Evidence Brief: Treatment of Comorbid Conditions

Supplemental Materials

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APPENDIX A: SEARCH STRATEGY

SYSTEMATIC REVIEWS

Search for current systematic reviews (limited to last 7 years) **Date Searched: 8/26/21**			
A. Bibliographic Databases:	**#**	**Search Statement**	**Results**
MEDLINE: Systematic Reviews **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily** 1946 to August 23, 2021	1	Stress Disorders, Post-Traumatic/	35691
	2	(post-traumatic stress or posttraumatic stress or PTSD).ti,ab,kw.	41585
	3	1 or 2	51088
	4	Anxiety Disorders/	36321
	5	anxiety.ti,ab,kw.	216389
	6	4 or 5	224089
	7	Depressive Disorder, Major/	33059
	8	(depression OR depressive OR MDD).ti,ab,kw.	416539
	9	7 or 8	420279
	10	Bipolar Disorder/	42266
	11	((bipolar adj2 disorder*) OR bipolar depression OR manic-depression OR manic-depressive).ti,ab,kw.	37987
	12	10 or 11	55074
	13	exp Brain Injuries, Traumatic/	17845
	14	(TBI OR TBIs OR traumatic brain injury OR traumatic brain injuries OR brain trauma OR brain traumas OR traumatic encephalopathy OR traumatic encephalopathies).ti,ab,kw.	48189
	15	13 or 14	55548
	16	Substance-Related Disorders/ OR Alcohol-Related Disorders/ OR Alcoholism/ OR Opioid-Related Disorders/ OR Cocaine-Related Disorders/ OR Amphetamine-Related Disorders/ OR Marijuana Abuse/	198922
	17	(((substance OR drug OR alcohol OR cocaine OR opioid OR opiate OR amphetamine OR inhalant OR marijuana OR narcotic) adj2 (abuse OR addiction OR dependence OR disorder*)) OR alcoholic* OR alcoholism).ti,ab,kw.	199016
	18	16 or 17	306140
	19	Chronic Pain/	17530
	20	chronic pain.ti,ab,kw.	42403
	21	19 or 20	49671
	22	6 or 9 or 12 or 15	618197
	23	3 and 22	20784
	24	3 or 6 or 9 or 12 or 15	648501
	25	18 or 21	352659
	26	24 and 25	40914
	27	6 or 9 or 12	566096
	28	15 and 27	3447
	29	23 or 26 or 28	60982
	30	Comorbidity/	117348

	31	(comorbid OR comorbidity OR comorbidities OR co-morbid OR co-morbidity OR co-morbidities OR concurrent OR concurrently OR co-occur OR co-occurs OR co-occurring OR co-occurrence OR cooccur OR coocurrs OR cooccurring OR cooccurrence OR integrated OR integrating).ti,ab,kw.	717375
	32	30 or 31	783277
	33	29 and 32	16071
	34	(systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/) or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or citation.tw. or citations.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment outcome/ or treatment outcome.tw. or pmcbook.mp.))) not (letter or newspaper article).pt.	471026
	35	33 and 34	714
	36	limit 35 to english language	681
	37	limit 36 to last 7 years	454
CDSR: Protocols and Reviews **EBM Reviews - Cochrane Database of Systematic Reviews** 2005 to August 23, 2021	1	(post-traumatic stress or posttraumatic stress or PTSD).ti,ab,kw.	42
	2	anxiety.ti,ab,kw.	411
	3	(depression OR depressive OR MDD).ti,ab,kw.	534
	4	((bipolar adj2 disorder*) OR bipolar depression OR manic-depression OR manic-depressive).ti,ab,kw.	36
	5	(TBI OR TBIs OR traumatic brain injury OR traumatic brain injuries OR brain trauma OR brain traumas OR traumatic encephalopathy OR traumatic encephalopathies).ti,ab,kw.	58
	6	(((substance OR drug OR alcohol OR cocaine OR opioid OR opiate OR amphetamine OR inhalant OR marijuana OR narcotic) adj2 (abuse OR addiction OR dependence OR disorder*)) OR alcoholic* OR alcoholism).ti,ab,kw.	394
	7	chronic pain.ti,ab,kw.	173

	8	2 or 3 or 4 or 5	732
	9	1 and 8	40
	10	1 or 2 or 3 or 4 or 5	734
	11	6 or 7	564
	12	10 and 11	119
	13	2 or 3 or 4	680
	14	5 and 13	6
	15	9 or 12 or 14	158
	16	(comorbid OR comorbidity OR comorbidities OR co-morbid OR co-morbidity OR co-morbidities OR concurrent OR concurrently OR co-occur OR co-occurs OR co-occurring OR co-occurrence OR cooccur OR coocurrs OR cooccurring OR cooccurrence OR integrated OR integrating).ti,ab,kw.	300
	17	15 and 16	17
	16	limit 17 to last 7 years	12
Search for current systematic reviews (limited to last 7 years) **Date Searched: 8/11/21**			
B. Non-bibliographic databases:	**Evidence**		
AHRQ	Search: Comorbid, PTSD, anxiety, depression, bipolar disorder, TBI, chronic pain, substance use, alcohol use		
CADTH	Search: Comorbid, PTSD, anxiety, depression, bipolar disorder, TBI, chronic pain, substance use, alcohol use		
VA HSR&D	Search: Comorbid, PTSD, anxiety, depression, bipolar disorder, TBI, chronic pain, substance use, alcohol use		

APPENDIX B: TABLE OF INCLUSION/EXCLUSION CRITERIA

PICOS	Inclusion/exclusion criteria	Exclusion code
Population	**Include:** Adults with PTSD comorbid with anxiety, depression, bipolar disorder, TBI, a substance use disorder, or chronic pain; adults with TBI comorbid with anxiety, depression, bipolar disorder, PTSD, a substance use disorder, or chronic pain; or adults with anxiety, depression, or bipolar disorder comorbid with a substance use disorder or chronic pain. *Include SRs on a broader population that synthesize a subgroup meeting criteria.* **Exclude:** Studies on children, studies on adults with a single condition only, studies on adults with comorbid conditions other than the combinations listed above, studies that do not require diagnosis of both conditions (symptoms only, subthreshold populations e.g., alcohol misuse).	E1
Intervention	**Include:** KQ1 & KQ2: Any treatment KQ3: Integrated treatment (designed to treat both conditions) of both the primary condition and comorbidity. *Include SRs on a broader group of interventions that synthesize a subgroup of integrated treatments.* **Exclude:** KQ3: Nonintegrated treatment (designed to treat primary condition only)	E2
Comparator	**Include:** KQ1: Group receiving the same treatment, but without the comorbidity KQ2: Any or none KQ3: Nonintegrated treatment (designed to treat primary condition only) *Include SRs on a broader group of comparators that synthesize a subgroup meeting our criteria.*	E3
Outcome	**Include:** Clinical outcomes (*eg*, symptom change, diagnosis) KQ2: Outcomes for the comorbidity **Exclude:** Non-clinical outcomes (*eg*, prevalence, dropout) KQ2: Outcomes for the primary condition being treated only	E4
Setting	**Include:** Any	E5
Study Design	**Include:** Any	E6
Publication type	**Include:** Systematic reviews meeting minimum criteria of Robison et al., 2016: - Explicit and adequate search - Application of predefined eligibility criteria to select studies - Risk of bias assessment for included studies - Synthesis or attempt to synthesize findings quantitatively and/or qualitatively **Exclude:** Reviews not meeting the above minimum criteria, narrative reviews, primary studies, commentaries, abstracts, et cetera.	E7
Outdated or Non-prioritized SR	Older or non-prioritized systematic reviews, systematic reviews with high risk of bias	E8
Language	**Include:** English **Exclude:** Any other language	E9

Abbreviations. KQ=key question; PTSD=posttraumatic stress disorder; SR=systematic review; TBI=traumatic brain injury.

APPENDIX C: EXCLUDED STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Ineligible outcome, 5=Ineligible timing, 6=Ineligible study design, 7=Ineligible publication type, 8=Outdated or ineligible systematic review.

Citation	Exclude Reason
Bailey K, Trevillion K, Gilchrist G. What works for whom and why: A narrative systematic review of interventions for reducing post-traumatic stress disorder and problematic substance use among women with experiences of interpersonal violence. Research Support, Non-U.S. Gov't Systematic Review. *J Subst Abuse Treat.* 04 2019;99:88-103.	E1
Barawi KS, Lewis C, Simon N, Bisson JI. A systematic review of factors associated with outcome of psychological treatments for post-traumatic stress disorder. Review. *Eur J Psychotraumatol*. Jul 01 2020;11(1):1774240.	E7
Benedict TM, Keenan PG, Nitz AJ, Moeller-Bertram T. Post-Traumatic Stress Disorder Symptoms Contribute to Worse Pain and Health Outcomes in Veterans With PTSD Compared to Those Without: A Systematic Review With Meta-Analysis. Meta-Analysis Systematic Review. *Mil Med*. 09 18 2020;185(9-10):e1481-e1491.	E2
Cerimele JM, Bauer AM, Fortney JC, Bauer MS. Patients With Co-Occurring Bipolar Disorder and Posttraumatic Stress Disorder: A Rapid Review of the Literature. Review. *J Clin Psychiatry*. May 2017;78(5):e506-e514.	E4
Cheng JOS, Cheng ST. Effectiveness of physical and cognitive-behavioural intervention programmes for chronic musculoskeletal pain in adults: A systematic review and meta-analysis of randomised controlled trials. Meta-Analysis Research Support, Non-U.S. Gov'tSystematic Review. *PLoS ONE*. 2019;14(10):e0223367.	E4
Coles AS, Sasiadek J, George TP. Pharmacotherapies for co-occurring substance use and bipolar disorders: A systematic review. Systematic Review. *Bipolar Disord*. 11 2019;21(7):595-610.	E7
Cooper DB, Bunner AE, Kennedy JE, et al. Treatment of persistent post-concussive symptoms after mild traumatic brain injury: a systematic review of cognitive rehabilitation and behavioral health interventions in military Service members and Veterans. ReviewSystematic Review. *Brain imaging behav*. Sep 2015;9(3):403-20.	E1
Coventry PA, Meader N, Melton H, et al. Psychological and pharmacological interventions for posttraumatic stress disorder and comorbid mental health problems following complex traumatic events: Systematic review and component network meta-analysis. Meta-AnalysisResearch Support, Non-U.S. Gov'tSystematic Review. *PLoS Med*. 08 2020;17(8):e1003262.	E1
Ecker AH, Hundt N. Posttraumatic stress disorder in opioid agonist therapy: A review. Review. *Psychol Trauma*. Nov 2018;10(6):636-642.	E1
Forster SE, DePhilippis D, Forman SD. "I's" on the prize: A systematic review of individual differences in Contingency Management treatment response. Research Support, U.S. Gov't, Non-P.H.S. Systematic Review. *J Subst Abuse Treat*. 05 2019;100:64-83.	E7
Foulds JA, Adamson SJ, Boden JM, Williman JA, Mulder RT. Depression in patients with alcohol use disorders: Systematic review and meta-analysis of outcomes for independent and substance-induced disorders. Meta-AnalysisReviewSystematic Review. *J Affect Disord*. Oct 01 2015;185:47-59.	E1

