# Appendix

## Scoping searches for evidence gaps

## Evidence gaps translated into evidence synthesis format

## Stakeholder input and feasibility scan results

## Scoping searches for evidence gaps

| **Source** | **Intervention evidence gaps** | **Diagnostic evidence gaps** | **Outcome evidence gaps** | **Population evidence gaps** | **Health services evidence gaps** |
| --- | --- | --- | --- | --- | --- |
| A. Management of Posttraumatic Stress Disorder and Acute Stress Disorder (2017) CPG1 | 1. Key components of Shared Decision Making and collaborative care and their effect on treatment effectiveness (p.76) 2. Treatment approaches for refractory PTSD and sequencing of treatments following partial response 3. Treatment dosing and duration and the impact on outcomes 4. Comparative efficacies of different trauma-focused psychotherapies in populations with cooccurring conditions 5. Management of sleep disturbance 6. Relative efficacy of PTSD treatment versus treatment as usual with CBT-Insomnia | N/A | 1. Treatment impact on biological systems beyond mental health symptoms (comorbid conditions, biomarkers, health outcomes, cost-effectiveness) 2. Potential advantages of technology-based modalities such as increased access and decreased stigma 3. Investigation of whether improvement of PTSD symptoms influences co-occurring conditions and/or if improvements to co-occurring conditions influence PTSD symptoms | 1. The influence of service connection, disability, and the process of evaluation on treatment choice, retention, and response in the short and long-term 2. Comparative studies of different methods of treatment provisions including couples, family, group, and individually provided interventions | 1. Factors affecting treatment delivery through secure video teleconferencing 2. Examination of the effectiveness of practice-based variations/modifications to established psychotherapy protocols to include variations in length, frequency, and number of sessions as well as variations in specific techniques resulting from specific patient population or logistical considerations |
| B. Assessment and Management of Patients at Risk For Suicide (2013) CPG2 | 1. There is a lack of strong evidence for any interventions in preventing suicide and suicide attempts” (p 5) 2. “In the face of insufficient and conflicting suicide prevention data…” (p. 6) | 1. Combining risk factors for suicide attempts and death by suicide may give a more thorough picture of suicide risk factors; however, doing so with the studies reviewed here does not shed substantially greater light on which risk factors are most predictive. (p. 149) | N/A | N/A | N/A |
| C. Management of Major Depressive Disorder (2016) CPG3 | 1. Open questions: Are particular treatment combinations more effective than others in treating MDD? (p 12) 2. New mechanisms for the treatment of MDD | 1. There also needs to be a better understanding of the value and use of measurement-based care, including the place of pharmacogenetics in the treatment of MDD 2. For patients with a diagnosis of MDD, we suggest using the PHQ-9 as a quantitative measure of depression severity in the initial treatment planning and to monitor treatment progress (weak recommendation, not reviewed; p.17) | N/A | Insufficient evidence:   1. Management of complex cases of MDD, unclear how and when to combine psychotherapy and medications (p 12) | Insufficient evidence:   1. Augmenting clinical care and improve outcomes using technology, including smartphones, social media, or computer therapies (p 12) |
| D. Management of Bipolar Disorder (BD) in Adults (2010) CPG4 | 1. These recommendations are based on insufficient evidence: 2. Quetiapine with valproate or lithium for mixed episode (p 10) 3. Ziprasidone with valproate or lithium (p 10) 4. Clozapine with valproate or lithium (p 10) 5. Use of agents that have been effective in treating prior episodes (p 12) 6. Clozapine, haloperidol, oxcarbazepine for mania or mixed episode (p 13) 7. Lithium or quetiapine for mixed episode (p 13) 8. Escalating pharmacotherapy (p 17) 9. Adjust medication to maximum range if not in therapeutic range (p 27) 10. Electro-convulsive therapy (27) 11. Lamotrigine with lithium, olanzapine or aripiprazole for history of severe or recent mania (p 39) 12. Reduce to monotherapy while monitoring patients 13. Antipsychotic or anti-epileptic agents for maintenance 14. Antiepileptic medications other than carbamazepine, valproate, gabapentin, and lamotrigine (p 66) 15. Valproate for acute depression (p. 69) 16. Carbamazepine for acute depression (p. 71) 17. Topiramate for acute depression (p 75) 18. Topiramate for maintenance (p 75) 19. Gabapentin for maintenance (p 75) 20. Olanzapine plus fluoxetine for maintenance (p 84) 21. Risperidone for acute depression (p 90) 22. Ziprasidone (p 94) 