by another; disagreements were resolved by consensus or discussion with a third reviewer.

We graded the strength of the evidence based on the AHRQ Methods Guide for Comparative Effectiveness Reviews.[41] This approach provides a rating of confidence in reported findings based on trial methodology (design, quality, and risk of bias), consistency (whether effects are in the same direction and have a consistent magnitude), and directness (whether assessed outcomes are clinically important to patients and providers). When information on precision of findings (*eg*, confidence intervals) is available, certainty of evidence is also evaluated. For this review, we applied the following general algorithm: *high strength* evidence consisted of at least 1 high-quality SR of multiple RCTs with consistent findings and either no or only minor methodological limitations of included RCTs; *moderate strength* evidence consisted of at least 1 moderate- or high-quality SR of multiple RCTs or non-randomized studies with consistent findings but some methodological limitations of included studies; *low strength* evidence consisted of at least 1 moderate- or high-quality SR of multiple RCTs or non-randomized studies with inconsistent

findings or significant methodological limitations of included studies; and *insufficient* evidence consisted of a single poor-quality SR or a single moderate- or high-quality SR with few relevant included studies with significant methodological limitations. Strength of evidence was graded for each KQ and combination of comorbid conditions where at least 1 SR included a synthesis of relevant results. All strength of evidence ratings were first completed by 1 reviewer then checked by another. All disagreements were resolved by consensus or discussion with a third reviewer.

SYNTHESIS

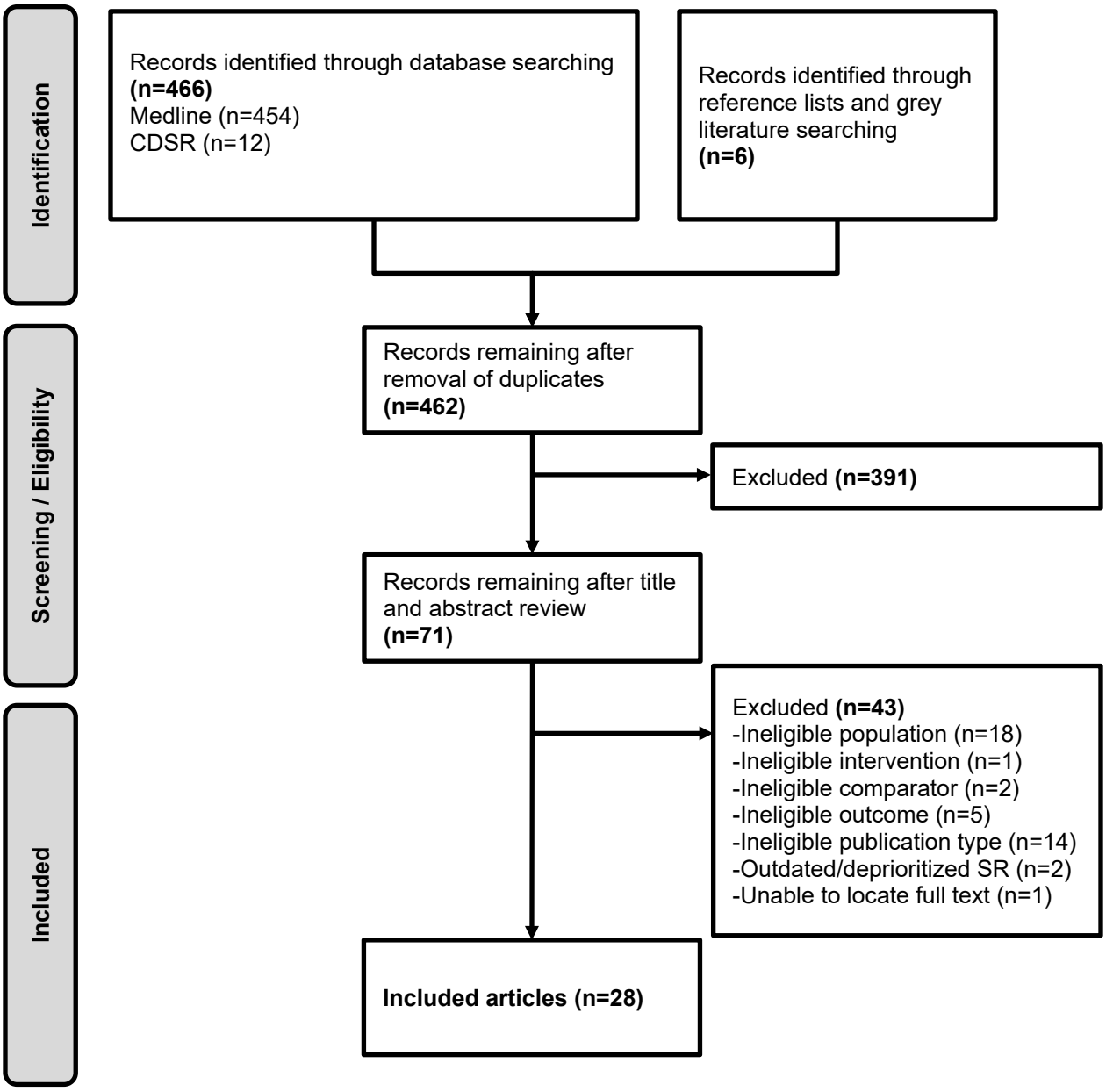
We synthesized evidence narratively from only the included SRs that: 1) conducted a quantitative analysis of 1 or more relevant studies; 2) graded the strength of evidence or certainty of evidence of 1 or more relevant studies; or 3) include a narrative synthesis of the results of 2 or more relevant studies. SRs that only report the results of relevant studies individually in narrative form were not synthesized for this review. Our findings are organized first by KQ then by comorbidity.

RESULTS

LITERATURE FLOW

The literature flow diagram (Figure 1) summarizes the results of the study selection process (full list of excluded studies available in Appendix C in Supplemental Materials).

Figure 1. Literature Flowchart



Note. Included articles consist of 26 studies in 28 publications.
Abbreviations. CDSR=Cochrane Database of Systematic Reviews; SR=systematic review.

LITERATURE OVERVIEW

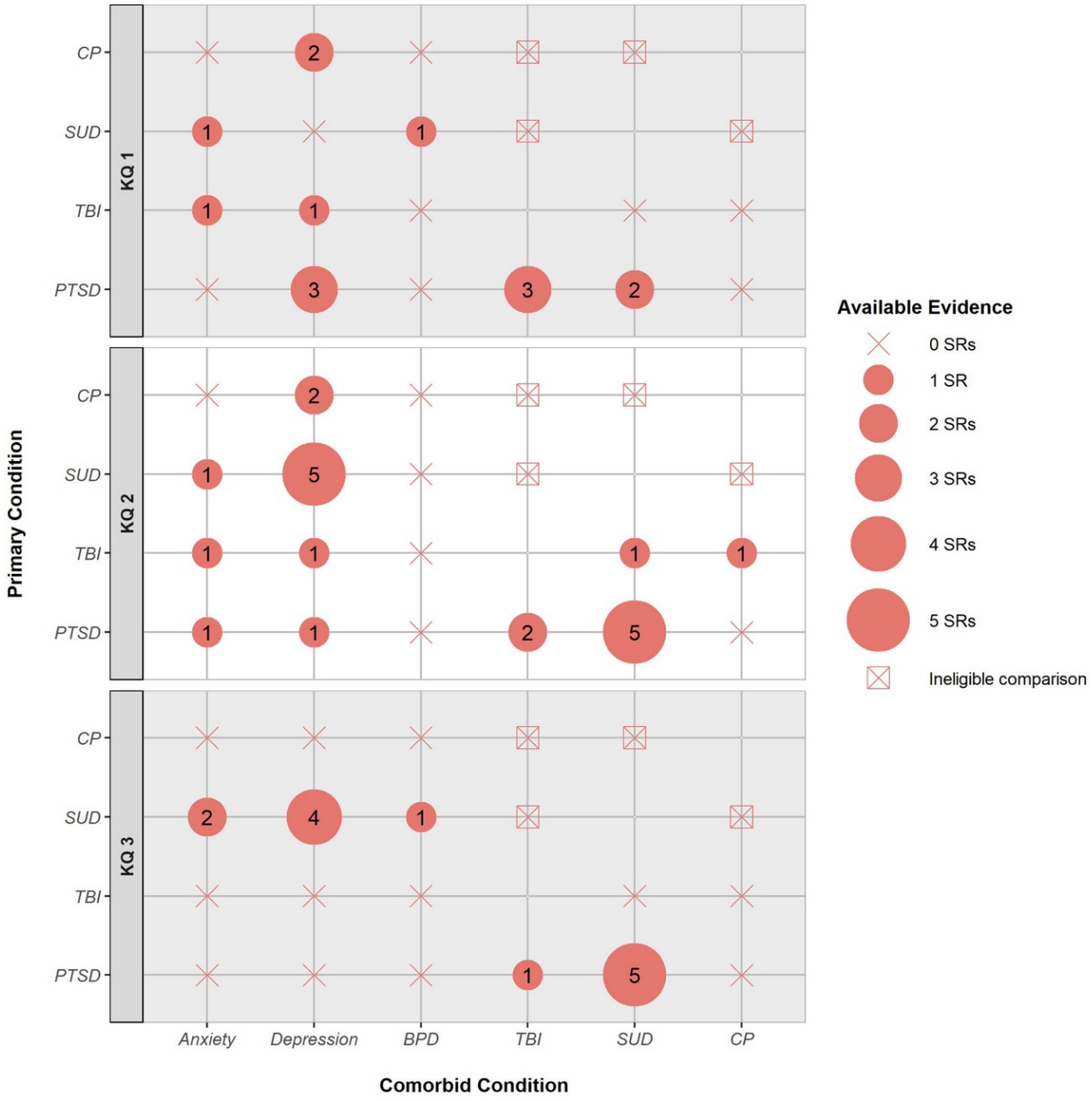
Our search identified 462 potentially relevant articles. We included 26 SRs in 28 publications. Five SRs met our inclusion criteria but did not synthesize results of the relevant studies, either quantitatively or qualitatively,[42-46] and are not discussed in the detailed synthesis for each KQ.