Ghabrash MF, Bahremand A, Veilleux M, et al. Depression and Outcomes of Methadone and Buprenorphine Treatment Among People with Opioid Use Disorders: A Literature Review. Research Support, Non-U.S. Gov'tReview. *J Dual Diagn*. Apr-Jun 2020;16(2):191-207.	E1
Gilmore AK, Wilson SM, Skopp NA, Osenbach JE, Reger G. A systematic review of technology-based interventions for co-occurring substance use and trauma symptoms. ReviewSystematic Review. *J Telemed Telecare*. Sep 2017;23(8):701-709.	E1
Gonzalez-Robles A, Diaz-Garcia A, Miguel C, Garcia-Palacios A, Botella C. Comorbidity and diagnosis distribution in transdiagnostic treatments for emotional disorders: A systematic review of randomized controlled trials. Research Support, Non-U.S. Gov'tSystematic Review. *PLoS ONE*. 2018;13(11):e0207396.	E4
Grubaugh AL, Brown WJ, Wojtalik JA, Myers US, Eack SM. Meta-Analysis of the Treatment of Posttraumatic Stress Disorder in Adults With Comorbid Severe Mental Illness. *J Clin Psychiatry*. May 25 2021;82(3):25.	E1
Haibach JP, Beehler GP, Dollar KM, Finnell DS. Moving toward integrated behavioral intervention for treating multimorbidity among chronic pain, depression, and substance-use disorders in primary care. Review. *Med Care*. Apr 2014;52(4):322-7.	E7
Hellem TL, Lundberg KJ, Renshaw PF. A review of treatment options for co-occurring methamphetamine use disorders and depression. Research Support, N.I.H., ExtramuralResearch Support, Non-U.S. Gov'tReview. J Addict Nurs. Jan-Mar 2015;26(1):14-23; quiz E1.	E1
Hillemacher T, Frieling H. Pharmacotherapeutic options for co-morbid depression and alcohol dependence. Review. *Expert Opin Pharmacother*. 04 2019;20(5):547-569.	E7
Holmes NA, van Agteren JE, Dorstyn DS. A systematic review of technology-assisted interventions for co-morbid depression and substance use. Systematic Review. *J Telemed Telecare*. Apr 2019;25(3):131-141.	E3
IsHak WW, Wen RY, Naghdechi L, et al. Pain and Depression: A Systematic Review. Systematic Review. *Harv Rev Psychiatry*. Nov/Dec 2018;26(6):352-363.	E1
Kip A, Priebe S, Holling H, Morina N. Psychological interventions for posttraumatic stress disorder and depression in refugees: A meta-analysis of randomized controlled trials. Review. *Clin.* Jul 2020;27(4):489-503.	E1
Marchard DK FC. Care for acquired brain injury and concurrent mental health conditions and/or substance use disorders: An environmental scan. *CADTH*. 2021;96	E7
Morgan L, Aldington D. Comorbid chronic pain and post-traumatic stress disorder in UK Veterans: a lot of theory but not enough evidence. *Br*. Nov 2020;14(4):256-262.	E7
Murthy P, Mahadevan J, Chand PK. Treatment of substance use disorders with co-occurring severe mental health disorders. Review. *Curr Opin Psychiatry*. 07 2019;32(4):293-299.	E7
Preuss UW, Gouzoulis-Mayfrank E, Havemann-Reinecke U, et al. Psychiatric comorbidity in alcohol use disorders: results from the German S3 guidelines. Review. *Eur Arch Psychiatry Clin Neurosci*. Apr 2018;268(3):219-229.	E7
Ralevski E, Olivera-Figueroa LA, Petrakis I. PTSD and comorbid AUD: a review of pharmacological and alternative treatment options. Review. *Subst*. 2014;5:25-36.	E7
Riper H, Andersson G, Hunter SB, de Wit J, Berking M, Cuijpers P. Treatment of comorbid alcohol use disorders and depression with cognitive-behavioural therapy and motivational interviewing: a meta-analysis. *Addiction.* 2014;109(3):394-406.	E1

Rogers AH, Zvolensky MJ, Ditre JW, Buckner JD, Asmundson GJG. Association of opioid misuse with anxiety and depression: A systematic review of the literature. Review. *Clin Psychol Rev*. Jan 24 2021;84:101978.	E1
Salloum IM, Brown ES. Management of comorbid bipolar disorder and substance use disorders. Review. *Am J Drug Alcohol Abuse*. 07 2017;43(4):366-376.	E7
Sanchez-Salcedo JA, Cabrera MME, Molina-Jimenez T, Cortes-Altamirano JL, Alfaro-Rodriguez A, Bonilla-Jaime H. Depression and Pain: use of antidepressant. *Curr Neuropharmacol*. Jun 09 2021;09:09.	E10
Schneider RL, Arch JJ, Wolitzky-Taylor KB. The state of personalized treatment for anxiety disorders: A systematic review of treatment moderators. ReviewSystematic Review. *Clin Psychol Rev*. Jun 2015;38:39-54.	E1
Sepede G, Lorusso M, Spano MC, Di Nanno P, Di Iorio G, Di Giannantonio M. Efficacy and Safety of Atypical Antipsychotics in Bipolar Disorder With Comorbid Substance Dependence: A Systematic Review. Systematic Review. *Clin Neuropharmacol*. Sep/Oct 2018;41(5):181-191.	E7

APPENDIX D: EVIDENCE TABLES

DATA ABSTRACTION OF INCLUDED SYSTEMATIC REVIEWS

Author, Year	Search details	Eligibility criteria	Included Studies[a] Patient Characteristics[a]	Intervention Characteristics[a]	Results[a]
Agabio, 2018[1]	Cochrane Drugs and Alcohol Group Specialized Register, Cochrane CENTRAL, MEDLINE, EMBASE through July 2017. Clinicaltrials.gov and WHO ICTRP for ongoing studies. Searched reference lists of all relevant papers and conference proceedings likely to contain relevant trials. Contacted investigators to seek information about unpublished or incomplete trials.	P: People with co-occurring depression and alcohol dependence I: Antidepressants alone or in combination with other drugs or psychosocial interventions (or both) C: Placebo, no intervention, other pharmacological interventions, any psychosocial intervention O: Depression severity, response to antidepressive treatment, depression remission, alcohol consumption, liver enzyme levels, acceptability, tolerability, suicide/suicide attempts, use of other substances of abuse, craving, severity of dependence, psychiatric symptoms/psychological distress S: RCTs, CCTs	14 RCTs N=1149 pts with depression and alcohol dependence	Antidepressants	KQ2: Moderate-quality evidence found that antidepressants increased the number of participants abstinent from alcohol during the trial (7 studies, 424 pts, RR 1.71, 95% CI 1.22 to 2.39) and reduced the number of drinks per drinking days (7 studies, 451 pts, mean difference -1.13 drinks per drinking days, 95%CI -1.79 to -0.46). Rate of abstinent days did not differ between antidepressants and placebo (9 studies, 821 pts, MD 1.34, 95% CI -1.66 to 4.34, low-quality evidence).
Banerjee, 2017[2]	PubMed, The Cochrane Library, CRD databases, Canadian and major international health technology	P: Adults with substance use disorder and trauma-related comorbidities (PTSD, anxiety, depression) I: KQ1 - concurrent treatment; KQ2 - treatment	3 RCTs N=191 pts with SUD & PTSD, N=41 pts	COPE vs RP, COPE vs RP vs active monitoring, integrated anxiety sensitivity intervention + TAU	KQ3: An RCT of COPE vs RP in pts with SUD & PTSD found lower depressive & PTSD symptoms in the COPE group & reduction in substance use was similar in both groups. In another RCT in pts with SUD & PTSD, in the subgroup of pts with full PTSD, there was significantly greater reduction in

Author, Year	Search details	Eligibility criteria	Included Studies[a] Patient Characteristics[a]	Intervention Characteristics[a]	Results[a]
	agencies, and a focused internet search. January 1, 2012-July 17, 2017. Final selection of articles was limited to 2015-2017.	for 1 condition alone C: KQ1 - treatment for primary condition alone, sequential treatment, TAU, no treatment, waitlist; KQ2 - treatment for remaining comorbidities alone, TAU, no treatment, waitlist O: Symptoms, duration of substance use or severity, duration of abstinence, relapse prevention, health-related quality of life S: HTAs, SRs, MAs, RCTs, non-randomized studies	with SUD & anxiety disorder	(addiction outpatient program) vs TAU alone	PTSD severity with COPE compared to RP. Both COPE and RP showed reduction in drinking days. In an RCT in pts with SUD & anxiety disorder, the anxiety sensitivity intervention + TAU led to a short-term benefit over TAU alone, with respect to anxiety sensitivity index but this benefit was not sustained at 3 months. Both groups showed improvement in percent days abstinent.
Barrett, 2016[3]	CINAHL, MEDLINE, PsycINFO, Google Scholar. Additional review of the reference sections in relevant articles was also performed. Included articles published between 1995 and 2015.	P: Adults I: Behavioral interventions designed to treat at least 2 of 3 conditions: chronic pain, depression, substance use disorder C: Not specified O: Not specified S: RCTs	2 RCTs N=66 pts with SUD & depression, N=73 pts with chronic pain & depression	ICBT vs TSF, ACT vs TAU	KQ2: One study comparing ACT to TAU in patients with comorbid chronic pain and depression in primary care found that posttreatment the ACT group had no change in disability ratings, slightly higher pain acceptance and no change in pain severity. At 3-month follow-up the ACT group had lower disability ratings, significantly higher pain acceptance, and no change in pain severity. KQ3: One study comparing ICBT to TSF in veteran outpatients with comorbid SUD and depression found that the ICBT group maintained a decrease in depressed mood at follow-up while the control group showed an increased in depressed mood at follow-up.
Crowe, 2021[4]	MEDLINE, PubMed, PsycINFO, and manual searching of the reference lists	P: Adults meeting diagnostic criteria for BD with a diagnosis of current SUD I: Manualized psychotherapy	5 RCTs N=578 pts with BD & SUD	Integrated group therapy vs group drug counseling, Step-BD intensive	KQ1: In 1 study evaluating Step-BD vs collaborative care, post-hoc analysis found that comorbid current SUD significantly predicted likelihood of recovery (odds ratio = 2.25, P = .025)