23. Haloperidol for maintenance (p 97) | N/A | These recommendations are based on insufficient evidence:   1. Switch to another treatment for side effects (p 27) 2. Assess compliance and blood serum concentration (p 27) 3. Mood destabilization or mania should be evaluated after initiating pharmacotherapy (p 25) 4. Medications with known therapeutic plasma concentrations should be increased until significant improvement is seen, side effects become intolerable, or dose reaches manufacturer suggested limit (p 27) 5. Monitor discontinuation syndrome and mood destabilization during treatment discontinuation 6. Consider pharmacokinetics, AE, drug-drug interactions 7. Monitor AE (p 42) | These recommendations are based on insufficient evidence:   1. Whether patients with a co-occurring SUD should be managed differently than other patients (p 45) 2. Antipsychotic medication in patients with comorbid psychotic features (p 25) | These recommendations are based on insufficient evidence:   1. Educational messages regarding medication therapy to increase adherence to treatment (p 15) 2. Patient, family and caregivers should be educated about the risk of relapse and be instructed to identify symptoms and the importance of contacting providers (p 15) 3. Patient, family and caregivers should be educated about the risk of switching to mania or hypomania and be instructed to identify symptoms and the importance of contacting providers (p 27) 4. Addiction treatment should be coordinated with bipolar disorder treatment (p 43) 5. Refer patients with co-occurring major psychiatric illnesses, significant suicidality or homicidality to specialty care |
| E. Management of Substance Use Disorders (2015) CPG5 | 1. “Additional research on the use of telehealth in SUD may be beneficial” to help address barriers to care that contribute to low engagement (p 64) – telehealth was not included in the search terms for the literature review 2. “Telephone or web-based brief interventions as sole treatment were beyond the scope of this guideline” (p 66) 3. For patients in need of withdrawal management for sedative hypnotics we suggest one of the following: gradually taper original benzodiazepine, substitute longer acting benzodiazepine then taper, substitute phenobarbital (weak recommendation, not reviewed; p. 29) | 1. For patients with alcohol or opioid use disorder in early abstinence, we suggest using standardized measures to assess the severity of withdrawal symptoms (weak recommendation, not reviewed) | N/A | N/A | 1. “Opioid use disorder … Research is needed on the effectiveness of sharing various components of addiction-focused medical management effectively among members of a patient-aligned care team and co-located primary care-mental health integration therapists and prescribers” (p 64) 2. For patients with a diagnosis of a substance use disorder, we suggest offering referral for specialty SUD care based on willingness to engage in specialty treatment (weak recommendation, not reviewed; p. 25) 3. Among patients in early recovery from SUD or following relapse, we suggest prioritizing other needs through shared decision making among identified biopsychosocial problems and arranging services to address them (weak recommendation, not reviewed; p. 27) |
| F. Management of Concussion-Mild Traumatic Brain Injury (2016) CPG6 | 1. “We suggest against offering medications, supplements, nutraceuticals or herbal medicines for ameliorating the neurocognitive effects attributed to mTBI.” (evidence not reviewed but suggested) (p. 21) | 1. For patients with new symptoms that develop more than 30 days after mild traumatic brain injury, we suggest a focused diagnostic work-up specific to those symptoms only (weak recommendation, not reviewed, p. 26) | N/A | N/A | Open questions:   1. The role of inter-disciplinary/multi-disciplinary teams in the management of patients with chronic or persistent symptoms attributed to a history of mild traumatic brain injury (p 43) 2. The efficacy of stepped collaborative care models of treatment delivered in primary care settings (p 43) |
| G. Environmental scan crosscheck CPG7 | 1. 62% of military treatment facilities offer stress management and relaxation therapy (p. 76) but stress management is not covered in mental health CPGs 2. 58% of CAM offering facilities offer progressive muscle relaxation (p xiii) but none of the mental health or the TBI CPG address this approach 3. The most frequent use of hypnotherapy was for alcohol-related disorders (p 120) but hypnosis is not addressed in the SUD CPG 4. The most frequent use of biofeedback was anxiety disorders (p 120) but there is no CPG for anxiety disorders | N/A | N/A | N/A | N/A |