Eligibility criteria of the 26 SRs are summarized in Table 1 (see Appendix D in Supplemental Materials for full study details). Twelve SRs reviewed evidence related to KQ1,[33,37,44-53] 16 reviewed evidence related to KQ2,[37,43,44,50-52,54-63], and 10 reviewed evidence related to KQ3. Sixteen SRs reviewed evidence on SUDs,[37,42-44,47,51,54-57,59,61,62,64-66] 15 reviewed evidence on depression,[33,42,43,49,53-59,61,63,65,66] 13 reviewed evidence on PTSD,[33,37,42,44,46,48,50-52,59,62,64,67] 7 (in 8 publications) reviewed evidence on anxiety,[42,45,50,53,56,58,64,66] 5 reviewed evidence on chronic pain,[43,49,53,60,63] 4 reviewed evidence on TBI,[50,52,60,64] and a single SR reviewed evidence on bipolar disorder.[47] Figure 2 shows the quantity of SRs included for each potential combination of comorbid conditions by each KQ. We found the largest volume of evidence (5 reviews each) for PTSD comorbid with SUD and for SUD comorbid with depression relevant to KQ2, and for the PTSD and SUD comparison applicable to KQ3. No evidence was identified for the combinations of PTSD and bipolar disorder, PTSD and chronic pain, TBI and bipolar disorder, chronic pain and anxiety, and chronic pain and bipolar disorder.

Most SRs focused on psychosocial interventions (13 SRs in 14 publications),[33,42-45,47,48,55,58,61,62,65-67] while a smaller number focused on pharmacological interventions (5 SRs)[37,49,54,56] or multiple treatment types (5 SRs in 6 publications).[50-53,60,64] There was 1 SR each evaluating the effectiveness of deep transcranial magnetic stimulation,[57] hyperbaric oxygen therapy,[46] and acupuncture.[63] One SR was specifically focused on Veterans and military Service members,[60] and there were 2 SRs where all relevant studies were conducted with Veterans and/or military Service members.[46,52] Other SRs included some relevant studies with Veteran and/or military Service member samples.[37,51,62,67]

Most SRs were rated as low (n = 13) or unclear (n = 7) risk of bias, and 15 SRs included only RCTs or controlled clinical trials. Reviews rated as unclear risk of bias were commonly limited by unclear eligibility criteria and insufficient information on study selection, data abstraction, and/or risk of bias assessment. Reviews rated as high risk of bias were further limited by insufficient efforts to identify studies, inadequate methods of data abstraction and risk of bias assessment, and failure to discuss individual studies' risk of bias when interpreting results. A range of tools was used to assess study quality and/or risk of bias across the SRs. Generally, the SRs reported some methodological concerns for most of the primary studies, and 2 SRs excluded studies rated as high risk of bias.[33,58]

Figure 2. Availability of Evidence from Included Systematic Reviews



Note. Figure represents distribution and quantity of available evidence according to the comorbid pairings examined in this report and does not reflect strength of evidence ratings for each pairing.
Abbreviations. BPD=bipolar disorder; CP=chronic pain; KQ=key question; PTSD=posttraumatic stress disorder; SUD=substance use disorder; SRs=systematic reviews; TBI=traumatic brain injury

Table 1. Eligibility Criteria of Prioritized Systematic Reviews

Study	Population	Interventions	Comparators	Outcomes	Study Designs
Agabio, 2018[54]	People with co-occurring depression and alcohol dependence	Antidepressants alone or in combination with other drugs, psychosocial interventions (or both)	Placebo, no intervention, other pharmacological interventions, any psychosocial intervention	Depression severity, response to anti-depressive treatment, depression remission, alcohol consumption, liver enzyme levels, acceptability, tolerability, suicide/suicide attempts	RCTs and CCTs
Banerjee, 2017[42]	Adults with substance use disorder and trauma-related comorbidities (PTSD, anxiety, depression)	KQ1 - concurrent treatment; KQ2 - treatment for 1 condition alone	KQ1 - treatment for primary condition alone, sequential treatment, TAU, no treatment, waitlist; KQ2 - treatment for comorbidities alone, TAU, no treatment, waitlist	Symptoms, duration of substance use or severity, duration of abstinence, relapse prevention, health-related quality of life	HTAs, SRs, MAs, RCTs, non-randomized studies
Barrett, 2016[43]	Adults	Behavioral interventions designed to treat at least 2 of 3 conditions: chronic pain, depression, substance use disorder	Not specified	Not specified	RCTs
Crowe, 2021[47]	Adults meeting criteria for bipolar disorder with a diagnosis of current SUD	Manualized psychotherapy as an adjunct to medication	Not specified	Not specified	RCTs
Dewar, 2020[48]	Adults with a PTSD diagnosis or a clinical level of PTSD symptomatology indicative of a probable PTSD diagnosis	PTSD psychotherapy	Not specified	Severity of PTSD across time points	Not specified
Forte, 2015[49]	Adults with fibromyalgia	Pharmacologic treatments for fibromyalgia	Placebo, sham, alternate dose or dosing regimen, any active pharmacologic or nonpharmacologic treatment	Change from baseline in overall pain, symptom improvement, physical and/or emotional function, participation in work or	RCTs, pooled analyses of individual patient-level RCT data,

Study	Population	Interventions	Comparators	Outcomes	Study Designs
				social activities, health-related quality of life, fatigue, sleep quality, adverse events. Reported outcomes in at least 1 subgroup	observational studies
Greer, 2019[50] Ackland, 2019[64]	US OEF/OIF/OND active-duty SMs and Veterans with a history of deployment-related TBI	Pharmacological and non-pharmacological interventions for the management of PTSD, depressive disorders, SUD, suicidal ideation or attempts, and anxiety disorders	Placebo, alternative pharmacological and non-pharmacological interventions including waitlist	Clinically important changes in symptoms and changes in function and quality of life	Observational or RCT designs
Hides, 2019[55]	Adults and adolescents diagnosed with comorbid depression and SUDs	Psychological treatments	No treatment, delayed treatment, TAU, other psychological treatments	Depression, substance use, treatment retention	RCTs
Hobden, 2018[65]	Individuals over 16 reporting some form of alcohol misuse or undergoing treatment for alcohol misuse as well as reporting elevated depressive symptoms or with a diagnosis of depression	Psychosocial treatment delivered via a dual-treatment model (sequential, parallel, or integrated)	Single-focused treatment	Studies measuring both alcohol use and depression with a standard instrument at baseline and post-intervention	RCTs, CCTs, controlled before and after studies, interrupted time series
Hoffman, 2018[51]	Adults with PTSD based on any DSM criteria	Psychological or pharmacological interventions	Another intervention, waitlist, usual care, no intervention, sham, placebo	Symptom reduction, loss of diagnosis, prevention or reduction of comorbid medical or psychiatric conditions, quality of life, disability or functional impairment, return to work or active-duty status, adverse events	RCTs