Author, Year	Search details	Eligibility criteria	Included Studies[a] Patient Characteristics[a]	Intervention Characteristics[a]	Results[a]
	from articles identified electronically. Included articles published up to November 2019.	as an adjunct to medication C: Not specified O: Not specified S: RCTs		psychotherapy (included CBT, IPSRT, family focused therapy) vs collaborative care, IPSRT vs supportive care, individual vs group psychoeducation	and time to recovery (odds ratio = 1.71, P = .006). Rates of recovery from BD were higher in pts with current SUD (74.5%) than those without current SUD (56.5%). A study comparing IPSRT to supportive care in young people (15-36 years) with BD, there was no impact of lifetime or current SUD on depressive symptoms, social functioning, and manic symptoms. The supportive care group had better outcomes on depressive symptoms in the context of SUD than the IPSRT group. In a study comparing group vs individual psychoeducation, pts with comorbid harmful substance use had the shortest survival times to admission. KQ3: The 2 studies designed specifically for both disorders had small numbers but demonstrated significant effects on both SUD and BD symptoms. One study found that pts receiving integrated group CBT had significantly fewer days of substance use, but higher levels of mood symptoms compared with those receiving group drug counseling. Another study randomized pts to the same treatments, modified for community settings, and found no statistically significant differences between groups for mood or SUD symptoms.
Dewar, 2020[5]	The Cochrane Library, EMBASE, PsycINFO, & PubMed. Additional searching of Google Scholar. Titles in identified articles' reference lists were hand searched and	P: Adults with a PTSD diagnosis or a clinical level of PTSD symptomatology indicative of a probable PTSD diagnosis I: PTSD psychotherapy C: Not specified O: Severity of PTSD across	1 Secondary analysis of RCTs N=313 female victims of interpersonal violence with PTSD	CPT, CPT components, and PE	KQ1: A baseline diagnosis of MDD significantly predicted assignment to a nonresponder pattern

Author, Year	Search details	Eligibility criteria	Included Studies[a] Patient Characteristics[a]	Intervention Characteristics[a]	Results[a]
	authors of identified articles were contacted about unpublished research. Search conducted in February 2018 with no date restriction.	time points S: Not specified			
Forte, 2015[6]	MEDLINE, EMBASE, PsycINFO, AMED, Cochrane CENTRAL (1985-August 2014), and reference lists of included studies and recent SRs	P: Adults with fibromyalgia I: Pharmacologic treatments for fibromyalgia C: Placebo, sham, alternate dose or dosing regimen, any active pharmacologic or nonpharmacologic treatment O: Change from baseline in overall pain, symptom improvement, physical and/or emotional function, participation in work or social activities, health-related quality of life, fatigue, sleep quality, adverse events. Reported outcomes in at least 1 subgroup (T: 3 months or more after initiation of treatment) S: RCTs, pooled analyses of individual patient-level RCT data, and observational studies	8 RCTs, 2 pooled IPD RCT analyses, 1 observational study Adults with fibromyalgia with and without depression	Duloxetine, milnacipran, fluoxetine	KQ1: Limited, low-strength evidence, mostly for duloxetine effects on pain in adults with fibromyalgia and major depressive disorder, suggests that treatment effects do not differ in this subgroup. Sparse, low-strength evidence suggests that duloxetine effects on global improvement and fibromyalgia impact do not differ in the MDD patient subgroup. Insufficient information on duloxetine effects on the depression measures was available for analysis for the MDD subgroup.
Greer, 2019[7] Ackland, 2018[8]	MEDLINE, PsycINFO, PILOTS, HSR&D, DVBIC website 2000-	P: US OEF/OIF/OND active-duty SMs and Veterans with a history of deployment-related TBI	1 pre-post & 2 secondary analyses of RCTs	PE vs CPT, PCT vs ACT, PE vs PCT	KQ1: In 1 pre-post study of CPT and PE in Veterans with PTSD with and without TBI (moderate-to-high RoB), improvements in PTSD symptoms in those with a history of TBI were

Author, Year	Search details	Eligibility criteria	Included Studies[a] Patient Characteristics[a]	Intervention Characteristics[a]	Results[a]
	October 2017. Suggested articles from operational partners and technical expert panel members were reviewed. Reference lists from relevant systematic reviews and included studies were searched.	I: Pharmacological and non-pharmacological interventions for the management of PTSD, depressive disorders, SUD, suicidal ideation or attempts, & anxiety disorders C: Placebo or alternative pharmacological or non-pharmacological interventions including waitlist O: Clinically important changes in symptoms and changes in function and quality of life S: Observational or RCT designs	N=63 pts with TBI & PTSD, N=129 pts with TBI & an anxiety disorder (including PTSD) or depressive disorder		similar to those with PTSD only (for CPT, ES 0.40 [-0.49-1.29], for PE, ES -0.39 [-1.26-0.49]). In a secondary analysis of an RCT comparing ACT to PCT in Veterans with anxiety/PTSD/depressive disorder (moderate RoB), symptoms of anxiety/depression, treatment response did not differ between TBI and non-TBI groups. In a secondary analysis of a RCT evaluating PE vs PCT for PTSD (moderate RoB), there was no effect of TBI status on PTSD symptoms (pooled across both interventions, CAPS-IV, ES -.01 [-0.87-0.86]). The strength of evidence is insufficient to adequately assess whether TBI modifies the effectiveness of these interventions. KQ2: No study examined the effectiveness of interventions for SUDs in Service members or Veterans with a history of mTBI. No studies examined the effectiveness of pharmacological interventions for PTSD, depressive disorders, SUD, & anxiety disorders in the target population.
Hides, 2019[9]	Cochrane CENTRAL, PubMed, EMBASE, CINAHL, Google Scholar, clinical trials registered up to February 2019. Hand-searched systematic reviews.	P: Adults and adolescents diagnosed with comorbid depression and substance use disorders, using structured clinical interviews I: Psychological treatments C: No treatment, delayed treatment, TAU, other psychological treatments O: Depression, substance use, treatment retention S: RCTs	5 RCTs N=398 pts with comorbid depression & SUD	IPT-D vs brief supportive psychotherapy (BSP)/ psychoeducation, ICBT vs TSF, BTDD vs structured relaxation	KQ2: Two studies compared IPT-D to brief supportive psychotherapy/psychoeducation. Both studies found very low-quality evidence of no significant differences in substance use outcomes at posttreatment (percentage of days abstinent, IPT-D vs BSP, MD -2.70, 95%CI -28.74 to 23.34, 26 pts) or at 3-month follow-up (relative risk of relapse, IPT-D vs psychoeducation, RR 0.67, 95%CI 0.30 to 1.50, 38 pts). KQ3: In a meta-analysis of 2 studies comparing ICBT to TSF in Veterans, very low-quality evidence revealed that the TSF group had lower depression scores at posttreatment (MD 4.05, 95%CI 1.43 to 6.66, 212 pts), there was no

Author, Year	Search details	Eligibility criteria	Included Studies[a] Patient Characteristics[a]	Intervention Characteristics[a]	Results[a]
					difference at 6- to 12-month follow-up (MD 1.53, 95%CI -1.73 to 4.79, 181 pts). At posttreatment there was no difference between groups in proportion of days abstinent (MD -2.84, 95%CI -8.04 to 2.35, 220 pts), but the ICBT group had a greater proportion of days abstinent than the TSF group at the 6- to 12-month follow-up (MD 10.76, 95%CI 3.10 to 18.42, 189 pts). Another study comparing BTDD to structured relaxation in pts on methadone maintenance therapy for opiate dependence meeting criteria for a depressive disorder found no differences in posttreatment depression scores and no significant differences in the proportion of weeks opiates, cocaine, and benzodiazepines were used throughout treatment.
Hobden, 2018[10]	PubMed, MEDLINE, PsycINFO searched on August 4th, 2017. The search had no year restriction.	P: Individuals over 16 years old reporting some form of alcohol misuse (DSM-IV dependence or abuse or researcher-defined harmful or risky use) or undergoing treatment for alcohol misuse as well as reporting elevated depressive symptoms on a validated measure of depression or have a diagnosis of depression I: Psychosocial treatment delivered via a dual-treatment model (sequential, parallel, or integrated) C: Single-focused treatment O: Studies measuring both alcohol use and depression with a standard instrument	4 RCTs, 3 non-randomized trials N=1194 pts with co-occurring alcohol misuse and depression	CBT for depression + single-focused alcohol treatment vs single-focused alcohol treatment, integrated intervention vs single-focused alcohol treatment	KQ3: Three studies compared a parallel model of care to usual care (single-focused alcohol treatment) and were low to moderate quality. In all 3 studies, pts in the parallel treatment condition reported greater improvements than those in the control condition for alcohol use or depression for at least 1 follow-up time point. In 1 pilot study, at the 3-month follow-up, pts in the intervention group had a significantly greater proportion of days abstinent compared to the control group. At 6-month follow-up, pts receiving CBT had significantly fewer drinking days, greater overall abstinence, and fewer drinks per day than the control group. In a larger replication study of the first, no significant differences in drinking outcomes were found between the 2 groups at the 6-week and 3-, 6- or 12-month follow-ups. Depression scores were significantly lower for the intervention group at 6-week follow-up, but no significant differences remained at the other

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		at baseline and postvention S: RCTs, non-randomized controlled trials, controlled before and after studies, interrupted time series			follow-up points. In a third study, the intervention group showed significantly lower depression scores at the 3- and 6-month follow-up and had significantly fewer drinking days at the 6-month follow-up. Four studies evaluated integrated models and were of reasonable quality. Two studies compared an integrated intervention to usual care (single-focused alcohol treatment). One study found improvements for alcohol outcomes and the other showed improvements for depression outcomes. Two studies compared integrated interventions to single-focused interventions for either alcohol or depression. One study found an effect for alcohol-related outcomes. No studies found differences for depression outcomes. There is little evidence to date that dual models achieve significantly better patient outcomes than single models. For dual treatment, the apparent superiority of parallel models of care relative to integrated care is tempered by their relatively low methodological quality.
Hoffman, 2018[11]	MEDLINE, the Cochrane Library, Cochrane CENTRAL, PsycINFO, CINAHL, PILOTS, ClinicalTrials.gov. May 2012 to September 29, 2017 for treatments included in prior review, no beginning date for new treatments	P: Adults with PTSD based on any DSM criteria I: Psychological or pharmacological interventions C: Another intervention, waitlist, usual care, no intervention, sham, placebo O: Symptom reduction, loss of diagnosis, prevention or reduction of comorbid medical or psychiatric conditions, quality of life, disability or functional	7 RCTs N=694, 2 studies with Veterans	CBT-mixed vs controls, SS vs usual care, PE vs IPT vs relaxation therapy, paroxetine + placebo vs desipramine + placebo	KQ1: One study examined the comparative effectiveness of PE, IPT, and relaxation therapy among those with vs without comorbid MDD. The authors reported no significant subgroup differences in PTSD symptom changes at posttreatment in the comparative effectiveness of any of the treatments tested. KQ2: One study of Veterans with comorbid PTSD and SUD found the CBT-mixed group had a lower mean percentage of heavy drinking days at posttreatment than controls; another found significant decreases in positive toxicology tests and self-reported amount and frequency of