| H. NDAA 20188 | 1. Ensure appropriate treatment for PTSD: Continue to explore complementary and integrative PTSD therapies such as art and music therapy and to research appropriate therapy drugs under development | N/A | N/A | 1. Training of dependents of service members with suicide risk factors: Investigation of methods and resources to train and educate dependents on suicide risk factors, ways to support their service member, promote healthy environments, reduce overall risk factors for suicide; emphasis on dependents living with service members diagnosed with PTSD | N/A |
| I. NDAA 20179 | 1. “The committee encourages the Department to continue their diverse TBI research programs, and supports the development and deployment of technologies that can be used to provide additional TBI treatments, including induced therapeutic hypothermia, to our service members” (p 94) 2. “Preventive Intervention for Suicide and Substance Abuse … The committee encourages the Army National Guard to continue its efforts by leveraging expertise to accelerate implementation of preventive measures such as those in the PRO program” (p 145) 3. “The committee applauds the efforts by the Department of Defense and the military services to reduce suicide and improve prevention programs, but the committee believes that the Department can and should improve its efforts, based on the Inspector General’s recommendations” (p 154) 4. “…the committee directs …to submit a report … on the Department’s efforts to prevent, educate and treat prescription opioid drugs abuse by military service members. The report shall include: research on more comprehensive treatments for opioid addiction; …addressing behavioral interventions; research on next generation analgesics in order to identify new pain relievers with reduced abuse, tolerance, and dependence risk; devising alternative delivery systems and formulations for existing drugs that minimize diversion” (p 174) | N/A | Report excerpt:   1. “…the committee directs …to submit a report … focus on developing more effective means for preventing overdose deaths” (p 174) | N/A | Report excerpt:   1. “…the committee directs …to submit a report …The report shall include: integration of drug treatment into healthcare settings” (p 174) |
| J. NRAP10 | 1. “There is limited evidence of the effectiveness of both pharmacological and nonpharmacological interventions, including rehabilitation treatments, [for TBI] due in part, to underpowered studies and the limited validated assessment tools that are sensitive enough to detect treatment effects” (p 17) 2. “Research …has also been hampered by difficulties in defining the active ingredient of many experience-based treatments that are commonly used in rehabilitation. The concurrent application of multiple treatments, including pharmacological and nonpharmacological interventions, poses another challenge” (p 17) 3. “Small proof-of-concept studies show promise for fast-acting medications (eg, ketamine) in reducing suicide ideation, but more research is needed” (p 23) 4. “Longer-term research is needed to better understand the factors that build resilience and offer protection from suicidal behaviors and promote wellness and recovery” (p 23) | 1. “More personalized treatments… individually tailored interventions with measurable responses” (p. 9) 2. “Review emerging genomic and molecular findings on causal pathways and changes that contribute to PTSD” (p. 12) | N/A | 1. “…research regarding the customization of therapies to an individual’s injury, predisposing factors, and co-occurring conditions” [is needed] (p 17) 2. “Major challenges to mechanistic and treatment-related research on TBI include difficulties in distinguishing the effects of PTSD and other comorbidities, such as sensory, endocrine, cognitive, behavioral, and sleep dysfunctions, from the central nervous system injury itself … pre-existing factors, be they physical, social, cultural, or health-related, have an effect upon the course and outcome of TBI (p 18) 3. Additional research investigating substance abuse in persons with TBI is needed including …. Brief intervention, and referral to treatment” (p 18) | 1. “Research is needed to identify effective integrated, team-based models of treatment for persons with TBI that address both pre-morbid and co-occurring conditions” (p 18) |
| K. 2011 Health Related Behaviors Survey of Active Duty Military Personnel (2013)11 | 1. The most frequently endorsed methods of coping with stress were thinking of a plan to solve the problem, …spending time alone, engaging in a hobby and exercising or playing sports (66%, p 188) but there is no CPG for stress and the SUD CPG does not mention exercise | N/A | N/A | 1. “The rates of substance use among female service members were higher than their civilian counterparts and more in line with their male colleagues… These results suggest the need to review existing programs and design new programs with the differences between subgroups within the population in mind.” 2. The most frequently endorsed methods of coping with stress were … talking to a friend or family member …(72%, p 188) but there is no CPG for stress and support for caregivers is not targeted in the MDD CPG | 1. “38% indicated seeking help for mental health would damage a person’s military career, 21% who had received mental health treatment through the military believed it negatively affected their career” (p 194) 2. “Attention should be paid to providing substance use education that does not result in associated stigma for those receiving the education” (p317) |