Study	Population	Interventions	Comparators	Outcomes	Study Designs
Ipser, 2015[56]	Individuals diagnosed with alcohol dependence or abuse and an anxiety disorder according to DSM criteria	Pharmacotherapy for anxiety	Placebo, standard treatment, other medications	Clinical treatment response, reduction of symptom severity, acceptability of medication, abstinence and reduction of alcohol use, reduction of comorbid symptoms of depression	RCTs
Kedzior, 2018[57]	Individuals with SUD	Deep transcranial magnetic stimulation with any type of H-coil	Not specified	SUD assessed at baseline and posttreatment	Any study design (except crossover RCTs)
Kline, 2021[33]	Adults with PTSD diagnosed with a validated clinical assessment	At least 1 face-to-face trauma-focused, standardized individual or group psychotherapy treatment conducted primarily in outpatient settings, of at least 4 sessions duration	Not specified	Posttreatment PTSD symptom outcomes with validated measures and information about baseline depression characteristics using a validated clinical interview or depression-specific measure	RCTs with at least 30 participants and a rating of low or moderate risk of bias
Larsen, 2019[58]	Not specified	Empirically supported psychosocial treatments for PTSD	Not specified	Residual PTSD symptoms, as well as symptoms of depression, anxiety, and quality of life	RCTs rated as low or medium risk of bias
Li, 2020[59]	Adults with comorbid AUD and depression or depressive symptoms (greater than the cutoff threshold of valid depressive symptom scales) based on DSM or ICD-10 criteria	Pharmaceutic interventions	Placebo, no-treatment control, another pharmacotherapy	AUD remission rate, percent abstinent days, depressive symptom scale scores	RCTs
Mehta, 2021[66]	Adults meeting DSM criteria for an AOD and at least 1 co-occurring mental health disorder	Integrated cognitive-behavioral (or based on a cognitive-behavioral approach) interventions. Excluded Seeking Safety.	Single-disorder intervention, usual care	Alcohol or other drug use and mental health symptoms at post-treatment through follow-up	RCTs

Study	Population	Interventions	Comparators	Outcomes	Study Designs
Meshberg-Cohen, 2021[44]	Individuals with OUD and PTSD diagnosed via standardized assessment, evidence-based PTSD checklist cut-off, and/or medical record diagnoses	Not specified	Not specified	Relationship between OUD and/or PTSD with OUD or PTSD outcomes	Peer-reviewed studies
Mikolic, 2019[52]	Adults (16+) diagnosed with both TBI and PTSD, provided with treatment for PTSD or diagnosed with TBI and provided with preventive intervention and/or early treatment for PTSD	All types of interventions aimed at treatment of PTSD or PTSD symptoms: psychological, pharmacological, complementary, alternative, and novel medical therapies	Not specified	PTSD symptoms, changes in PTSD diagnosis, treatment adherence and retention, side effects and harms of treatment	Longitudinal studies (*eg*, RCTs, prospective cohort studies, retrospective cohort studies, case-control studies, pre-post studies)
Oliveira, 2018[45]	Adults (17+) with AUD with and without SAD	Not specified	Studies comparing participants with AUD and comorbid SAD versus participants with AUD without SAD	Clinical outcomes (*eg,* alcohol relapse, suicidal thoughts, suicide plan or attempt, treatment response, readmissions, psychiatric comorbidities, treatment compliance)	Review articles and preclinical studies excluded
O'Neil, 2020[60]	US Veterans or Service members with mTBI and chronic pain or headaches	Pharmacologic, nonpharmacologic, and complementary and integrative health interventions	Placebo, active comparator, usual care, waitlist control, pre-post	Prevalence, estimates of suicide risk, benefits, and harms of interventions	For intervention studies, only RCTs and CCTs
Parr, 2021[46]	Patients with TBI, PTSD, or the co-occurrence of TBI and PTSD	Hyperbaric oxygen therapy	Any	Benefits (mortality, morbidity, quality of life, functional capacity, TBI and/or PTSD symptom improvement/symptom response) and harms	SRs, RCTs, and concurrently controlled cohort studies.
Petrakis, 2017[37]	Individuals diagnosed with AUD and PTSD	Pharmacotherapy with or without behavioral intervention	Not specified	AUD and PTSD outcomes, treatment dropout	RCTs

Study	Population	Interventions	Comparators	Outcomes	Study Designs
Pott, 2021[61]	Adult substance users with clinically significant depression symptoms	Behavioral activation	Passive or active control	Depressive symptomatology, substance use, abstinence from substances	RCTs
Roberts, 2015[67] Roberts, 2016[62]	Individuals with comorbid PTSD and SUD based on DSM or ICD criteria	Any psychological therapy designed to reduce symptoms of PTSD, substance usage, or both	No intervention, minimal intervention such as waiting-list control, TAU, minimal or placebo condition, or an active psychological therapy	PTSD symptom severity, reduction in drug or alcohol use, treatment completion	RCTs
Skelly, 2020[53]	Adults with the following chronic pain conditions: low back pain, neck pain, osteoarthritis pain, fibromyalgia, tension headache	Exercise, psychological therapies, physical modalities, manual therapies, mindfulness practices, mind-body practices, acupuncture, multidisciplinary/ interdisciplinary rehabilitation	Sham, waitlist, usual care, no treatment, attention control, nonopioid pharmacological therapy, topical agents, medical cannabis, exercise, biofeedback	Function/disability/pain interference, pain, harms and adverse events, psychological distress, quality of life, opioid use, sleep quality, sleep disturbance, healthcare utilization	RCTs or high-quality SRs
Yan, 2020[63]	Patients diagnosed with chronic pain and depression	Acupuncture alone or in combination with other therapy	Other therapy without acupuncture	Pain scores, depression severity, adverse events	RCTs

Abbreviations. AOD=alcohol or other drug use disorder; AUD=alcohol use disorder; CCT=controlled clinical trial; DSM=Diagnostic and Statistical Manual of Mental Disorders; HTA=health technology assessment; ICD=International Classification of Diseases; KQ=key question; MA=meta-analysis; mTBI=mild traumatic brain injury; OEF/OIF/OND=Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn; OUD=opioid use disorder; PTSD=posttraumatic stress disorder; RCT=randomized controlled trial; SAD=social anxiety disorder; SM=Service member; SR=systematic review; SUD=substance use disorder; TAU=treatment as usual; TBI=traumatic brain injury; US=United States.

IMPACT OF PRESENCE OR SEVERITY OF COMORBIDITIES ON TREATMENT OF PRIMARY CONDITION

PTSD and Depression

Findings from 2 SRs[33,48] suggest that a diagnosis of comorbid depression may have a negative impact on PTSD treatment outcomes. This evidence is limited by indirect, imprecise, and inconsistent information. One well-conducted SR of trajectories and predictors of response to psychotherapy for PTSD[48] reported that a baseline diagnosis of MDD negatively impacted PTSD treatment response. This finding was based on a single study that conducted a trajectory analysis using data from 2 RCTs of cognitive processing therapy (CPT), CPT components, and prolonged exposure (PE). The results indicated that a baseline diagnosis of MDD significantly predicted assignment to a 'nonresponder' trajectory among patients with PTSD (*ie,* pre- and post-intervention scores were both above the clinical PTSD cutoff). Though it was not a focus of the current review, this SR also included 8 SRs that examined baseline symptoms of depression, most of which found a strong association between baseline depression symptoms and PTSD treatment response.

Another SR examined the effect of comorbid depression on PTSD outcomes in trauma-focused psychotherapy.[33] Among 18 RCTs reporting categorical depressive disorder baseline data, the proportion of the sample meeting a depressive disorder diagnosis at baseline was not significantly associated with pre- to post-treatment PTSD effect sizes across all conditions. This SR identified a larger number of studies that reported depression symptoms only. Though these data do not meet criteria for the current review, it is worth noting that greater pre-treatment depression scores, measured continuously, were associated with attenuated PTSD symptom change. This SR conducted a limited literature search, primarily relying on 2 prior SRs to identify studies, and the use of proportions in this SR may misrepresent the actual within-study relationship between PTSD and depression (*ie*, aggregation bias).

PTSD and TBI

Based on information from 2 SRs,[50,52] it is unclear whether a history of TBI has a negative impact on PTSD treatment outcome. One well-conducted SR investigating the relationship between deployment-related mild TBI (mTBI), PTSD, depressive disorders, SUD, suicidal ideation, and anxiety disorders included 3 studies of psychosocial interventions in Veterans with PTSD with and without a history of TBI.[50] Two of these studies were secondary analyses of RCTs, and the third was a pre-post study. Psychosocial interventions included CPT, PE, and present-centered therapy (PCT). These studies were rated as moderate and moderate-to-high risk of bias, and 1 study included a mixed sample of Veterans with anxiety, PTSD, and depressive disorders. The 3 studies found no significant effect of TBI status on PTSD symptoms, but the review rated the strength of evidence as insufficient.