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		impairment, return to work or active-duty status, adverse events S: RCTs			substance use among CBT-mixed group pts as compared with controls (moderate SOE). A study testing paroxetine + placebo vs desipramine + placebo among Veterans with comorbid alcohol dependence found greater decreases in the percentage of heavy drinking days (p=0.009) and drinks per drinking day (p=0.027) among subjects in the desipramine + placebo group than among those in the paroxetine + placebo group (low SOE). KQ3: Three studies comparing SS to usual care each found that the intervention participants had greater decreases in PTSD symptoms than usual care, but between-group differences did not reach statistical significance. Two studies compared substance use outcomes between SS and usual care. Posttreatment, 1 study found no between-group differences for abstinence and substance use severity, and the other study found significantly greater decreases in drug use (but not alcohol use; insufficient SOE).
Ipser, 2015[12]	Specialized registers of The Cochrane Collaboration Depression, Anxiety, and Neurosis Review Group (to January 2014) and the Cochrane Drugs and Alcohol Group (to March 2013). Complementary searches on EMBASE, PubMed,	P: Individuals diagnosed with alcohol dependence or abuse and an anxiety disorder according to DSM-III, DSM-IV, or DSM-IV-TR criteria I: Pharmacotherapy for anxiety C: Placebo, standard treatment, other medications O: Clinical treatment response, reduction of symptom severity, acceptability of medication,	5 RCTs N=290 pts with comorbid anxiety and alcohol use disorders. 2 studies with pts with PTSD, 2 with SAD, and 1 with GAD.	Paroxetine, sertraline, buspirone, desipramine, naltrexone	KQ2: There was no evidence of an effect for any of the medications tested on abstinence from alcohol use. For SAD, very low-quality evidence for the proportion of days during the trial in which pts were abstinent was inconclusive with respect to the efficacy of short-term treatment with paroxetine relative to placebo (MD 0.08, 95% CI -0.26 to 0.43, 2 trials, 54 pts). Although the number of drinks consumed on a drinking day was numerically smaller in the paroxetine and placebo groups (4.73 with paroxetine versus 7.36 with placebo),and was observed to a similar extent in both trials providing data on this outcome (I2 = 0%, Chi2 = 0.52, P value = 0.47),

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	PsycINFO, and the Alcohol and Alcohol Problems Science Database (to August 2013). Located unpublished trials through NIH RePORTER and WHO ICTRP (to August 2013). Screened reference lists of retrieved articles for additional studies	abstinence & reduction of alcohol use, reduction of comorbid symptoms of depression S: RCTs			there was no evidence that paroxetine reduced the number of drinks consumed (MD -2.42, 95% CI -4.97 to 0.14, 2 trials, 64 pts, very low-quality evidence). There were no differences over the course of the treatment for sertraline versus placebo on percentage of drinking days (23.0% with sertraline versus 20.4% with placebo), number of drinks consumed per day (mean (SD): 2.0 (2.9) with sertraline versus 1.4 (1.9) with placebo), number of drinks consumed per drinking day (mean (SD): 6.8 (6.5) with sertraline versus 6.3 (7.8) with placebo) and number of heavy drinking days (mean (SD): 10.4 (2.3) with sertraline versus 8.9 (2.5) with placebo). In a study comparing paroxetine plus placebo versus desipramine plus placebo, there were greater reductions on drinking outcomes for the desipramine plus placebo group, including endpoint assessments for mean number of drinking days, drinks per drinking day and proportion of heavy drinking days.
Kedzior, 2018[13]	PsycINFO, MEDLINE, Google Scholar through April 2017	P: Individuals with SUD I: Deep transcranial magnetic stimulation with any type of H-coil C: Not specified O: SUD assessed at baseline and posttreatment S: Any study design (except crossover RCTs)	4 studies, 2 case studies and 2 open-label studies N=25 pts with AUD and MDD or dysthymic disorder	DTMS	KQ2: Depression severity was alleviated, both acutely and at follow-up (6-12 months) relative to baseline in all studies.
Kline, 2021[14]	PsycINFO search 1980-2019. Reviewed references from recent	P: Adults with PTSD diagnosed with a validated clinical assessment I: At least 1 face-to-face trauma-focused,	18 RCTs reporting categorical depressive disorder baseline data	Cognitive behavioral therapy, cognitive processing therapy,	KQ1: Across conditions, within all active psychotherapy conditions, and within all control conditions, the proportion of the sample meeting a depressive disorder diagnosis at baseline was not associated with pre- to posttreatment PTSD effect

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	comprehensive meta-analyses on RCTs for PTSD treatments. Reviewed the PTSD Trials Standardized Data Repository.	standardized individual or group psychotherapy treatment conducted primarily in outpatient settings, of at least 4 sessions duration C: Not specified O: Posttreatment PTSD symptom outcomes with validated measures and information about baseline depression characteristics using a validated clinical interview or depression-specific measure S: RCTs with at least 30 pts and a rating of low or moderate RoB	N=2098 pts with PTSD with & without comorbid depression	cognitive therapy, exposure therapy	sizes.
Larsen, 2019[15]	Identified eligible studies based on articles included in 2 recent systematic reviews of empirically supported treatments for PTSD (one searched 1980-2014, the other searched 2012-2016)	P: Not specified I: Empirically supported psychosocial treatments for PTSD C: Not specified O: Residual PTSD symptoms, as well as symptoms of depression and anxiety and quality of life S: RCTs rated as low or medium risk of bias	54 study arms included for depression 38 study arms included for anxiety N=290 pts with PTSD	Empirically supported psychosocial treatments for PTSD	KQ2: Nearly all study populations were within the clinical range for depression at pre-treatment (88.9%). At posttreatment, studies most commonly were in the subthreshold range (53.0%), and depression continued to drop further at follow-up, with roughly equal levels of subthreshold and minimal symptoms (each 37.3%). Further inspection of the data revealed that pre-treatment depression levels had some relationship to posttreatment levels: study arms with posttreatment clinical or subthreshold symptom levels all had pretreatment depression at clinical levels, whereas those with posttreatment minimal/absent depression levels were either at clinical (n = 11) or subthreshold (n=6) levels at pre-treatment. For anxiety, at pre-treatment, all study arms were within the clinical range for impairment and most remained in the

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					clinical range at posttreatment (55.3%) and at follow-up (54.3%). At posttreatment, roughly equal numbers of studies were categorized as subthreshold (23.7%) and minimal symptoms (21.1%). At follow-up, anxiety symptoms were roughly the same (21.2% subthreshold and 24.2% minimal). Depression remained at a clinical level in one-fifth of all study arms, and anxiety in one-half of all study arms at posttreatment, generally paralleling the results for PTSD improvement.
Li, 2020[16]	PubMed, EMBASE, Cochrane CENTRAL, PsycINFO, Cochrane Drugs and Alcohol Group, CINAHL from inception to January 15, 2020. Also reviewed reference lists of related studies and searched ClincalTrials.gov	P: Adults with comorbid alcohol use disorders and depression or depressive symptoms (greater than the cutoff threshold of valid depressive symptom scales) based on DSM or ICD-10 diagnostic criteria. I: Pharmaceutic interventions C: Placebo, no-treatment control, or another pharmacotherapy O: AUD remission rate & percent of abstinent days, depressive symptom scale scores S: RCTs	38 RCTs included in sensitivity analysis for depression scores SUD & depression	Pharmacotherapies	KQ2: For AUD remission rate: In sensitivity analysis, after excluding 11 studies in which pts had only mild depressive symptoms, results indicated that disulfiram (OR 4.33, 1.14 to 17.51) and naltrexone plus SSRI (OR 2.55, 1.24 to 5.37) remained significantly better than controls in increasing the AUD remission rate. For percent abstinent days: In sensitivity analysis where only studies with pts having at least moderate depressive symptoms or having depression diagnosis were included, results from 28 studies showed that no intervention revealed significantly better efficacy than controls in increasing the abstinent days. For score of depression scales: In sensitivity analysis, after excluding 9 studies in which pts had only mild depressive symptoms, in addition to NRI (SMD -3.60, -4.91 to -2.29), mirtazapine was also demonstrated to be better in controls in reducing the scores of depression scales (SMD -0.99, -1.91 to -0.07. Results of ranking probabilities were similar to the main analysis with NRI (SUCRA 99.9%) still the first rank followed by mirtazapine (SUCRA 76.0%).
Mehta, 2021[17]	Cochrane Register, Medline,	P: Adults (age ≥ 18) meeting criteria for an AOD and at	11 RCTs (14 study sites/arms)	Integrated CBT vs single disorder	KQ3: Primary study effect sizes were pooled for AOD outcome as well as by primary mental health

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	PsycARTICLES through December 2019	least 1 co-occurring mental health disorder (DSM III-R through V) I: Integrated cognitive-behavioral (or based on a cognitive-behavioral approach) interventions. Excluded SS. C: Single-disorder intervention, usual care O: Alcohol or other drug use and mental health symptoms at posttreatment through follow-up S: RCTs	N=1646 pts with AOD and PTSD, depression, or anxiety	treatment or usual care	disorder group. For substance use outcomes, pooling by mental health disorder yielded positive and significant results only for PTSD samples with g = 0.245 (95% CI = 0.002, 0.489, P = 0.048; I2 = 54%, τ = 0.253; k = 8). Results were non-significant for depression and/or anxiety disorder samples with g = 0.262 (95% CI = −0.244, 0.768, P = 0.310; I2 = 93%, τ = 0.639; k = 7).
Meshberg-Cohen, 2021[18]	PubMed, PsycINFO, and EMBASE through June 2020	P: Individuals with OUD and PTSD diagnosed via standardized assessment, evidence-based PTSD checklist cut-off, and/or medical record diagnoses I: Not specified C: Not specified O: Reported relationships between OUD and/or PTSD with OUD or PTSD outcomes S: Peer-reviewed studies	5 studies (2 RCTs, 1 secondary analysis of an RCT, 1 feasibility pilot, 1 prospective observational study) N=366 pts with PTSD with and without OUD	Integrated CBT, PE, PE with incentives, modified PE (with psychoeducation & breathing retraining)	KQ1: In 1 study comparing modified PE (mPE) to a non-trauma-focused comparison treatment where all pts had PTSD+AUD and a subset had OUD, for pts with OUD, mPE was associated with large reductions in PTSD symptomatology, sleep disturbances, and symptoms of anxiety and depression, ds = 1.08-2.56. Moreover, pts with OUD reported decreases in alcohol cravings that were significantly greater than those reported by the non-OUD comparison group. KQ2: In 1 study comparing modified PE (mPE) to a non-trauma-focused comparison treatment, mPE was observed to improve PTSD symptoms, depression, anxiety, alcohol cravings, and sleep, in pts with PTSD and alcohol dependence with and without OUD. In a feasibility study, 12 Israeli women on methadone maintenance treatment (average duration 6 years) had good results with PE, with reductions in PTSD and depressive symptoms and no relapse to opioids or other