| L. Published psychological health future research needs$ | 1. Alcoholism research priority areas: …Combination and sequencing of treatments … Mechanism of action of treatment (McCaul and Monti, 2003) 2. There are many other current and new therapies for TBI [than covered in the 1995 Guidelines for the Management of Severe Head Injury addressing acute care] for which there are still no evidence-based guidelines (Zitnay et al., 2008) 3. Post-acute care rehabilitation [for TBI]: Most clinically critical and societally relevant: … comparative efficacy of models of care… interventions to facilitate recovery and/or lessen neurological impairment … application of emergent, state-of-the-art technologies (Zitnay et al., 2008) 4. Intervention studies were ranked as the highest future priority [in suicide research] by the majority of stakeholder groups (Robinson et al., 2008) | 1. Patient-treatment matching [alcoholism] (McCaul and Monti, 2003) | 1. Attempted suicide or deliberate self-harm was considered to the be highest priority [for suicide research] (Robinson et al., 2008) | 1. The need to develop and test service delivery models [for drug treatment] tailored to Hispanics' circumstances and special needs (Alegría et al,. 2006) 2. Alcoholism research priority areas: concurrent disorders … intervention testing in special populations, Help agent behaviors, (McCaul and Monti, 2003) 3. Poisoning by drugs and hanging were prioritized for suicide research (Robinson et al., 2008) 4. Young people and people with mental health problems were frequently ranked [as high priority for suicide research] (Robinson et al., 2008) | 1. Alcoholism research priority areas: technology transfer; health seeking patterns and processes (McCaul and Monti, 2003) |
| M. Ongoing RAND-DCoE projects | 1. Collaborative care established as key area of interest, no review planned for bipolar disorder, suicide prevention, substance use, or traumatic brain injury. The TBI CPG explicitly highlights the role of inter-disciplinary / multi-disciplinary teams as a knowledge gap (p 43). The SUD CPG does not address collaborative care but reviewed psychosocial interventions in combination with first-line treatment. The CPG for bipolar disorder has recommendations for collaborative chronic care models (but not other inter-disciplinary, coordinated, or co-located care). The suicide prevention CPG references inter-disciplinary discharge planning (p. 69) and references stepped, collaborative care models in older adults with depression, but not other models | 1. “Sees value in further evaluation of the effectiveness … use of technology such as computerized assessment” 12 | N/A | 1. Systematic review …. for a comprehensive identification of the gaps in knowledge about women’s health issues in the military and the subsequent development of research priorities is required to produce the evidence that will drive sex-and gender-appropriate health care in the military health system13 | 1. “It is essential to identify predictors of dropout in an effort to develop interventions that address them more successfully” 14 |
| N. DCoE Resources | N/A | N/A | N/A | 1. TBI caregiver perspectives and knowledge gaps 15Support for caregivers 2. Women in combat: DoD should continue to explore and address policy, research, and practice related to the complex ongoing needs of military females (McGraw et al., 2016) | 1. TBI caregiver perspectives and knowledge gaps, including caregivers in care 15 |
| O. DCoE Psychological Health Research Priorities | 1. Determinants of care adherence and engagement 2. System-level interventions (e.g., collaborative care, stepped-care approaches, preference-based approaches, alternative models of care) | N/A | N/A | 1. Effect of clinical complexity on treatment course and outcomes | 1. Effectiveness of existing evidence-based interventions adapted for telehealth delivery 2. Implementation models for effective and sustainable dissemination and implementation of high-quality research findings 3. Interventions to increase uptake and consistent practice of CPGs 4. Identification of common components of evidence-based treatment |
| **N**  **(9/9/2018)** | **58** | **9** | **12** | **19** | **24** |