An SR of treatment for PTSD in patients with a history of TBI included 7 pre-post or observational cohort studies that compared treatment outcomes of cognitive and/or behavioral psychotherapies for PTSD in patients with history of TBI versus those without.[52] Results of the included studies in this SR were inconsistent and the studies were moderate to high risk of bias in most domains. This SR did not have a pre-published protocol, provided inadequate information on robustness of findings, and risk of bias was not addressed in the synthesis. Overall, this evidence is limited by indirect, inconsistent information from these 2 SRs.

Chronic Pain and Depression

Findings from 2 SRs[49,63] suggest that a diagnosis of comorbid depression may not have an impact on chronic pain outcomes. An update to an AHRQ comparative effectiveness review[53] on noninvasive nonpharmacological treatment for chronic pain looked at the effects of comorbidities on estimates of benefits and harms. This well-conducted SR identified only 1 relevant, fair-quality trial and concluded that there was insufficient evidence that baseline depression status modifies the effect of exercise in patients with osteoarthritis of the knee. Another AHRQ review[49] looked at the comparative effectiveness of treatments for fibromyalgia in different patient subgroups, including adults with comorbid mental health conditions. This well-conducted SR found that drug treatments did not appear to have a differential effect in adults with fibromyalgia and depression versus those without depression, but this was based on limited, low-strength evidence, mostly for the effect of duloxetine on pain outcomes. Both SRs identified very little evidence on patients with comorbid depression and chronic pain, which is limited by imprecise and inconsistent information.

ASSOCIATION OF TREATMENT OF PRIMARY CONDITION WITH IMPROVEMENT IN COMORBIDITIES

PTSD and Anxiety

Findings from 1 SR[58] do not suggest that treatment of PTSD is associated with improvements in comorbid anxiety. This SR included RCTs of empirically supported trauma-focused cognitive behavioral psychological treatments for PTSD and categorized residual comorbidity (anxiety) symptoms as either clinical, subthreshold, or minimal/absent using established symptom cutoffs. Most study arms reporting anxiety symptoms stayed in the 'clinical' range from pre- to post-treatment and follow-up. This SR relied on 2 prior SRs to identify studies and did not conduct any additional searches. RCTs rated as high risk of bias were excluded from the review; however, the review reported the proportion of study arms with residual symptoms, which may misrepresent an actual within-study relationship between PTSD and anxiety. The evidence is limited by indirect, imprecise information from a single SR.

PTSD and Depression

Findings from the same SR[58] cited in the previous comparison suggest that treatment of PTSD may lead to an improvement in comorbid depression. Most study arms with data on depression symptoms were in the clinical range pre-treatment. At post-treatment, most were in the subthreshold range and continued to improve at follow-up. Again, this SR reported the proportion of study arms with residual symptoms, which may misrepresent an actual within-study relationship between PTSD and depression. The evidence is limited by indirect, imprecise information from a single SR.

PTSD and SUD

Findings from 3 SRs[37,56,62] examining whether treatment of PTSD leads to improvements in comorbid substance use disorder (SUD) do not suggest that treatment of PTSD is associated with improvements in comorbid SUD. One SR of pharmacological treatments for comorbid PTSD and AUD found mixed results and had unclear eligibility criteria, inadequate information about the search, study selection, and data abstraction, and inadequate methods of risk of bias assessment.[37] A well-conducted SR of pharmacotherapy for anxiety and comorbid AUD[56]

included 2 RCTs with PTSD samples and did not identify a significant effect of any tested medication on abstinence from alcohol use. Another well-conducted SR of psychological therapies for PTSD and comorbid SUD[62] did not find a significant difference between trauma-focused psychological therapy versus control interventions (3 studies; very low quality of evidence), trauma-focused psychological therapy versus psychological therapy for SUD only (1 study; low quality of evidence), or non-trauma-focused psychological therapy versus psychological therapy for SUD (2 studies; low quality of evidence) on SUD outcomes. Evidence was sparse in the 2 well-conducted SRs and is limited by imprecise information.

Chronic Pain and TBI

It is unclear whether treatment of chronic pain leads to improvements in TBI-related outcomes based on information from a single well-conducted SR.[60] This SR examined chronic pain in Veterans and Service members with a history of mild traumatic brain injury (mTBI). Two studies were included that reported outcomes relevant to mTBI. Both studies tested the efficacy of repetitive transcranial magnetic stimulation (rTMS) in individuals with chronic headaches following mTBI, finding greater reduction in persistent headaches and debilitating headache exacerbation in the rTMS group compared to sham rTMS. Both studies were small and were rated as high risk of bias. It is not clear whether headache can be considered a TBI outcome, since the chronic pain condition studied was headache, and the evidence from this SR was considered indirect as a result. The evidence is limited by indirect and imprecise information from 2 small studies with methodological issues.

Anxiety and SUD

It is unclear whether treatment of anxiety impacts alcohol use outcomes in individuals with comorbid AUD, based on information from a single SR.[56] This well-conducted SR synthesized results from 2 included studies that reported alcohol use outcomes. These studies were small RCTs that evaluated the efficacy of paroxetine for social anxiety disorder compared to placebo. There was no significant effect for medication on abstinence from alcohol use, and the authors rated this evidence as very low quality. The evidence is limited by imprecise information from 2 small RCTs.

Depression and SUD

Findings from 1 SR[54] suggest that treatment with antidepressants may result in improvements in some alcohol outcomes. A well-conducted SR on antidepressants for co-occurring depression and alcohol dependence found moderate-quality evidence that antidepressants increased the number of participants abstinent from alcohol during the trial (7 RCTs) and reduced the number of drinks per drinking day (7 RCTs) compared to placebo. Rate of abstinent days did not significantly differ between antidepressant and placebo groups (9 RCTs), based on low-quality evidence.

One well-conducted SR[59] included a network meta-analysis of pharmacotherapeutics for patients with AUD and comorbid depression symptoms. Sensitivity analyses were conducted excluding studies in which participants had only mild depressive symptoms. However, in their analyses, drug treatments for depression and AUD are combined, and results are not reported separately for the effect of AUD treatments only on depressive outcomes, or depression treatments only on AUD outcomes.

Findings from 2 SRs[55,61] do not suggest that treatment with interpersonal therapy or behavioral activation is associated with improvements in comorbid substance use. One well-conducted SR of psychological interventions for co-occurring depression and SUDs included 2 small, low-quality RCTs comparing Interpersonal Psychotherapy for Depression (IPT-D) to supportive psychotherapy/psychoeducation. Neither study found significant differences in substance use outcomes post-treatment or at 3-month follow-up. The second SR conducted a meta-analysis of 5 studies comparing behavioral activation to passive or active control conditions for individuals with co-occurring depression and SUDs (not all included studies required a full SUD diagnosis).[61] Behavioral activation was not associated with significant improvements in substance use outcomes compared with controls at post-treatment or follow-up. This SR was limited by discrepancies in eligibility criteria between the protocol and the review, and inadequately reported its search strategy.

One SR synthesized evidence related to whether deep transcranial magnetic stimulation (dTMS) treatment for SUD leads to improvements in comorbid depression.[57] In 4 very small studies (2 case studies and 2 open-label studies), depression severity was reduced both post-treatment and at follow-up. This SR had unclear eligibility criteria, reported inadequate information about study selection, and lacked risk of bias assessment for our studies of interest. Additionally, although depression was the secondary condition in this SR, TMS is more commonly considered a treatment for depression.

Chronic Pain and Depression

Findings from 1 SR[63] suggest that treatment of chronic pain with acupuncture may result in improvements in depression outcomes. This SR investigated the efficacy of acupuncture in individuals with chronic pain and depression and included 7 RCTs comparing acupuncture to either drug therapy or traditional Chinese medicine. In a meta-analysis of 6 trials using the Hamilton Depression Scale (HAMD), improvement in depression symptoms was significantly greater for the acupuncture group after 4 weeks of treatment. This SR had unclear eligibility criteria and insufficiently described its search and data abstraction. This evidence is limited by the unclear risk of bias of the SR and the low quality of the included studies.

EFFECTIVENESS OF INTEGRATED TREATMENT COMPARED TO NONINTEGRATED TREATMENT

PTSD and SUD

Findings from 3 SRs[51,66,67] suggest that integrated treatments may be more effective than usual care or treatments for either condition alone. An update to an AHRQ comparative effectiveness review on psychological and pharmacological treatments for adults with PTSD[51] included 3 studies on Seeking Safety, an intervention that targets both PTSD and SUD symptoms. These studies compared Seeking Safety to usual care and found greater improvements in PTSD symptoms in the experimental group, but these differences were not statistically significant. Two of these studies reported substance use outcomes. One study found no significant difference for abstinence and substance use severity between the groups, and the other found significantly greater decreases in drug use (but not alcohol use), in the Seeking Safety group. In these studies, usual care consisted of a residential substance use treatment program, community care, or group therapy sessions.