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					substances. In a study comparing PE + incentives vs PE alone, better attendance in the incentivized group was associated with better SUD treatment retention, and no increased drug use. In secondary analysis of that study, visual analog scales showed no within-session increases in craving, except for cocaine, within Session 8. Across sessions, craving scores dropped for heroin, methadone, benzodiazepines, and cocaine; no increases in craving were found. Past-week substance use reported at each session did not differ. KQ3: In a study comparing standard care (SC) alone, ICBT plus SC, or Individual Addiction Counseling (IAC) plus SC, results revealed that individuals on medications for OUD (MOUD) who received ICBT had a 93.0% decrease in odds of having a positive drug screen compared to those without MOUD receiving SC only. Patients without MOUD who received ICBT had significantly larger decreases in PTSD symptoms compared to patients without MOUD assigned to IAC or SC-only. Results also showed significant decreases in PTSD symptoms at 6-months among those receiving MOUD, with no main effects of psychosocial treatment condition.
Mikolic, 2019[19]	EMBASE, Medline Ovid, Web of science, Cochrane CENTRAL, PsycINFO Ovid and Google scholar 1980 through February 20th, 2018. To include the most	P: Adult (16+) civilian or military participants diagnosed with both TBI and PTSD and provided with treatment for PTSD, or diagnosed with TBI and provided with preventive intervention and/or early treatment for PTSD.	14 studies (1 RCT, 12 pre-post studies, 1 observational cohort) All studies with Service members or Veterans	PE, CPT, MBSR, brain and vestibular rehabilitation, light touch manual therapy (LTMT), HBOT, Flexyx Neurotherapy System (FNS)	KQ1: For cognitive and/or behavioral psychotherapies, when patients with and without history of TBI or with varying TBI severity were compared directly, results were inconsistent. For instance, 1 study observed greater improvements with greater TBI severity, but an overlapping study with greater sample size did not confirm the interaction between TBI severity and outcome. Several other studies did not find TBI history or

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	recent articles, a narrower version of this search, encompassing treatments for PTSD, was conducted for the period until February 21st, 2019. Additionally, to encompass gray literature, such as unpublished articles, theses and reports, Google scholar and a database of clinical trials (clinicaltrials.gov) were searched.	Diagnosis of PTSD had to have been confirmed by a clinician, with a structured diagnostic interview, or a medical record. I: All types of interventions aimed at treatment of PTSD or PTSD symptoms: psychological, pharmacological, complementary, alternative and novel medical therapies C: Not specified O: 1) changes in PTSD symptoms measured by a valid self-report 2) changes in diagnosis of PTSD in accordance with DSM or ICD classification systems 3) treatment adherence and retention in PTSD treatment 4) side effects and harms associated with PTSD treatment" S: Longitudinal studies (*eg*, randomized controlled trials (RCTs), prospective cohort studies, retrospective cohort studies, case-control studies, pre post studies) involving a treatment aimed at PTSD.			severity to be predictive of treatment outcomes. Nevertheless, 1 study found smaller treatment effects when TBI was present, and 1 found more rapid improvements with greater TBI severity. KQ2: MBSR) showed an improvement in attention in a small sample (n=9) of Veterans with history of TBI. Two studies used brain and vestibular rehabilitation, an exercise-based therapy focused on resolving vestibular symptoms. They reported short- and long-term reduction in PTSD symptoms after strategies for gaze stabilization in pts who did not react to other PTSD treatments. Following HBOT in an uncontrolled study, there were clinically significant reductions in PTSD and improvements in neurocognitive functioning in pts with chronic complaints, which persisted after 6 months. However, 1 withdrawal and middle-ear barotrauma, bronchospasm, anxiety associated with aggravation of PTSD and temporary worsening of symptoms were also reported. In a RCT that compared HBOT to sham-control with air, observed posttreatment reductions in PTSD regressed over 6 and 12 months. In another study FNS was applied to a small sample with persistent symptoms. According to the authors, this novel variant of electroencephalograph biofeedback, resulted in beneficial PTSD outcomes. After a medical massage treatment called LTMT, which preceded the full-program in patients with chronic PTSD, contrary findings were observed: an increase in PTSD, maintenance of depression and anxiety, and improvement in immediate headache and anxiety. KQ3: Comparing standard CPT to CPT

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					augmented with cognitive rehabilitation and modifications for cognitive deficits (SMART-CPT) showed equivalent PTSD reductions in patients with history of predominantly mild TBI and persistent cognitive complaints. SMART-CPT was, however, beneficial for cognitive functioning, and it resulted in improved attention, memory and problem solving.
Oliveira, 2018[20]	PubMed, EMBASE, Web of Science from January 1, 1960 to May 6, 2018	P: Adults (17+) with AUD with and without SAD I: Not specified C: Studies comparing pts with AUD + comorbid SAD versus pts with AUD without SAD O: Clinical outcomes, such as alcohol relapse, suicidal thoughts, suicide plan or attempt, treatment response, readmissions, psychiatric comorbidities, treatment compliance S: Review articles and preclinical studies excluded	3 studies (2 clinical trials, 1 cohort) N=1360 pts with AUD with and without SAD	TSF, AA, CBT	KQ1: A 12-month longitudinal study of 266 pts with AUD, of whom 133 had comorbid SAD, showed higher rates of relapse with TSF treatment in females with comorbid AUD; by the end of treatment about 60% of the females without social phobia did not relapse to heavy drinking whereas only 40% of the females with social phobia had not relapsed. A 6-month follow-up study of 300 AUD pts, of whom 74 had SAD, reported that the efficacy of treatment at AA for alcohol dependence was no different between patients with and without SAD. In addition, a retrospective study of 794 AUD patients (half with comorbid SAD) showed no difference between groups for treatment response either to CBT or TSF therapy. When stratified for gender, this study found that female outpatients with SAD who were treated with CBT presented delayed relapse to heavy drinking (during and following treatment) compared to SAD females treated with TSF. Moreover, this study found a reverse trend in the male sample, with delaying relapse effect of TSF being greater than CBT.
O'Neil, 2020[21]	Ovid Medline; Ovid EBM Reviews: Cochrane Central Register of	P: US Veterans or SMs with mTBI and chronic pain or headaches I: Pharmacologic,	2 RCTs	Repetitive transcranial magnetic stimulation (rTMS)	KQ2: The 2 rTMS studies reported significantly greater reduction in persistent headaches in the rTMS group compared to the group randomized to the sham treatment condition. Similar results

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	Controlled Trials, Cochrane Database of Systematic Reviews; Ovid PsycINFO; CINAHL; Scopus; Google Scholar; and Epistemonikos, clinical trial registries and reference lists from database inception through February 7, 2020	nonpharmacologic, and complementary and integrative health interventions C: Placebo, active comparator, usual care, wait-list control, pre-post O: Prevalence, estimates of suicide risk, benefits and harms of interventions S: For intervention studies, only randomized and nonrandomized controlled trials	N=73 US Veterans with mTBI and chronic headaches		were obtained for debilitating headache exacerbation, with significantly greater reductions observed in the rTMS group compared to the sham group in both studies.
Parr, 2021[22]	Ovid MEDLINE, Ovid PsycINFO, Ovid CENTRAL, PTSDpubs, Cochrane Database of Systematic Reviews, ClinicalTrials.gov, AHRQ, & HSR&D through October 2020.	P: Patients with TBI, PTSD, or the co-occurrence of TBI and PTSD I: HBOT, any protocol C: Any (*eg*, sham HBOT, no treatment, standard care) O: Benefits (mortality, morbidity, quality of life, functional capacity, TBI and/or PTSD symptom improvement/symptom response) and harms S: SRs, RCTs, and concurrently controlled cohort studies. We considered case series only to address gaps in evidence from studies with control groups	2 sham-controlled trials (N=132) and 2 secondary analyses (N=204) Active-duty military personnel with mTBI with and without comorbid PTSD	HBOT	KQ1: Using uncorrected significance tests, 1 trial found that post-concussion symptoms significantly favored HBOT immediately following treatment among pts with PTSD but not among those without PTSD. Improvements seen at 6 months were nonsignificant, while symptoms did not differ or worsened compared to sham at 12 months. The second trial, which reported post-concussion outcomes 5.5 months from baseline, did not find evidence of moderation by PTSD status. Results of a secondary analysis of data from 2 studies with PTSD subgroups using a composite outcome (including cognitive, physical, and emotional symptoms and based on several existing measurement tools) reported similar findings, and a pooled analysis of included trials found that a PTSD status-by-intervention group interaction was nonsignificant.
Petrakis, 2017[23]	PsycINFO and MEDLINE/PUBMED	P: Individuals diagnosed with AUD and PTSD	9 RCTs	3 studies focused on medications to	KQ1: A secondary analysis of an RCT conducted with Veterans evaluated whether the presence of

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	databases	I: Pharmacotherapy with or without behavioral intervention C: AUD and PTSD outcomes, treatment dropout O: Not specified S: RCTs	N=718 pts with comorbid PTSD and AUD, 5 studies with Veterans (1 study included subthreshold PTSD)	treat PTSD, 4 on AUD, and 3 to target both PTSD w/ AUD	PTSD compared to the absence of PTSD influenced alcohol outcomes. Comparing any medication vs no medication, naltrexone vs disulfiram, and naltrexone + disulfiram vs each medication alone, results suggested that pts with PTSD had better alcohol use outcomes, specifically on the percent of heavy drinking days and consecutive days of abstinence in the presence of active medication compared to no medication. For number of heavy drinking days and consecutive days of abstinence there were no significant differences between active medication groups and no significant effect of the combination of medications compared to either alone. KQ2: Of the 3 studies investigating medications to treat PTSD, neither of the sertraline studies found the medication more effective than placebo in terms of alcohol use outcomes. One study comparing paroxetine to desipramine (active control) in Veterans found that desipramine was more effective in terms of alcohol use outcomes. This study also paired paroxetine and desipramine with either naltrexone (medication for AUD) or placebo. None of the medications were associated with significant between group differences on PTSD outcomes. Another study randomized pts receiving PE to alcohol-oriented supportive treatment with naltrexone vs placebo. There was not a main effect of medication on PTSD outcomes at any time point, though post hoc analysis indicated that people assigned to receive both naltrexone and PE were more likely to have clinically significant improvements in PTSD outcomes at the 6-month follow-up than the

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					other 3 conditions. In another study comparing topiramate to placebo in Veterans, there was a significant effect of time for PTSD symptoms and a trend regarding overall PTSD symptom severity and the hyperarousal symptom cluster indicating an effect of topiramate over placebo. In 2 studies evaluating prazosin vs placebo (both including Veterans), 1 suggested that prazosin was effective in decreasing alcohol use, and the other did not. In an RCT comparing aprepitant to placebo, there was no effect on alcohol craving.
Pott, 2021[24]	PsycINFO, PubMED, and Cochrane CENTRAL from inception to June 7, 2020. Additional hand-searching of reference lists of retrieved papers and of a previous review on this topic (Martínez-Vispo et al., 2018) to identify additional studies.	P: Adult substance users with clinically significant depression symptoms as measured using diagnostic interviews or validated case-finding measures. The study defined substance users as individuals who met at least 1 of the following criteria: (i) enrolled in community or inpatient addiction treatment program, (ii) had used substances recently as assessed by a screening questionnaire, and (iii) met criteria for SUD assessed by a structured clinical interview. I: BA C: Passive or active control O: Must include depression outcomes, substance use outcomes, or both. The primary outcome measure was depressive	5 RCTs N=195 adults with substance use and comorbid depression	BA (Note: In 4/5 studies the BA intervention appears to have substance use treatment components, but these aren't labeled as 'integrated' interventions)	KQ2: The study team included all studies reporting substance use outcomes in a random effects meta-analysis of BA versus controls for posttreatment substance use outcomes (k = 4; N = 151). One of these studies did not assess pts until 12 weeks after BA treatment had finished (N = 50). The pooled SMD indicated that BA was not associated with significant improvements in posttreatment substance use outcomes compared to controls (SMD = 0.14; 95% CI –0.33 to 0.6; Z = 0.57; p = 0.57; GRADE = Low). Four comparisons evaluated the effects of BA versus controls on substance use outcomes at follow-up (k = 5; N = 151). The pooled SMD indicated that BA was not associated with significant improvements in follow-up substance use outcomes compared to controls (SMD = 0.17; 95% CI –0.34 to 0.69; Z = 0.65; p = 0.51; GRADE = Low). For posttreatment substance use outcomes, results of sensitivity analyses indicated that neither substance type nor type of comparator (k= 2; N = 63; SMD = 0.02; 95% CI –0.64 to 0.68; Z = 0.06; p = 0.95) affected the size of the effect for substance use outcomes. For substance use outcomes at follow-up, results indicated that neither type of