**Notes**

Abbreviations: AE adverse event, CBT cognitive behavioral therapy, CPG clinical practice guideline, DCoE Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury, MDD major depressive disorder, N number, NDAA national defense authorization act, NRAP national research action plan, SUD substance use disorder, TBI traumatic brain injury

Methodology: The rationale for choosing the search and the approach to identify gaps are described in the main manuscript.

$ Literature review search strategy (L. Published psychological health future research needs):

Database: PubMed

Publication dates: 2000-7/2016

Language: English

Search strategy:

evidence gap\*[ti]

OR

(knowledge gap\*[Title] OR research gap\*[Title] OR research priorit\*[Title]

AND "Depressive Disorder"[Mesh]) OR "Stress Disorders, Post-Traumatic"[Mesh]) OR "Substance-Related Disorders"[Mesh]) OR "Brain Injuries"[Mesh]) OR "Comorbidity"[Mesh] OR depression OR depressive OR depressed OR “post-traumatic stress disorder” OR “posttraumatic stress disorder” OR “post traumatic stress disorder” OR PTSD OR “post-traumatic stress” OR “post traumatic stress” OR “posttraumatic stress” OR cannabis OR marijuana OR marihuana OR cocaine OR heroin OR methamphetamin\* OR methadone\* OR street drug\* OR substance abus\* OR substance misus\* OR drug abus\* OR addict\* OR drinking behavior[mh] OR (chemical AND dependen\*) OR traumatic brain injur\* OR tbi OR multi-morbidity OR multiple morbidit\* OR co-morbidity OR comorbid\*)

Database: PsycINFO

Publication dates: 1/1/2000-7/27/2016

Language: English

TI evidence n3 (gap OR gaps)

TI ( ((knowledge OR research) n3 (gap OR gaps) ) OR (research n3 (priority OR priorities) ) ) OR TI ( research n3 (priority OR priorities) ) ) )

AND HUMAN

NOT child\* OR adolescen\* OR gerontol\* OR geriatric\* OR alzheimer\* OR dementia OR schizophren\*

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## Evidence gaps translated into evidence synthesis format

The topics were translated into different systematic reviews and evidence map products. The main manuscript describes the approach.

### Potential PTSD synthesis topics

1. Systematic review of components of shared decision making
   1. Using meta-regression and/or QCA to identify key components
2. Systematic review of components of collaborative care
   1. Using meta-regression and/or QCA to identify key components
3. Systematic review of the effects of PTSD treatment dosing, duration, and sequencing
   1. Summarizing direct and indirect comparisons
4. Systematic review of treatment for refractory PTSD
   1. Incorporating all published interventions for this patient group in a network meta-analysis
5. Systematic review of trauma-focused psychotherapy treatment for PTSD
   1. Exploring the effects of different interventions in a network meta-analysis
6. Systematic review of the comparative effectiveness of sleep management interventions in PTSD
   1. Exploring evidence-based treatment options
   2. Determining the relative importance of interventions in a network meta-analysis
7. Systematic review of PTSD treatment on outcomes other than mental health clinical symptoms
   1. Determining the effects of interventions on other outcomes including costs)
8. Evidence map or systematic review of technology-based modalities in PTSD treatment
   1. Determining the effects on increased access and decreased stigma
9. Systematic review of dually diagnosed patients with PTSD and another mental health condition
   1. Incorporating all published interventions for this patient group in a network meta-analysis
10. Systematic review of PTSD treatment on co-occurring conditions
    1. Determining the effects of PTSD treatment on other conditions
11. Systematic review of psychological treatment on PTSD symptoms
    1. Exploring effects of psychological treatment for other conditions than PTSD on PTSD symptoms
12. Systematic review of effect modifiers on retention and treatment response
    1. Determining the effects in meta-regressions
13. Systematic review of PTSD of treatment choice determinants
    1. Using published and grey literature
14. Systematic review or scoping review of barriers and facilitators of video teleconferencing in psychotherapy
    1. Identifying and summarizing factors associated with the mode of delivery
15. Systematic review of barriers and facilitators of video teleconferencing in PTSD treatment
    1. Identifying and summarizing factors affecting treatment delivery
16. Systematic review of the effects of PTSD treatment characteristics
    1. Determining the effects of characteristics such as number of sessions in meta-regressions and/or a QCA
17. Systematic review of different treatment modalities
    1. Determining the comparative effectiveness of different methods of treatment provisions (e.g., couples, family, group, and individually provided interventions)
18. Evidence map of complementary and integrative PTSD therapies
    1. Exploring evidence-based treatment options
19. Systematic review of genomic and molecular findings in PTSD
    1. Exploring the effect on causal pathways and changes that contribute to PTSD