A well-conducted SR of integrated cognitive-behavioral interventions for individuals with an alcohol or other drug use disorder (AOD) and a co-occurring mental health disorder[66] included 8 RCTs of individuals with PTSD and an AOD. Interventions included Integrated Cognitive Behavioral Therapy (ICBT), Thinking Forward (a web-based self-management intervention based on CBT targeting PTSD symptoms and hazardous substance use), Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure (COPE), and Treatment of Integrated Posttraumatic Stress and Substance Use (TIPSS). This review excluded studies on Seeking Safety. Primary study effect sizes were pooled by contrast condition (usual care, single-disorder intervention) or mental health disorder, but not both. For substance use outcomes, a meta-analysis found significant positive results for PTSD samples. Risk of bias results were not provided for this subset of studies, but half of all studies included in this SR were rated as high risk of bias.

An SR of psychological therapies for PTSD and comorbid SUD[67] found that individual-based psychological therapies with a trauma-focused component plus adjunctive SUD intervention were more effective than treatment as usual/minimal intervention for PTSD severity post-treatment (4 studies) and at follow-up, but there was no evidence of a significant effect for level of drug/alcohol use posttreatment (4 studies). A post-hoc analysis for Seeking Safety showed reduced drug/alcohol use post-treatment (2 studies), but not at follow-up assessments.

Overall, this evidence is limited by inconsistent information across different outcomes and time points. Though usual care often consists of treatment for a single condition, this was not always clearly specified. Two of the SRs graded the strength of evidence, with assessments ranging from low to very low to insufficient. Of note, 3 recently published trials on COPE,[68-70] an integrated treatment for PTSD and SUD, were not included in any SRs.

SUD and Anxiety/Depression

Findings from a single SR[66] do not suggest that integrated cognitive-behavioral interventions for individuals with an AOD and co-occurring anxiety or depression are associated with improvements in substance use outcomes, compared to usual care only or a single-disorder intervention. This well-conducted SR of integrated cognitive-behavioral interventions for individuals with an AOD and a co-occurring mental health disorder included 7 RCTs of individuals with anxiety/depression and an AOD. Anxiety and depression diagnoses were included together in a single category. Primary study effect sizes were pooled by contrast condition (usual care, single-disorder intervention) or mental health disorder category, but not both. Substance use outcomes were not significantly improved for depression and/or anxiety samples. Risk of bias results were not provided for this subset of studies, but half of all studies included in this SR were rated as high risk of bias. This evidence is limited by indirect information from 1 SR that included several studies with methodological limitations.

SUD and Depression

Two SRs[55,65] provide mixed evidence on the effectiveness of integrated treatments for comorbid SUD and depression compared to usual care or interventions for SUD or depression alone. A well-conducted SR of psychological interventions for co-occurring depression and SUDs[55] included a meta-analysis of 2 RCTs comparing integrated cognitive-behavioral therapy (ICBT) to Twelve-Step Facilitation (TSF; an SUD treatment) in Veterans. The TSF group had lower depression scores posttreatment, but there was no significant difference at follow-up (very low-

quality evidence). At posttreatment there was no significant difference in proportion of days abstinent, but at follow-up the ICBT group had a greater proportion of days abstinent. A third study comparing Behavioral Therapy for Depression in Drug Dependence (BTDD) to a structured relaxation intervention in participants with opiate dependence and a comorbid depressive disorder found no significant differences in posttreatment depression scores and no significant differences in the proportion of weeks during which opiates, cocaine, and benzodiazepines were used throughout treatment.

A well-conducted SR comparing different treatment models for individuals with co-occurring alcohol misuse and depression[65] included 4 moderate-quality RCTs evaluating integrated treatments. Two studies compared an integrated intervention to usual care. One study found significant improvements for certain alcohol outcomes while the second showed significant improvements for depression outcomes. Two further studies compared integrated interventions to single condition interventions for either alcohol or depression. One study reported significant improvements in alcohol-related outcomes among those receiving integrated interventions compared to single condition treatments, while neither study reported improvements in depression outcomes. Overall, this evidence is limited by indirect information. One of the SRs included some studies where not all participants were required to have a diagnosis of both conditions. Both SRs graded the strength of evidence with assessments ranging from low to very low.

SUD and Bipolar Disorder

It is unclear whether integrated CBT-based interventions for SUD and bipolar disorder are more effective than interventions for SUD alone, based on information from 1 SR.[47] This SR included 2 small RCTs of integrated psychotherapy for comorbid bipolar disorder and SUD which found mixed results. One study found that participants receiving integrated group CBT had significantly fewer days of substance use but worse mood symptoms comparing to participants receiving group drug counseling. Another study randomized participants to the same treatments, modified for a community setting, and found no significant differences for either SUD or mood symptoms. This SR lacked a pre-published protocol and had unclear eligibility criteria. This evidence is limited by imprecise information from a single SR.

DISCUSSION

This review synthesizes recent evidence from SRs on the impact of psychiatric comorbidities on patient care and the treatment of comorbid conditions. Six SRs synthesized evidence related to whether response to treatment of a primary condition is impacted by the presence or severity of a comorbid condition.[33,48-50,52,53] These SRs reviewed evidence for 3 combinations of conditions: PTSD and depression, PTSD and TBI, and chronic pain and depression. Only 1 SR[48] concluded that the presence of a comorbid condition had a negative impact on treatment outcomes. Based on data from a single study, this SR found that a baseline diagnosis of MDD significantly predicted nonresponse to PTSD treatment. Though the other SRs did not find that the presence of a comorbid condition impacts response to treatment, the number of relevant studies identified by these SRs was small, and the evidence was inconsistent.

There was mixed evidence from SRs that treatment of a primary condition leads to clinical improvement of comorbidities. For SRs that evaluated PTSD comorbid with another condition (depression, anxiety, or SUD), only comorbid depression appeared to improve as a result of PTSD treatment. This evidence is limited by indirect and imprecise information from a single SR that included studies of trauma-focused psychotherapy for PTSD. One well-conducted SR on comorbid depression and SUD found that treatment with antidepressants resulted in improvements in certain alcohol outcomes. This finding was not replicated in other SRs evaluating the effect of psychosocial depression treatments on SUD outcomes. Findings from 1 SR suggest that treatment of chronic pain with acupuncture may also result in improvements in depression outcomes, although the included studies were rated as low quality.

The included SRs evaluated integrated treatments for 4 comorbid conditions (PTSD and SUD, SUD and anxiety/depression, SUD and depression, and SUD and bipolar disorder). Our findings suggest that integrated treatments for PTSD/SUD may be more effective than usual care or treatments for either condition alone. There was evidence from 1 SR that integrated cognitive-behavioral interventions were associated with greater improvements in substance use outcomes compared to usual care and single-condition interventions. Evidence from 2 SRs on Seeking Safety was inconsistent across different outcomes and time-points. Results on treatments that target the other comorbid conditions were mixed or did not indicate benefit of integrated treatments compared to usual care interventions.

Of note, multiple recently published trials of COPE with Veterans[68-70] were not included in an SR, including 1 which compared COPE to Seeking Safety.[70] A literature review that included these trials concluded that COPE is effective for comorbid PTSD and SUD and may be more effective than Seeking Safety for PTSD outcomes.[9] However, this review did not perform risk of bias assessment and thus did not meet our criteria for inclusion. Additionally, SMART-CPT, a new treatment for comorbid PTSD and history of TBI that integrates components of compensatory cognitive training from the Cognitive Symptom Management and Rehabilitation Therapy (CogSMART) program into cognitive processing therapy (CPT) for PTSD, was evaluated in a recent trial with Veterans.[71] This trial was identified by 1 of our prioritized SRs,[52] but the trial results are not synthesized by that SR and therefore are not included in our synthesis. This trial found that SMART-CPT resulted in equivalent reductions in PTSD symptoms and greater improvements to cognitive functioning compared to CPT alone.

Inconsistent findings across the included evidence may reflect different ways of defining and measuring comorbidity, heterogeneous study samples, and methodological variation across the SRs and their included studies. Moreover, there was considerable variability across the SRs with respect to their diagnostic requirements for study eligibility. Some SRs only included studies where all participants met full diagnostic criteria for 2 conditions, while others included studies that defined comorbidity in a variety of ways, such as individuals with elevated symptoms on self-report scales or those in treatment. Differences in diagnostic requirements may lead to different conclusions and may affect the ability to generalize results to a truly comorbid population. For example, an SR examining the effect of comorbid depression on PTSD outcomes in trauma-focused psychotherapy found no association between depression and PTSD treatment response when looking at the proportion of the sample meeting a depressive disorder diagnosis, but found that greater pre-treatment depression scores, measured continuously, were associated with attenuated PTSD symptom change.[33] This highlights the importance of defining and measuring comorbidity consistently.