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		symptomatology as measured using any validated self-report measure or clinician-rated measures. The secondary outcome was substance use as measured using any validated self-report scale or assessment or abstinent/not abstinent from substances. S: RCTs			substance nor type of comparator (k = 2; N = 63; SMD = 0.08; 95% CI –0.78 to 0.95; Z = 0.19; p = 0.95) affected the size of the effect for substance use outcomes.
Roberts, 2015[25] Roberts, 2016[26]	Cochrane Depression, Anxiety and Neurosis Group's Specialized Register all years to 11 March 2015. WHO ICTRP, ClinicalTrials.gov, contacted experts, hand search of bibliographies of included studies, and performed citation searches of identified articles	P: Individuals with comorbid PTSD and SUD. At least 80% of participants had to be diagnosed as suffering from PTSD according to ICD or DSM. At least 80% of participants met formal diagnostic criterion for a substance misuse disorder according to DSM or equivalent ICD definitions. I: Any experimental psychological therapy designed to reduce symptoms of PTSD, substance usage, or both. C: A control intervention (including no intervention, or any minimal intervention such as waiting-list control, TAU, minimal or placebo condition) or an active psychological therapy O: Severity of traumatic	14 RCTs N=1506 pts with comorbid PTSD and SUD, 1 study with Veterans	CBT-based interventions, both trauma-focused and non-trauma focused, some were integrated treatments	KQ2: Individual-based psychological therapy with a trauma-focused component did not perform better than psychological therapy for SUD only for PTSD severity (mean difference (MD) -3.91; 95% CI -19.16 to 11.34; 1 study; n = 46; low-quality evidence) or drug/alcohol use (MD -1.27; 95% CI -5.76 to 3.22; 1 study; n = 46; low-quality evidence). Findings were based on 1 small study. For non-trauma-focused psychological therapies compared to TAU/minimal intervention there were no data on the effects on drug/alcohol use for individual therapy. There was no evidence of an effect on the level of drug/alcohol use for group-based therapy (SMD -0.03; 95% CI -0.37 to 0.31; 4 studies; n = 414; very low-quality evidence). Non-trauma-focused psychological therapy did not perform better than psychological therapy for SUD only for PTSD severity (SMD -0.26; 95% CI -1.29 to 0.77; 2 studies; n = 128; very low-quality evidence) or drug/alcohol use (SMD 0.22; 95% CI -0.13 to 0.57; 2 studies; n = 128; low-quality evidence). KQ3: Individual-based psychological therapies with a trauma-focused component plus adjunctive

Author, Year	Search details	Eligibility criteria	Included Studies[a] Patient Characteristics[a]	Intervention Characteristics[a]	Results[a]
		stress symptoms, reduction in drug use, alcohol use, treatment completion as measured by number of participants who were identified as treatment completers by study authors. S: RCTs			SUD intervention was more effective than treatment as usual (TAU)/minimal intervention for PTSD severity posttreatment (SMD -0.41; 95% CI -0.72 to -0.10; 4 studies; n = 405; very low-quality evidence) and at 3 to 4 and 5 to 7 months' follow-up. There was no evidence of an effect for level of drug/alcohol use posttreatment (SMD -0.13; 95% CI -0.41 to 0.15; 3 studies; n = 388; very low-quality evidence), but there was a small effect in favor of individual psychological therapy at 5 to 7 months (SMD -0.28; 95% CI -0.48 to -0.07; 3 studies; n = 388) when compared against TAU. A post-hoc analysis for full dose of SS showed reduced drug/alcohol use posttreatment (SMD -0.67; 95% CI -1.14 to -0.19; 2 studies; n = 111), but not at subsequent follow-ups.
Skelly, 2020[27]	Ovid MEDLINE, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews from September 1, 2017 - September 20, 2019 as well as searches from a previous AHRQ report through November 1, 2017	P: Adults with the following chronic pain conditions: low back pain, neck pain, osteoarthritis pain, fibromyalgia, or tension headache I: Exercise, psychological therapies, physical modalities, manual therapies, mindfulness practices, mind-body practices, acupuncture, multidisciplinary/interdisciplinary rehabilitation C: Sham, waitlist, usual care, no treatment, attention control, nonopioid pharmacological therapy, topical agents, medical cannabis, exercise,	1 RCT N=439 older adults with osteoarthritis of the knee	Exercise vs attention control	KQ1: There is insufficient evidence from 1 fair-quality trial that depression status modifies the effect of exercise in pts with osteoarthritis of the knee. A second publication of this trial looked at whether the effects of exercise on pain, disability, and depression were modified by baseline depression status, that is, high versus low depressive symptomology according to the Center for Epidemiologic Studies Depression scale over time (using an adjusted repeated measures analysis of variance). However, the authors do not provide results that directly examined modification by baseline depression without the time component

Author, Year	Search details	Eligibility criteria	Included Studies[a] Patient Characteristics [a]	Intervention Characteristics[a]	Results [a]
		biofeedback, O: Function/disability/pain interference, pain, harms and adverse events, secondary outcomes (psychological distress, quality of life, opioid use, sleep quality, sleep disturbance, & healthcare utilization) S: RCTs or high quality SRs of RCTs published in English; cross-over trials with random assignment of initial treatment			
Yan, 2020[28]	Cochrane CENTRAL, PubMed, EMBASE, Chinese Biomedical Database (SinoMed), China National Knowledge Infrastructure, and Wanfang database, inception to March 17, 2020 (included studies 2000-2018)	P: Patients diagnosed with chronic pain combined with depression or depression combined with chronic pain. The author must explain the definition or diagnostic criteria for chronic pain and depression. I: Acupuncture alone or in combination with other therapy C: Other therapy without acupuncture O: Pain scores, depression severity, adverse events S: RCTs	7 RCTs N=535 pts with comorbid chronic pain and depression. All studies conducted in China.	Acupuncture alone or combined with traditional Chinese medicine or medication	KQ2: All trials assessed depression, and 6 used the Hamilton Rating Scale for Depression (HAMD). There was no significant difference in HAMD between the 2 groups before therapy. After 4 weeks of treatment, HAMD decreased significantly in both groups, especially in the experimental group, which indicates that there was a significant difference between the 2 groups (MD = −2.18 (−3.09, −1.26), P < 0.00001, I2 = 52%).

Abbreviations. AA=Alcoholics Anonymous; ACT=Acceptance and Commitment Therapy; AHRQ=Agency for Healthcare Research and Quality; AMED=Allied and Complementary Medicine Database; AOD=alcohol or other drug use disorder; AUD=alcohol use disorder; BA=behavioral activation; BD=bipolar disorder; BSP=brief supportive psychotherapy; BTDD=Behavioral Therapy for Depression in Drug Dependence; C=comparator; CAPS=Clinician Administered PTSD Scale; CBT=cognitive behavioral therapy; CCT=controlled clinical trial; CI=confidence interval; CINAHL=Cumulative Index to Nursing and Allied Health Literature; Cochrane CENTRAL=Cochrane Central Register of Controlled Trials; COPE=Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure; CPT=cognitive processing therapy; CRD=Centre for Reviews and Dissemination;

Supplemental Materials

DSM=Diagnostic and Statistical Manual of Mental Disorders; DTMS=deep transcranial magnetic stimulation; DVBIC=Defense and Veterans Brain Injury Center; ES=effect size; FNS=Flexyx Neurotherapy System; GAD=generalized anxiety disorder; HAMD=Hamilton Rating Scale for Depression; HBOT=hyperbaric oxygen therapy; HSR&D=VA Health Services Research & Development; HTA=health technology assessment; I=intervention; ICBT=Integrated Cognitive Behavioral Therapy; ICD=International Classification of Diseases; IPD=individual participant data; IPSRT= interpersonal and social rhythm therapy; IPT=interpersonal therapy; IPT-D=interpersonal therapy for depression; KQ=key question; LTMT=light touch manual therapy; MA=meta-analysis; MBSR=mindfulness-based stress reduction; MD=mean difference; MDD=major depressive disorder; MOUD=medications for opioid use disorder; mPE=modified prolonged exposure; mTBI=mild traumatic brain injury; NRI=noradrenaline reuptake inhibitor; O=outcome; OEF/OIF/OND=Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn; OR=odds ratio; OUD=opioid use disorder; P=population; PCT=present centered therapy; PE=prolonged exposure; PILOTS=Published International Literature on Traumatic Stress; pts=participants; PTSD=posttraumatic stress disorder; RCT=randomized controlled trial; RP=relapse prevention; RoB=risk of bias; RR=relative risk; S=setting; SAD=social anxiety disorder; SD=standard deviation; SM=service member; SMART-CPT=cognitive symptom management and rehabilitation therapy + cognitive processing therapy; SMD=standardized mean difference; SOE=strength of evidence; SR=systematic review; SS=Seeking Safety; SSRI=selective serotonin reuptake inhibitor; SUCRA=surface under the cumulative ranking; SUD=substance use disorder; TAU=treatment as usual; TBI=traumatic brain injury; TSF=Twelve Step Facilitation; US=United States; WHO ICTRP= World Health Organization International Clinical Trials Registry Platform.