### Potential suicide prevention synthesis topics

1. Evidence map of suicide prevention interventions
   1. To explore the breadth of public research and to identify evidence-based approaches
2. Systematic review on the effects of suicide prevention interventions on suicide and suicide attempts
   1. Systematic review of empirical evidence reporting on the outcome of interest (suicide attempts, not suicide ideation), evaluating specific interventions in adults
3. Systematic review of risk factors for suicide attempts and death by suicide
   1. Summarizing the presence and absence of associations for potential risk factors and risk factor combinations
4. Systematic review of suicide risk assessment instruments
   1. Identifying evidence-based diagnostic accuracy and measurement instruments
5. Systematic review of training for dependents of adults with suicide risk
   1. Identifying approaches ready for implementation
6. Systematic review of suicide aftercare interventions for suicide attempters and family members
   1. Identifying approaches ready for implementation
7. Evidence map of interventions to prevent suicide
   1. Exploring promising approaches
8. Systematic review of interventions for adults with suicide risk and substance use
   1. Reviewing the comparative effectiveness in a network meta-analysis
9. Systematic review of ketamine effects on suicide ideation and suicide attempts
   1. Systematic identification of existing evidence to determine whether ketamine is effective and safe
10. Evidence map of long-term effects of interventions aiming to prevent suicide
    1. To systematically explore existing approaches and to identify potentially successful interventions
11. Evidence map of suicide prevention interventions (see also suicide prevention section)
    1. To explore the breadth of public research and to identify evidence-based approaches
12. Evidence map of interventions targeting self-harm
    1. To explore existing approaches
13. Systematic review of a specific intervention for suicide prevention
    1. Meta-regression to determine whether the type of suicide attempt, patient age, or comorbidities systematically affect treatment effects
14. Systematic review of collaborative care in suicide prevention
    1. Systematic review of interventions with defined collaborative care models reporting on effects of the intervention compared to the status before the intervention or a concurrent comparator (pre-post, RCT)

### Potential depression synthesis topics

1. Systematic review to determine the comparative effectiveness of treatment combinations for major depressive disorder
   1. Comparing treatment combinations regardless of the comparator in a meta-analysis across studies
2. Evidence map of novel interventions
   1. To explore treatment approaches for major depressive disorder that are not currently covered in clinical practice guidelines
3. Systematic review of the effects of measurement-based care in depression
   1. Documenting the effects on patient and treatment outcomes
4. Evidence map of pharmacogenetics in depression care
   1. Exploring the available evidence
5. Systematic review of the PHQ-9 as a measure of depression severity
   1. Documenting the psychometric properties and impact
6. Evidence map of interventions for complex patients with major depressive disorder
   1. Exploring available treatment approaches
7. Systematic review of a specific telehealth intervention for major depressive disorder
   1. Systematic identification and synthesis of RCTs evaluating a specific telehealth intervention, e.g., an intervention identified as promising in the evidence map
8. Evidence map of stress management in major depressive disorder
   1. To explore existing evidence-based approaches
9. Systematic review of progressive muscle relaxation for major depressive disorder
   1. Systematic identification and synthesis of RCTs assessing the effects of progressive muscle relaxation

### Potential bipolar disorder treatment synthesis topics

1. Systematic review of effects of antiepileptic drugs in the treatment of bipolar disorder
   1. Systematic identification and synthesis of RCTs reporting on efficacy and safety
2. Systematic review of effects of atypical antipsychotic medications in the treatment of bipolar disorder
   1. Systematic identification and synthesis of RCTs reporting on efficacy and safety
3. Systematic review of effects of combining atypical antipsychotic medication with antiepileptic medications in the treatment of bipolar disorder
   1. Systematic identification and synthesis of RCTs reporting on efficacy and safety
4. Systematic review of combining atypical antipsychotic medication with lithium in the treatment of bipolar disorder
   1. Systematic identification and synthesis of RCTs reporting on efficacy and safety
5. Systematic review of atypical vs typical antipsychotic medications for treatment of bipolar disorder
   1. Systematic identification and synthesis of RCTs reporting on efficacy and safety
6. Evidence map of interventions targeting patients diagnosed with bipolar disorder and substance use disorder
   1. To explore emerging evidence for this complex patient population
7. Evidence map of stress management in bipolar disorder
   1. To explore existing evidence-based approaches
8. Systematic review of progressive muscle relaxation for bipolar disorder
   1. Identification and synthesis of RCTs assessing the effects of progressive muscle relaxation
9. Systematic review of collaborative care models beyond chronic care models in the management of patients with bipolar disorder
   1. Systematic review of interventions with defined collaborative care models reporting on effects of the intervention compared to the status before the intervention or a concurrent comparator (pre-post, RCT)