In addition to differences in diagnostic requirements, there was considerable heterogeneity among studies included in SRs in study samples, experimental interventions and comparators, and outcome measurement, making comparison across studies difficult. Strength of evidence was rated as low to insufficient across all but 1 outcome for this review. This is not surprising given that few methodologically rigorous studies have been designed and conducted to explicitly evaluate the Key Questions. As such, our conclusions, and those of the included SRs, generally rely on indirect, imprecise, and inconsistent information. However, they do provide an overview of knowledge on treatment of comorbid conditions.

Despite the absence of strong evidence from recent SRs to guide treatment of comorbid conditions, there is an emerging pattern of research findings and clinical practice guideline recommendations indicating that: 1) comorbidity should be taken into consideration in the treatment of mental health conditions, substance use, TBI, and chronic pain; and 2) concurrent treatment of comorbid conditions appears to be effective, in particular for the treatment of comorbid PTSD and SUD.[35] Current Veterans Affairs/Department of Defense (VA/DoD) clinical practice guidelines (CPGs) advise that comorbid conditions can modify treatment priorities, selection of interventions, and care setting.[72] The 2017 VA/DoD CPG for the management of PTSD recommends that the presence of co-occurring disorders should not prevent patients from receiving VA/DoD guideline-recommended treatments for PTSD and recommends VA/DoD guideline-based treatments for PTSD in the presence of co-occurring SUD.[72] The 2021 VA/DoD CPG for the treatment of SUD also states that use of a substance should not automatically preclude treatment for a co-occurring condition, and recommends providers address comorbid conditions concurrently with PTSD symptoms.[73] Moreover, recognition by clinicians that individuals with comorbid conditions have unique treatment needs has led to increased interest in fully integrated treatment, as evidenced by recent randomized clinical trials of novel treatment approaches that incorporate evidence-based components targeting multiple comorbid conditions and that can be delivered by a single provider (*eg*, COPE and SMART-CPT).[74]

LIMITATIONS

Rapid Review Limitations

The primary limitation of our review methodology is that we prioritized rapid synthesis of the best available evidence, rather than all available evidence. This approach included: 1)

synthesizing the most recent and relevant systematic reviews; and 2) having a single reviewer assess study eligibility, study quality, and strength of evidence with a second reviewer checking instead of dual, independent review. Search terms used may not have captured studies that were not explicitly focused on comorbidity. It is possible that because of these steps, we missed eligible evidence. Evidence from primary studies not included in systematic reviews is not captured in the current rapid review. This limitation is particularly salient for combinations of comorbid conditions with smaller evidence bases and bodies of evidence that have emerged very recently, such as trials on COPE for comorbid PTSD and SUD.

Limitations of Included Studies

The SRs identified often had broader research questions than those of our review and included primary studies that did not meet our criteria. When possible, we included only evidence from primary studies that met our inclusion criteria. However, this was not possible in all cases, such as when all studies were combined in a quantitative synthesis. Additionally, there may be overlap in the primary studies between included SRs. While we excluded reviews that were entirely redundant, we did not systematically account for overlap between the SRs.

Some reviews did not require that participants meet diagnostic criteria for both a primary condition and comorbid condition, including some studies that examined comorbid symptoms only. Findings from SRs that included studies with samples that did not consist entirely of participants with a diagnosed comorbid condition may have limited generalizability to patients with comorbidities. Reviews examining the impact of treatment for a primary condition in a comorbid population also did not consistently report outcomes related to the 'secondary' comorbid condition, leaving the impact of this treatment on the comorbid condition unknown. For reviews on integrated treatments, some studies did not require that an integrated treatment be compared to a nonintegrated treatment. In cases when an integrated treatment was compared to usual care, usual care sometimes consisted of treatment of a single condition alone, but this was not always clearly specified.

Common methodological limitations of SRs included absence of a pre-published protocol; unclear eligibility criteria; insufficient reporting of information on study selection, data abstraction, and risk of bias assessment; and failure to discuss individual studies' risk of bias when interpreting results. Primary studies within SRs often had methodological limitations, including small sample sizes and other risks of bias, such as unclear methods of sequence generation and/or allocation concealment, lack of blinding of outcome assessors, and incomplete outcome data. In most cases no information was provided about additional treatments that participants were receiving outside of the study. Many studies used self-report instruments for diagnosis, which can be less accurate and more susceptible to biases than structured clinical interviews.

FUTURE RESEARCH

Existing SRs reported mixed results with limitations in study methodologies, sample sizes, and measurement of outcomes. There is a need for better-conducted studies on this topic to provide guidance to providers and policymakers on the treatment of comorbid conditions. Future research is needed that: 1) appropriately and consistently defines and measures comorbidity; 2) utilizes appropriate methodology to allow for conclusions about the impact of comorbidity on treatment outcomes; and 3) specifically aims to examine the treatment of comorbid conditions.

Recommendations for Future Systematic Reviews

In our review, some SRs cited inclusion criteria for individual studies that required that all participants meet full diagnostic criteria for both a primary and comorbid condition, while others required only elevated symptoms on self-report scales or that participants be undergoing treatment. Some SRs did not clearly describe diagnostic requirements and included studies that define and measure comorbidity in different ways. Future SRs should clearly describe their requirements for diagnosis and measurement of comorbid conditions in their eligibility criteria, as overall conclusions from SRs that include studies that look at comorbid symptoms may not be applicable to populations with comorbid conditions. Currently, several trials on integrated treatments are not yet included in SRs. An up-to-date SR is needed to evaluate the current evidence base for integrated treatment of PTSD and SUD, for both PTSD and SUD outcomes.

Recommendations for Future Studies

To increase generalizability, clinical trials should recruit samples that reflect "real-world" clinical complexity, rather than excluding patients with comorbid conditions. Clinical trials investigating treatments for conditions with high rates of comorbidity should include outcome measures related to comorbidity. To determine the impact of the presence or severity of a comorbid condition on treatment of a primary condition, studies are needed that are specifically designed to examine differential effectiveness by comorbidity status. Individual studies are often insufficiently powered to detect the effects of pretreatment sample differences, or "hidden moderators," such as comorbid conditions.[33,75,76] Studies that incorporate pooling of individual participant-level data from multiple sources are better able to identify such moderator effects, and should be more widely implemented.[33]

We found very little research examining the treatment of patients with certain combinations of conditions, despite a high prevalence of comorbidity. For example, over half of individuals with bipolar disorder have a comorbid SUD, but scant research specifically targets treatment of these individuals.[47] Randomized trials are needed to evaluate the comparative effectiveness of different treatment models. Trials evaluating integrated treatments should be designed with an appropriate comparator, such as empirically supported treatment for a single disorder alone. When comparing integrated treatment to usual care, studies should clearly delineate whether usual care consists of treatment for a single disorder alone. To inform treatment of patients with additional related comorbidities, novel transdiagnostic approaches that target the common processes underlying comorbid conditions should be investigated.[77]

Finally, more studies are needed that evaluate the impact and treatment of comorbid conditions in Veterans/military Service members. Several prioritized SRs included studies on Veteran or military Service member populations, but only 1 targeted these populations.[50] Findings from civilian studies may not be generalizable to Veteran/military Service member populations. For example, evidence suggests that Veterans do not respond as well to psychotherapy for PTSD as civilians.[78]

CONCLUSIONS

Although psychiatric comorbidity among Veterans is common, evidence captured in SRs on this topic is limited. Clinicians and policy makers should take this into account when developing tools to improve care for this population. Overall, findings were inconsistent, precluding any

definitive conclusions. The negative impact of a comorbid condition on treatment is unclear and likely depends on the specific comorbidity. For example, 1 SR concluded that a baseline diagnosis of MDD significantly predicted nonresponse to PTSD treatment. For individuals with mental health conditions comorbid with an additional mental health condition, SUD, TBI, or chronic pain, it remains unclear whether treatment for 1 disorder results in improvements in a second disorder. One exception appears to be that treatment with antidepressants results in improvements in certain alcohol outcomes in individuals with comorbid depression and alcohol dependence. In recent years integrated treatments have been developed that address both disorders at once. There is some evidence from SRs that integrated treatments are effective, mostly for PTSD and SUD, but the evidence is mixed, and it was not always possible to determine whether the comparator was nonintegrated treatment. Inconsistent findings across the included SRs may reflect different ways of defining and measuring comorbidity, heterogeneous study samples, and methodological differences across the SRs and their included studies. These findings highlight the importance of consistency in the definition and measurement of comorbidity and suggest that future research is needed that: 1) utilizes appropriate methodology to allow conclusions to be made about the impact of comorbidity on treatment outcomes; and 2) specifically aims to examine the treatment of comorbid conditions.