QUALITY ASSESSMENT OF INCLUDED SYSTEMATIC REVIEWS (ROBIS)

Author Year	**Eligibility Criteria Concerns**	**Identification and Selection of Studies Concerns**	**Data Collection and Study Appraisal Concerns**	**Synthesis and Findings Concerns**	**Overall Bias** *(High, Low, Unclear)*
Agabio, 2018[1]	Low Pre-defined criteria, appropriate criteria for inclusion.	Low Multiple databases searched, no language or date restrictions, reference checking of included articles, dual study selection.	Low Dual independent data abstraction, dual independent quality assessment with the Cochrane Risk of Bias Tool. Includes characteristics of included studies tables.	Low Analyses pre-defined, heterogeneity assessed. Looked at potential confounders in sensitivity analyses.	Low
Banerjee, 2017[2]	High Criteria not unambiguous, the date range was restricted post hoc.	High Multiple databases searched, no reference checking of included articles. Search strategy not provided. A single person performed study selection.	Unclear No information provided on data abstraction or risk of bias assessment processes. Different risk of bias tools used for different study designs. Includes characteristics of included studies tables.	High Analyses not pre-defined. Findings not robust. Did not discuss how quality of studies may have impacted results.	High Used rapid review methodology.
Barrett, 2016[3]	Unclear No protocol cited, some criteria appear to have been altered post hoc.	Unclear Full search strategy not provided, unclear if there were restrictions based on date or language.	Unclear No information provided on data abstraction or risk of bias assessment processes. Rated studies with a PRISMA Quality Appraisal Score. Study characteristics available in supplemental table.	High Methods do not describe a plan for analysis. Findings not robust. Did not discuss how quality of studies may have impacted results.	Unclear
Crowe, 2021[4]	Unclear Criteria not unambiguous.	Low Multiple databases searched, no language or date restrictions, reference checking of included articles, dual independent study selection.	Low Dual independent data abstraction, dual independent quality assessment with the Cochrane Risk of Bias Tool. Table of study characteristics.	Unclear Analyses not pre-defined. Findings not robust.	Unclear

Author Year	**Eligibility Criteria Concerns**	**Identification and Selection of Studies Concerns**	**Data Collection and Study Appraisal Concerns**	**Synthesis and Findings Concerns**	**Overall Bias** *(High, Low, Unclear)*
Dewar, 2020[5]	Low Pre-defined criteria, appropriate criteria for inclusion.	Low Multiple databases searched, no language or date restrictions, reference checking of included articles, dual independent study selection.	Low Dual independent data abstraction, quality assessment with the Downs and Black Inventory. Table of study characteristics.	Unclear Analyses pre-defined, robustness of findings was not assessed.	Low
Forte, 2015[6]	Low Pre-defined criteria, appropriate criteria for inclusion.	Low Multiple databases searched, no language restrictions, date restriction appears reasonable, reference checking of included articles, dual independent study selection.	Low Sequential data abstraction, dual independent quality assessment based on study design. Tables of study characteristics.	Low Analyses pre-defined, heterogeneity addressed by not pooling studies. Risk of bias taken into account in strength of evidence assessments.	Low
Greer, 2019[7] Ackland, 2019[8]	Low Pre-defined criteria, appropriate criteria for inclusion.	Low Multiple databases searched, restrictions appear reasonable, reference checking of included articles, dual independent study selection.	Low Sequential data abstraction. Adapted criteria from the JBI Critical Appraisal Tool, but do not describe the process for risk of bias assessment. Includes characteristics of included studies tables in appendix.	Low Analyses pre-defined, heterogeneity addressed by not pooling studies. Risk of bias taken into account in strength of evidence assessments.	Low
Hides, 2019[9]	Low Appropriate criteria for inclusion. Criteria in the protocol were revised, but justification was provided.	Low Multiple databases searched, no language or date restrictions, handsearching and grey literature searching conducted, dual independent study selection.	Low Dual independent data abstraction, dual independent quality assessment with the Cochrane Risk of Bias Tool. Includes characteristics of included studies tables.	Low Analyses pre-defined, heterogeneity assessed. Risk of bias taken into account in strength of evidence assessments.	Low
Hildebrand, 2015[29]	Low	High Multiple databases searched, reference checking of	High Single person data abstraction, process for risk	Unclear Analyses not pre-defined. Findings do not	High

Author Year	Eligibility Criteria Concerns	Identification and Selection of Studies Concerns	Data Collection and Study Appraisal Concerns	Synthesis and Findings Concerns	Overall Bias *(High, Low, Unclear)*
	Defined criteria, appropriate criteria for inclusion.	included articles. Full search strategy not provided; search terms do not appear comprehensive. Unclear if there were date restrictions, study selection likely performed by a single person.	of bias assessment not described. Studies were given a score for 'excellence.' Tables of study characteristics.	appear robust. Biases not addressed.	
Hobden, 2018[10]	Low Defined criteria, appropriate criteria for inclusion.	Low Multiple databases searched, restrictions appear reasonable, reference checking of included articles, single person study selection with a random 20% reviewed by a second person.	Low Sequential data abstraction, dual independent quality assessment with Cochrane EPOC criteria. Table of study characteristics.	Unclear Analyses not pre-defined. Biases not addressed in synthesis.	Low
Hoffman, 2018[11]	Low Pre-defined criteria, appropriate criteria for inclusion.	Low Multiple databases searched, restrictions were appropriate, grey literature searches conducted, dual independent study selection.	Low Sequential data abstraction, dual independent quality assessment based on AHRQ criteria. Includes characteristics of included studies tables.	Low Analyses pre-defined, heterogeneity assessed. Risk of bias taken into account in strength of evidence assessments.	Low
Ipser, 2015[12]	Low Appropriate criteria for inclusion. Criteria in the protocol were revised, but justification was provided.	Low Multiple databases searched, no language or date restrictions, reference checking of included articles, dual independent screening of full texts.	Low Dual independent data abstraction, dual independent quality assessment with the Cochrane Risk of Bias Tool. Includes characteristics of included studies tables.	Low Analyses pre-defined, heterogeneity assessed. Risk of bias taken into account in GRADE assessments.	Low
Kedzior, 2018[13]	Unclear Defined criteria, criteria were not unambiguous.	High Multiple databases searched. No additional methods used to identify studies. Methods of	Unclear Dual independent data abstraction. The Cochrane Risk of Bias Tool was used, but the process is not described. Non-randomized	High Analyses not pre-defined.	High

Author Year	Eligibility Criteria Concerns	Identification and Selection of Studies Concerns	Data Collection and Study Appraisal Concerns	Synthesis and Findings Concerns	Overall Bias *(High, Low, Unclear)*
		study selection are not described.	studies were not assessed. Tables of study characteristics.	Findings not robust. Biases not addressed in synthesis.	
Kline, 2021[14]	Low Defined criteria, appropriate criteria for inclusion.	Unclear Conducted limited database searches and identified studies from 2 prior SRs. Methods of study selection not described.	Low Dual independent data abstraction. Dual independent quality assessment based on AHRQ criteria for studies not assessed by prior reviews. Tables of study characteristics.	Unclear Analyses not pre-defined. Heterogeneity addressed. High risk of bias studies were excluded.	Unclear
Larsen, 2019[15]	Unclear Defined criteria, appropriate criteria for inclusion. Criteria and restrictions not unambiguous.	High No database searches were conducted. Identifies studies from 2 prior SRs. Methods of study selection not described.	Low Dual independent data abstraction. Dual independent quality assessment based on 3 typical indicators of quality for studies not assessed by prior reviews. Table of study characteristics in supplement.	Unclear Analyses not pre-defined. Heterogeneity addressed by not pooling studies. High risk of bias studies were excluded.	Unclear
Li, 2020[16]	Low Defined criteria, appropriate criteria for inclusion.	Low Multiple databases searched, no restrictions on date or language, reference checking of included articles, dual independent study selection.	Low Dual independent data abstraction. Quality assessment with the Cochrane Risk of Bias Tool. Table of study characteristics in supplement.	Unclear Analyses not pre-defined. Heterogeneity assessed. Sensitivity analyses were conducted and funnel plots were used to assess publication bias.	Low
Martinez-Vispo, 2018[30]	Low Pre-defined criteria, appropriate criteria for inclusion.	Low Multiple databases searched, restrictions appear reasonable, reference	Low Dual independent data abstraction. Dual independent quality	Unclear Analyses pre-defined. Heterogeneity addressed by not pooling studies.	Low

Author Year	Eligibility Criteria Concerns	Identification and Selection of Studies Concerns	Data Collection and Study Appraisal Concerns	Synthesis and Findings Concerns	Overall Bias *(High, Low, Unclear)*
		checking of included articles, dual independent study selection.	assessment with the Effective Public Health Practice Project Quality Assessment Tool. Table of study characteristics.	Findings were not robust.	
Mehta, 2021[17]	Low Pre-defined criteria, appropriate criteria for inclusion.	Unclear Multiple databases searched. Full search strategy not provided, and search terms may not be adequate. No justification given for date restrictions. Reference checking of relevant SRs, dual study selection.	Low Dual independent data abstraction. Risk of bias assessment based on the Cochrane Risk of Bias Tool. Table of study characteristics.	Low Analyses not pre-defined. Heterogeneity assessed. Subgroup analyses and sensitivity analyses were conducted and address risk of bias.	Low
Meshberg-Cohen, 2021[18]	Low Defined criteria, appropriate criteria for inclusion.	Unclear Multiple databases searched. Full search strategy not provided. No additional sources searched. Dual independent review of full-text articles.	High Sequential data abstraction. Interventions were given a 'quality index rating'; this process is not described. Table of study characteristics.	High Analyses not pre-defined. Heterogeneity addressed by not pooling studies. No information on robustness of findings or risk of bias.	High
Mikolic, 2019[19]	Low Defined criteria, appropriate criteria for inclusion.	Low Multiple databases searched, no language or date restrictions, grey literature searches conducted, dual study selection.	Low Sequential data abstraction. Dual risk of bias assessment using the Research Triangle Institute item bank. Table of study characteristics.	High Analyses not pre-defined. Heterogeneity addressed by not pooling studies. No information on robustness of findings. Risk of bias not addressed in the synthesis.	Unclear
Oliveira, 2018[20]	Unclear Pre-defined criteria. Criteria were not unambiguous.	Low Multiple databases searched, restrictions appear reasonable, reference checking of included articles,	Unclear Data abstraction process not described. Dual quality assessment with the Newcastle-Ottawa Quality	High Pre-defined analytic plan is unclear. Heterogeneity addressed by not pooling studies. No information on robustness of	High

Author Year	**Eligibility Criteria Concerns**	**Identification and Selection of Studies Concerns**	**Data Collection and Study Appraisal Concerns**	**Synthesis and Findings Concerns**	**Overall Bias** *(High, Low, Unclear)*
		dual independent study selection.	Assessment Scale. Table of study characteristics.	findings. Risk of bias not addressed in the synthesis.	
O'Neil, 2020[21]	Low Defined criteria, appropriate criteria for inclusion.	Low Multiple databases searched, no language or date restrictions, reference checking of included articles, dual independent study selection for full-text articles.	Low Sequential data abstraction, dual independent quality assessment with the tool dependent on study design. Tables of study characteristics.	Low Analyses not pre-defined, heterogeneity assessed by not pooling studies (for KQ of interest). Risk of bias taken into account in strength of evidence assessments.	Low
Parr, 2021[22]	Low Pre-defined criteria, appropriate criteria for inclusion.	Low Multiple databases searched, restrictions were reasonable, reference checking of included articles, sequential study selection.	Low Sequential data abstraction, sequential quality assessment with the Cochrane Risk of Bias Tool. Tables of study characteristics.	Low Analyses pre-defined, heterogeneity addressed by not pooling the studies. Findings were robust. Risk of bias taken into account in strength of evidence assessments.	Low
Petrakis, 2017[23]	Unclear Defined criteria, criteria not unambiguous.	High Multiple databases searched, unclear whether the search strategy was adequate, no description of study selection process.	High No description of data abstraction. Dual independent risk of bias assessment based on 3 domains. Tables of study characteristics.	High Analyses not pre-defined, heterogeneity addressed by not pooling studies. No information on robustness of findings. Risk of bias not addressed in the synthesis.	High
Pott, 2021[24]	High Some discrepancies in criteria between protocol and review that affect inclusion.	Unclear Multiple databases searched, authors of included articles were contacted to identify additional studies. Unclear whether the search strategy	Low Sequential data abstraction, dual independent risk of bias assessment using the Cochrane Risk of Bias Tool.	Low Analyses pre-defined, heterogeneity assessed. Findings were robust.	Unclear