### Potential substance use disorder synthesis topics

1. Evidence map of telehealth in substance use disorder
   1. To explore available interventions for substance use disorder across the spectrum of telehealth
2. Systematic review of a specific telehealth intervention in substance use disorder
   1. Systematic identification and synthesis of evidence from RCTs for a specific intervention
3. Systematic review of severity of withdrawal measures
   1. Summarizing the psychometric properties as well as the impact of using scales
4. Systematic review of collaborative care in the management of patients with substance use disorder
   1. Systematic review of interventions with defined collaborative care models reporting on effects of the intervention compared to the status before the intervention or a concurrent comparator (pre-post, RCT)
5. Evidence map of stress management in substance use disorders
   1. To explore existing evidence-based approaches
6. Systematic review of progressive muscle relaxation for substance use disorder
   1. Systematic identification and synthesis of RCTs assessing the effects of progressive muscle relaxation
7. Systematic review of the effects of hypnotherapy on substance use disorders
   1. Systematic identification and synthesis of RCTs assessing the effects of hypnotherapy
8. Systematic review of comprehensive treatments for opioid addiction
   1. Systematic identification and synthesis of multi-discipline interventions for opioid addiction
9. Systematic review of behavioral interventions to prevent or treat opioid addiction
   1. Systematic identification and synthesis of defined behavioral interventions evaluated in RCTs
10. Systematic review of next generation analgesics
    1. Systematic identification and synthesis of RCTs testing next generation analgesics
11. Evidence map of alternative delivery systems for existing opioids
    1. To explore alternative options of delivery
12. Evidence map of approaches to prevent overdose deaths
    1. To explore approaches that target the outcome specifically
13. Systematic review of summarize substance use disorder treatment delivered in primary care
    1. Systematically identify and synthesize existing evidence
14. Systematic review of exercise interventions in the management of substance use disorders
    1. Systematic identification and synthesis of RCTs assessing the effects of defined exercise interventions
15. Evidence map of interventions for substance use disorder for women
    1. To explore preventative and treatment programs targeting women to reduce substance us
16. Evidence map exploring combination treatments in alcohol abuse
    1. To identify most promising approaches
17. Systematic review of specific intervention combinations to treat alcohol abuse
    1. Systematic identification and synthesis of RCTs to determine effectiveness
18. Systematic review of combination treatments for alcohol abuse
    1. Meta-regressions and subgroup analyses, alone or in combination with qualitative comparative analysis, aiming to detect active treatment ingredients in multi-component interventions
19. Systematic review of studies assessing the sequence of treatment in alcohol abuse
    1. Systematic identification and synthesis of the available evidence
20. Evidence map of approaches addressing patients with alcohol abuse and comorbidities
    1. To identify promising approaches
21. Systematic review of a specific intervention addressing patients with alcohol abuse and specific comorbidities
    1. Systematic identification and synthesis of RCTs to determine effectiveness
22. Evidence map of intervention approaches aimed at Hispanic drug users
    1. To explore existing approaches
23. Systematic review of provider interventions to increase uptake of clinical practice guidelines for alcoholism treatment
    1. Systematic identification and synthesis of existing research testing provider interventions (RCTs and pre-post studies)
24. Systematic review of patient-treatment matching
    1. Determining the comparative effectiveness