REFERENCES

1. Commander John Scott Hannon Veterans Mental Health Care Improvement Act of 2019, S.785 — 116th Congress (2019-2020), (2020).
2. Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. *Journal of chronic diseases.* 1970;23(7):455-468.
3. Bosco MA, Gallinati JL, Clark ME. Conceptualizing and treating comorbid chronic pain and PTSD. *Pain research and treatment.* 2013;2013.
4. CDC. *Health Status Of Vietnam Veterans: Volume Iv -Psychological And Neuropsychological Evaluation.* Centers for Disease Control;1998.
5. Lew HL, Otis JD, Tun C, Kerns RD, Clark ME, Cifu DX. Prevalence of chronic pain, posttraumatic stress disorder, and persistent postconcussive symptoms in OIF/OEF veterans: polytrauma clinical triad. *Journal of Rehabilitation Research & Development.* 2009;46(6).
6. Marmar CR, Schlenger W, Henn-Haase C, et al. Course of posttraumatic stress disorder 40 years after the Vietnam War: Findings from the National Vietnam Veterans Longitudinal Study. *JAMA Psychiatry.* 2015;72(9):875-881.
7. Richardson JD, Ketcheson F, King L, et al. Psychiatric comorbidity pattern in treatment-seeking veterans. *Psychiatry Res.* 2017;258:488-493.
8. Yurgil KA, Barkauskas DA, Vasterling JJ, et al. Association between traumatic brain injury and risk of posttraumatic stress disorder in active-duty Marines. *JAMA Psychiatry.* 2014;71(2):149-157.
9. Pedersen ER, Bouskill KE, Holliday SB, et al. *Improving Substance Use Care: Addressing Barriers to Expanding Integrated Treatment Options for Post-9/11 Veterans.* Santa Monica, CA: RAND Corporation; 2020.
10. Drag LL, Spencer RJ, Walker SJ, Pangilinan PH, Bieliauskas LA. The Contributions of Self-reported Injury Characteristics and Psychiatric Symptoms to Cognitive Functioning in OEF/OIF Veterans with Mild Traumatic Brain Injury. *J Int Neuropsychol Soc.* 2012;18(3):576-584.
11. Hefner K, Rosenheck R. Multimorbidity among Veterans diagnosed with PTSD in the Veterans Health Administration nationally. *Psychiatric Quarterly.* 2019;90(2):275-291.
12. Nichter B, Norman S, Haller M, Pietrzak RH. Psychological burden of PTSD, depression, and their comorbidity in the US veteran population: suicidality, functioning, and service utilization. *J Affect Disord.* 2019;256:633-640.
13. Outcalt SD, Kroenke K, Krebs EE, et al. Chronic pain and comorbid mental health conditions: independent associations of posttraumatic stress disorder and depression with pain, disability, and quality of life. *Journal of Behavioral Medicine.* 2015;38(3):535-543.
14. Schneiderman AI, Braver ER, Kang HK. Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan: persistent postconcussive symptoms and posttraumatic stress disorder. *American Journal of Epidemiology.* 2008;167(12):1446-1452.
15. Arnow BA, Hunkeler EM, Blasey CM, et al. Comorbid depression, chronic pain, and disability in primary care. *Psychosom Med.* 2006;68(2):262-268.
16. Bedard-Gilligan M, Duax Jakob JM, Doane LS, et al. An investigation of depression, trauma history, and symptom severity in individuals enrolled in a treatment trial for chronic PTSD. *J Clin Psychol.* 2015;71(7):725-740.

17. Blanco C, Xu Y, Brady K, Pérez-Fuentes G, Okuda M, Wang S. Comorbidity of posttraumatic stress disorder with alcohol dependence among US adults: Results from National Epidemiological Survey on Alcohol and Related Conditions. *Drug and Alcohol Dependence.* 2013;132(3):630-638.
18. Drapkin ML, Yusko D, Yasinski C, Oslin D, Hembree EA, Foa EB. Baseline functioning among individuals with posttraumatic stress disorder and alcohol dependence. *J Subst Abuse Treat.* 2011;41(2):186-192.
19. Ouimette P, Goodwin E, Brown PJ. Health and well being of substance use disorder patients with and without posttraumatic stress disorder. *Addict Behav.* 2006;31(8):1415-1423.
20. Saladin ME, Brady KT, Dansky BS, Kilpatrick DG. Understanding comorbidity between PTSD and substance use disorders: Two preliminary investigations. *Addict Behav.* 1995;20(5):643-655.
21. Schäfer I, Najavits LM. Clinical challenges in the treatment of patients with posttraumatic stress disorder and substance abuse. *Curr Opin Psychiatry.* 2007;20(6):614-618.
22. Steinert C, Hofmann M, Leichsenring F, Kruse J. The course of PTSD in naturalistic long-term studies: high variability of outcomes. A systematic review. *Nord J Psychiatry.* 2015;69(7):483-496.
23. Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. *Ann Fam Med.* 2009;7(4):357-363.
24. Krawczyk N, Feder KA, Saloner B, Crum RM, Kealhofer M, Mojtabai R. The association of psychiatric comorbidity with treatment completion among clients admitted to substance use treatment programs in a U.S. national sample. *Drug and Alcohol Dependence.* 2017;175:157-163.
25. Hunter G, Yoon J, Blonigen DM, Asch SM, Zulman DM. Health care utilization patterns among high-cost VA patients with mental health conditions. *Psychiatr Serv.* 2015;66(9):952-958.
26. Yu W, Ravelo A, Wagner TH, et al. Prevalence and costs of chronic conditions in the VA health care system. *Medical Care Research and Review.* 2003;60(3_suppl):146S-167S.
27. Mills KL, Lynskey M, Teesson M, Ross J, Darke S. Post-traumatic stress disorder among people with heroin dependence in the Australian treatment outcome study (ATOS): prevalence and correlates. *Drug and Alcohol Dependence.* 2005;77(3):243-249.
28. Read JP, Brown PJ, Kahler CW. Substance use and posttraumatic stress disorders: Symptom interplay and effects on outcome. *Addict Behav.* 2004;29(8):1665-1672.
29. VA/DoD. VA/DoD Clinical Practice Guidelines. https://www.healthquality.va.gov/guidelines/. Published 2021. Accessed 09/21/21, 2021.
30. Clarkin JF, Kendall PC. Comorbidity and treatment planning: summary and future directions. 1992.
31. Angelakis S, Nixon RD. The comorbidity of PTSD and MDD: Implications for clinical practice and future research. *Behaviour Change.* 2015;32(1):1-25.
32. Flory JD, Yehuda R. Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. *Dialogues in clinical neuroscience.* 2015;17(2):141.
33. Kline AC, Cooper AA, Rytwinski NK, Feeny NC. The Effect of Concurrent Depression on PTSD Outcomes in Trauma-Focused Psychotherapy: A Meta-Analysis of Randomized Controlled Trials. *Behav.* 2021;52(1):250-266.