Author Year	Eligibility Criteria Concerns	Identification and Selection of Studies Concerns	Data Collection and Study Appraisal Concerns	Synthesis and Findings Concerns	Overall Bias *(High, Low, Unclear)*
		was adequate. Dual independent review of full-text articles.	Tables of study characteristics.	Risk of bias taken into account in the synthesis.	
Roberts, 2015[25] Roberts, 2016[26]	Low Pre-defined criteria, appropriate criteria for inclusion.	Low Multiple databases searched, no language or date restrictions, reference checking of included articles, dual independent study selection.	Low Dual independent data abstraction, dual independent quality assessment using Cochrane criteria. Includes characteristics of included studies tables.	Low Analyses pre-defined, heterogeneity assessed. Findings were robust. Risk of bias taken into account in the synthesis.	Low
Skelly, 2020[27]	Low Pre-defined criteria, appropriate criteria for inclusion.	Low Multiple databases searched, date restrictions were appropriate for an update of an existing review, reference checking of included articles, dual study selection.	Low Sequential data abstraction, dual independent risk of bias assessment with the Cochrane Risk of Bias Tool. Tables of study characteristics.	Low Analyses pre-defined, heterogeneity assessed. Findings were robust. Risk of bias taken into account in the synthesis	Low
Yan, 2020[28]	Unclear Defined criteria, criteria were not unambiguous.	High Multiple databases searched. No additional sources searched. Full search strategy was not provided. Dual independent study selection.	Unclear No description of dual data abstraction. Dual independent risk of bias assessment with the 5-point Jadad Score. Tables of study characteristics.	Low Analyses not pre-defined, heterogeneity assessed. Findings were robust. Risk of bias addressed in the synthesis.	Unclear

Abbreviations. AHRQ=Agency for Healthcare Research and Quality; EPOC=Effective Practice and Organisation of Care; GRADE=Grading of Recommendations, Assessment, Development and Evaluations; KQ=Key Question; SR=systematic review

STRENGTH OF EVIDENCE FOR INCLUDED STUDIES

Strength of Evidence for KQ1

Comorbidity	Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Rating and Summary of Evidence
PTSD & depression	2 SRs[5,14]	Low to unclear RoB	Indirect	Inconsistent	Imprecise	None detected	Low SOE: A diagnosis of MDD may have a negative impact on PTSD treatment outcome, based on indirect, inconsistent, and imprecise information from 2 SRs. In 1 SR with a low risk of bias, a trajectory analysis found that baseline MDD diagnosis significantly predicted assignment to a non-responder trajectory (based on data from 1 included study). A second SR with unclear risk of bias found no association between comorbid depression diagnosis and PTSD symptom change, but the analysis used the proportion of the sample diagnosed with MDD from each study, which may misrepresent the actual within-study relationship between depression and PTSD.
PTSD & TBI	2 SRs[7,19]	Low to unclear RoB	Indirect	Inconsistent	Imprecise	None detected	Low SOE: It is unclear whether a history of TBI has a negative impact on PTSD treatment outcome, based on indirect, inconsistent information from 2 SRs. One of the 3 relevant studies from 1 SR was with a mixed sample of individuals diagnosed with anxiety, depression, or PTSD. This SR generally found no difference in treatment effects between individuals with PTSD with versus without TBI. The second SR had inconsistent results. Most of the evidence comes from nonrandomized studies.
Chronic pain & depression	2 SRs[6,27]	Low RoB	Direct	Unknown	Imprecise	None detected	Low SOE: A diagnosis of MDD does not appear to have an impact on chronic pain outcomes, based on direct, but inconsistent evidence from 2 SRs. In 1 SR, there is low-strength evidence that the effect of drug treatment does not differ in adults with fibromyalgia with and without depression. A second SR found the evidence is insufficient that depression status modifies the effect of exercise on osteoarthritis of the knee.

Abbreviations. MDD=major depressive disorder; PTSD=posttraumatic stress disorder; RoB=risk of bias; SOE=strength of evidence; SR=systematic review; TBI=traumatic brain injury

Strength of Evidence for KQ2

Comorbidity	Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Rating and Summary of Evidence
PTSD & anxiety	1 SR[15]	Unclear RoB	Indirect	Unknown	Imprecise	None detected	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 that reported the percent of study arms with residual symptoms, which may misrepresent an actual within-study relationship between PTSD and anxiety.
PTSD & depression	1 SR[15]	Unclear RoB	Indirect	Unknown	Imprecise	None detected	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 that reported the percent of study arms with residual symptoms, which may misrepresent an actual within-study relationship
PTSD & SUD	3 SRs[12,23,26]	Low to high RoB	Direct	Consistent	Imprecise	None detected	Low SOE: Treatment of PTSD may not be associated with improvement in comorbid SUD, based on direct and consistent, but imprecise, information from 2 low risk of bias SRs. Evidence was sparse in these 2 SRs, and the quality of evidence was rated low to very low in the SR on psychological therapies. A third SR with high risk of bias had mixed results.
TBI & chronic pain	1 SR[21]	Low RoB	Indirect	Unknown	Imprecise	None detected	Insufficient SOE: One SR included 2 small studies with high risk of bias. Outcomes were headache-related, and it's not clear if this can be considered an outcome of the secondary condition (TBI)
SUD & anxiety	1 SR[12]	Low RoB	Direct	Unknown	Imprecise	None detected	Insufficient SOE: One low risk of bias SR found very low-quality evidence that treatment with paroxetine had no impact on alcohol use outcomes
SUD & depression	5 SRs[1,9,13,16,24]	Low to high RoB	Direct	Consistent	Precise	None detected	Moderate SOE: One low risk of bias SR found moderate quality evidence that treatment with antidepressants resulted in improvements in some alcohol outcomes. Low SOE: Two other SRs found low to very low-quality evidence of no effect for interpersonal therapy and behavioral activation on substance use outcomes.
Chronic pain & depression	1 SR[28]	Unclear RoB	Direct	Unknown	Precise	None detected	Low SOE: Based on 1 SR with unclear risk of bias, acupuncture treatment for chronic pain may result in improvements in depression outcomes. Our confidence is limited by the low quality of the included studies

Abbreviations. PTSD=posttraumatic stress disorder; RoB=risk of bias; SOE=strength of evidence; SR=systematic review; SUD=substance use disorder; TBI=traumatic brain injury

Strength of Evidence for KQ3

Comorbidity	Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Rating and Summary of Evidence
PTSD & SUD	3 SRs[11,17,26]	Low RoB	Direct	Inconsistent	Unknown	None detected	Low SOE: Based on 3 low risk of bias SRs, integrated treatments may be more effective than usual care or treatments for either condition alone (low strength of evidence). Results were inconsistent across time points and outcomes. Though usual care often consists of treatment for a single condition, this is not always specified. Two of the SRs graded the SOE, with assessments ranging from low to very low/insufficient.
SUD & anxiety/ depression	1 SR[17]	Low RoB	Indirect	Unknown	Precise	None detected	Low SOE: Integrated cognitive-behavioral interventions for individuals with alcohol or drug use and co-occurring anxiety or depression may lead to no change 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. Half of all studies included in this SR were rated as high risk of bias. Anxiety and depression were combined in the analysis, and comparators (usual care, single-disorder intervention) are not analyzed separately for this subgroup.
SUD & depression	2 SRs[9,10]	Low RoB	Indirect	Consistent	Unknown	None detected	Low SOE: Evidence is mixed on the effectiveness of integrated treatments for comorbid SUD & depression compared to usual care or interventions for SUD or depression alone, based on indirect, consistent information from 2 low risk of bias SRs. One of the SRs included some studies where not all participants were required to have a diagnosis of both conditions.
SUD & bipolar disorder	1 SR[4]	Unclear RoB	Direct	Unknown	Imprecise	None detected	Insufficient SOE: Based on 1 SR with unclear risk of bias, it is uncertain whether integrated CBT-based interventions for SUD and bipolar disorder are more effective than interventions for SUD alone. Our confidence is limited by the small number and sample sizes of the included studies.

Abbreviations. CBT=cognitive behavioral therapy; PTSD=posttraumatic stress disorder; RoB=risk of bias; SOE=strength of evidence; SR=systematic review; SUD=substance use disorder

APPENDIX E: PEER REVIEW DISPOSITION

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	2	Yes	*None*
2	3	Yes	*None*
3	4	Yes	*None*
Is there any indication of bias in our synthesis of the evidence?			
1	2	No	*None*
2	3	No	*None*
3	4	No	*None*
Are there any published or unpublished studies that we may have overlooked?			
1	2	No	*None*
2	3	No	*None*
3	4	No	*None*
Additional suggestions or comments can be provided below.			
1	4	Thank you for letting me review this article. It's extremely relevant to clinical practice and I enjoyed reading it. This was well written, and the methodology was well thought out and executed. I had only one comment on the literature flow table that questioned the 100 studies eliminated before the title/abstract review. Please see my attached PDF.	*We have corrected the number of articles excluded during title and abstract review in the literature flow diagram.*
2	1	I understand why [limiting to SRs] was done, but I think it prevents definitive conclusions from this report because so much of the relevant literature is not presented in SRs and even is not reported in a straightforward way. For example, the primary outcome paper for a trial might also report some predictor analyses. I think this needs to be discussed. I have been looking at this literature because I am currently doing a paper on predictors of treatment outcome in PE and CPT and definitely could not use SRs only to inform the paper.	*We agree that the rapid review methodology employed limits the conclusions of the current review. We have added in language to make it clearer that the purpose of the current review is to review evidence available from recent systematic reviews, and have refined the language about the lack of evidence found.*

Comment #	Reviewer #	Comment	Author Response
		For example, this paper reported no prescriptive predictors of outcome between PE and PCT in female Veterans, but did find comorbid disorder was a prognostic predictor. The strategy of looking only at SRs is probably OK for larger literatures, including PTSD/SUD, but I don't think it is sufficient for other PTSD comorbidities.	
3	1	Actually, there is much more evidence that presented here or that was included in the review. The information is often not presented in separate studies.	*We have removed the first part of this sentence referring to the 'dearth of evidence' regarding the treatment of patients with comorbidities.*
4	1	The findings of this study should be more fully reported. There were major differences between drug and psychotherapy trials.	*We have removed the sentence referencing this study, as we agree that an accurate description of the study would require more explanation and context than is feasible to provide in this section.*
4	1	The discussion here does not account for the issues of safety and feasibility that would also come into play in practice. For example, active suicidality or homicidality is often an exclusion, but it also would preclude initiation of a new treatment in practice until the issue was resolved, e.g., it would not be appropriate to start PE in a person with intent and a plan. As another example, moderate to severe cognitive impairment might prevent someone from participating in treatments that are cognitively demanding. Thus, the fact that epi and clinical samples have comorbidities that would exclude them from some trials does not mean that patients with those comorbid combinations would be candidates for specific treatments in practice.	*We agree that these are important clinical issues, but as they are not necessarily specific to the comorbid conditions reviewed here, we believe that a full discussion of these issues is outside of the scope of this review.*

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