34. Cook JM, Dinnen S, Simiola V, Thompson R, Schnurr PP. VA residential provider perceptions of dissuading factors to the use of two evidence-based PTSD treatments. *Professional Psychology: Research and Practice.* 2014;45(2):136.
35. Norman SB, Hamblen JL. Promising directions for treating comorbid PTSD and substance use disorder. 2017.
36. Capehart B, Bass D. Managing posttraumatic stress disorder in combat veterans with comorbid traumatic brain injury. *Journal of Rehabilitation Research & Development.* 2012;49(5).
37. Petrakis IL, Simpson TL. Posttraumatic Stress Disorder and Alcohol Use Disorder: A Critical Review of Pharmacologic Treatments. *Alcohol Clin Exp Res.* 2017;41(2):226-237.
38. Petrillo LA, Ritchie CS. The challenges of symptom management for patients with multimorbidity in research and practice: a thematic review. *Progress in palliative care.* 2016;24(5):262-267.
39. Robinson KA, Brunnhuber K, Ciliska D, et al. Evidence-Based Research Series-Paper 1: What Evidence-Based Research is and why is it important? *J Clin Epidemiol.* 2021;129:151-157.
40. Whiting P, Savović J, Higgins JP, et al. ROBIS: a new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol.* 2016;69:225-234.
41. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. *J Clin Epidemiol.* 2015;68(11):1312-1324.
42. Banerjee S SC. Concurrent treatment for substance use disorder and trauma-related comorbidities: A review of clinical effectiveness and guidelines. *Ottawa (ON): Canadian Agency for Drugs and Technologies in Health.* 2017.
43. Barrett K, Chang YP. Behavioral Interventions Targeting Chronic Pain, Depression, and Substance Use Disorder in Primary Care. *J Nurs Scholarsh.* 2016;48(4):345-353.
44. Meshberg-Cohen S, Ross MacLean R, Schnakenberg Martin AM, Sofuoglu M, Petrakis IL. Treatment outcomes in individuals diagnosed with comorbid opioid use disorder and Posttraumatic stress disorder: A review. *Addict Behav.* 2021;122:107026.
45. Oliveira LM, Bermudez MB, Macedo MJA, Passos IC. Comorbid social anxiety disorder in patients with alcohol use disorder: A systematic review. *J Psychiatr Res.* 2018;106:8-14.
46. Parr NJ, Anderson J, Veazie S. Evidence brief: Hyperbaric oxygen therapy for traumatic brain injury and/or post-traumatic stress disorder. *Washington DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs.* 2021(#09-199).
47. Crowe M, Eggleston K, Douglas K, Porter RJ. Effects of psychotherapy on comorbid bipolar disorder and substance use disorder: A systematic review. *Bipolar Disord.* 2021;23(2):141-151.
48. Dewar M, Paradis A, Fortin CA. Identifying Trajectories and Predictors of Response to Psychotherapy for Post-Traumatic Stress Disorder in Adults: A Systematic Review of Literature. *Can J Psychiatry.* 2020;65(2):71-86.
49. Forte ML, Butler M, Andrade KE, Vincent A, Schousboe JT, Kane RL. Treatments for Fibromyalgia in Adult Subgroups. *Agency for Healthcare Research and Quality (US).* 2015:01.
50. Greer N, Ackland R, Sayer N, et al. Relationship of deployment-related mild traumatic brain injury to posttraumatic stress disorder, depressive disorders, substance use

disorders, suicidal ideation, and anxiety disorders: A systematic review. *Washington DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs.* 2019(#09-009).
51. Hoffman V, Middleton JC, Feltner C, et al. Psychological and pharmacological treatments for adults with posttraumatic stress disorder: A systematic review update. *Agency for Healthcare Research and Quality (US).* 2018;Comparative Effectiveness Review No. 207(Publication No. 18-EHC011).
52. Mikolic A, Polinder S, Retel Helmrich IRA, Haagsma JA, Cnossen MC. Treatment for posttraumatic stress disorder in patients with a history of traumatic brain injury: A systematic review. *Clin Psychol Rev.* 2019;73:101776.
53. Skelly AC, Chou R, Dettori JR, et al. Noninvasive nonpharmalogical treatment for chronic pain: A systematic review update. *Agency for Healthcare Research and Quality (US).* 2020(Publication No. 20-EHC009).
54. Agabio R, Trogu E, Pani PP. Antidepressants for the treatment of people with co-occurring depression and alcohol dependence. *Cochrane Database Syst Rev.* 2018;4:CD008581.
55. Hides L, Quinn C, Stoyanov S, Kavanagh D, Baker A. Psychological interventions for co-occurring depression and substance use disorders. *Cochrane Database Syst Rev.* 2019;11(11):26.
56. Ipser JC, Wilson D, Akindipe TO, Sager C, Stein DJ. Pharmacotherapy for anxiety and comorbid alcohol use disorders. *Cochrane Database Syst Rev.* 2015;1:CD007505.
57. Kedzior KK, Gerkensmeier I, Schuchinsky M. Can deep transcranial magnetic stimulation (DTMS) be used to treat substance use disorders (SUD)? A systematic review. *BMC Psychiatry.* 2018;18(1):137.
58. Larsen SE, Bellmore A, Gobin RL, Holens P, Lawrence KA, Pacella-LaBarbara ML. An initial review of residual symptoms after empirically supported trauma-focused cognitive behavioral psychological treatment. *J Anxiety Disord.* 2019;63:26-35.
59. Li J, Wang H, Li M, et al. Efficacy of pharmacotherapeutics for patients comorbid with alcohol use disorders and depressive symptoms-A bayesian network meta-analysis. *CNS Neurosci Ther.* 2020;26(11):1185-1197.
60. O'Neil ME, Carlson KF, Holmer HK, et al. Chronic Pain in Veterans and Servicemembers with a History of Mild Traumatic Brain Injury: A Systematic Review. *Department of Veterans Affairs (US).* 2020;08:08.
61. Pott SL, Delgadillo J, Kellett S. Is behavioral activation an effective and acceptable treatment for co-occurring depression and substance use disorders? A meta-analysis of randomized controlled trials. *J Subst Abuse Treat.* 2021;132:108478.
62. Roberts NP, Roberts PA, Jones N, Bisson JI. Psychological therapies for post-traumatic stress disorder and comorbid substance use disorder. *Cochrane Database Syst Rev.* 2016;4:CD010204.
63. Yan B, Zhu S, Wang Y, Da G, Tian G. Effect of Acupuncture on Chronic Pain with Depression: A Systematic Review. *Evid Based Complement Alternat Med.* 2020;2020:7479459.
64. Ackland PE, Greer N, Sayer NA, et al. Effectiveness and harms of mental health treatments in service members and veterans with deployment-related mild traumatic brain injury. *J Affect Disord.* 2019;252:493-501.
65. Hobden B, Bryant J, Carey M, et al. Finding the optimal treatment model: A systematic review of treatment for co-occurring alcohol misuse and depression. *Aust N Z J Psychiatry.* 2018;52(8):737-750.

66. Mehta K, Hoadley A, Ray LA, Kiluk BD, Carroll KM, Magill M. Cognitive-Behavioral Interventions Targeting Alcohol or Other Drug Use and Co-Occurring Mental Health Disorders: A Meta-Analysis. *Alcohol Alcohol.* 2021;29:29.
67. Roberts NP, Roberts PA, Jones N, Bisson JI. Psychological interventions for post-traumatic stress disorder and comorbid substance use disorder: A systematic review and meta-analysis. *Clin Psychol Rev.* 2015;38:25-38.
68. Back SE, Killeen T, Badour CL, et al. Concurrent treatment of substance use disorders and PTSD using prolonged exposure: A randomized clinical trial in military veterans. *Addict Behav.* 2019;90:369-377.
69. Lancaster CL, Gros DF, Mullarkey MC, et al. Does trauma-focused exposure therapy exacerbate symptoms among patients with comorbid PTSD and substance use disorders? *Behavioural and Cognitive Psychotherapy.* 2020;48(1):38-53.
70. Norman SB, Trim R, Haller M, et al. Efficacy of integrated exposure therapy vs integrated coping skills therapy for comorbid posttraumatic stress disorder and alcohol use disorder: A randomized clinical trial. *JAMA Psychiatry.* 2019;76(8):791-799.
71. Jak AJ, Jurick S, Crocker LD, et al. SMART-CPT for veterans with comorbid post-traumatic stress disorder and history of traumatic brain injury: a randomised controlled trial. *J Neurol Neurosurg Psychiatry.* 2019;90(3):333-341.
72. VA/DoD. *VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder.* Washington, DC: Department of Veteran Affairs, Department of Defense;2017.
73. VA/DoD. *VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders.* Washington, DC: Department of Veteran Affairs, Department of Defense;2021.
74. Simpson TL, Lehavot K, Petrakis IL. No Wrong Doors: Findings from a Critical Review of Behavioral Randomized Clinical Trials for Individuals with Co-Occurring Alcohol/Drug Problems and Posttraumatic Stress Disorder. *Alcohol Clin Exp Res.* 2017;41(4):681-702.
75. DeRubeis RJ, Gelfand LA, German RE, Fournier JC, Forand NR. Understanding processes of change: How some patients reveal more than others—and some groups of therapists less—about what matters in psychotherapy. *Psychother.* 2014;24(3):419-428.
76. Van Bavel JJ, Mende-Siedlecki P, Brady WJ, Reinero DA. Contextual sensitivity in scientific reproducibility. *Proceedings of the National Academy of Sciences.* 2016;113(23):6454-6459.
77. Vujanovic AA, Meyer TD, Heads AM, Stotts AL, Villarreal YR, Schmitz JM. Cognitive-behavioral therapies for depression and substance use disorders: An overview of traditional, third-wave, and transdiagnostic approaches. *American Journal of Drug and Alcohol Abuse.* 2017;43(4):402-415.
78. Bisson JI, Roberts NP, Andrew M, Cooper R, Lewis C. Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. *Cochrane Database Syst Rev.* 2013(12).