### Potential traumatic brain injury treatment synthesis topics

1. Evidence map of medications, supplements, nutraceuticals, or herbal medicine for neurocognitive effects of mild traumatic brain injury
   1. Exploring effects of interventions for the outcome of interest
2. Systematic review of screening approaches for symptoms that develop more than 30 days after mild traumatic brain injury
   1. Comparing the effect of different screening approaches
3. Systematic review of inter-disciplinary or multi-disciplinary teams in the management of patients with chronic or persistent symptoms attributed to a history of mild traumatic brain injury
   1. Systematic review of interventions with defined multi-disciplinary teams reporting on effects of the intervention compared to the status before the intervention or a concurrent comparator (pre-post, RCT)
4. Systematic review of stepped collaborative care models of treatment delivered in primary care settings
   1. Systematic review of interventions with defined stepped collaborative care models reporting on effects of the intervention compared to the status before the intervention or a concurrent comparator (pre-post, RCT)
5. Systematic review of progressive muscle relaxation for mild traumatic brain injury
   1. Systematic identification and synthesis of RCTs assessing the effects of progressive muscle relaxation
6. Evidence map of emerging treatment options for traumatic brain injury
   1. To systematically explore available approaches
7. Systematic review of therapeutic hypothermia on patient health outcomes
   1. Systematic identification and synthesis of RCTs on therapeutic hypothermia on patient health outcomes
8. Systematic review of rehabilitation interventions for traumatic brain injury
   1. Meta-analysis to increase statistical power to detect treatment effects across small and underpowered studies for selected traumatic brain injury interventions
9. Systematic review of multi-component rehabilitation interventions for traumatic brain injury
   1. Meta-regressions and subgroup analyses, alone or in combination with qualitative comparative analysis aiming to detect active treatment ingredients in multi-component traumatic brain injury interventions
10. Evidence map of treatment approaches for comorbidities in traumatic brain injury
    1. Evidence map to explore available approaches
11. Systematic review of substance use interventions for patients with traumatic brain injury
    1. Systematic identification and synthesis of RCTs
12. Systematic review of collaborative care approaches for patients with traumatic brain injury
    1. Systematic review of defined collaborative care interventions for patients with traumatic brain injury
13. Evidence map of new treatment approaches in acute care for traumatic brain injury
    1. Identifying most promising approaches among those not yet addressed in existing clinical practice guidelines
14. Systematic review to determine the comparative effectiveness of post-acute rehabilitation approaches in traumatic brain injury
    1. Network meta-analysis to rank and compare interventions
15. Evidence map of neurorehabilitation interventions in traumatic brain injury
    1. Exploring interventions to identify evidence-based approaches
16. Evidence map of technological interventions in traumatic brain injury
    1. Identifying promising approaches
17. Systematic review of specific technological interventions in traumatic brain injury
    1. Systematic identification and synthesis of RCTs to determine effects of specific technological interventions, e.g., robotic technology
18. Systematic review of interventions for caregivers of patients with traumatic brain injury
    1. Identifying effective support for caregivers
19. Systematic review of approaches to incorporate caregivers in the traumatic brain injury care process
    1. Exploring evidence-based approaches
20. Evidence map of approaches intending to meet the needs of these women
    1. Exploring promising approaches

### Potential anxiety synthesis topics

1. Systematic review of the effects of biofeedback on anxiety disorder symptoms
   1. Systematic identification and synthesis of RCTs assessing the effects of biofeedback on effectiveness and safety measures for patients diagnosed with anxiety disorders

### Potential cross-cutting synthesis topics

1. Evidence map of hypnotherapy
   1. Exploring existing evidence-based approaches
2. Evidence map of biofeedback
   1. Exploring the use of biofeedback in healthcare research
3. Evidence map of effects of exercise on stress
   1. Exploring for which clinical conditions exercise interventions have been tested for their effects on stress
4. Systematic review of the comparative effectiveness of delivering mental health care in primary or specialty care
   1. Empirical evidence from head-to-head trials comparing mental health care delivered in primary or specialty care
5. Evidence map of personalized treatment approaches
   1. Exploring the emerging research field
6. Systematic review of determinants for treatment adherence
   1. Meta-regressions and QCA could identify critical factors
7. Systematic review of collaborative care in a specific clinical area
   1. Determining the intervention effect on patient outcomes
8. Systematic review of stepped care in a specific clinical area
   1. Determining the intervention effect on patient outcomes
9. Systematic review of preference-based approaches in a specific clinical area
   1. Determining the comparative effectiveness
10. Systematic review of alternative models of care in a specific clinical area
    1. Determining the intervention effect on patient outcomes
11. Systematic review of associations between patient variables such as psychosocial functioning and treatment outcomes
    1. Determining the effect of clinical complexity
12. Systematic review of the effectiveness of evidence-based interventions adapted for telehealth delivery
    1. Examining non-inferiority
13. Evidence map of dissemination models
    1. Identifying the most promising approaches
14. Systematic review of components of evidence-based treatment
    1. Establishing a framework of interventions

Notes: QCA qualitative comparative analysis, PTSD posttraumatic stress disorder, RCT randomized controlled trial

## Stakeholder input and feasibility scan results

| **N** | **Topic** | **Stakeholder impact rating** | **Search strategy** | **Estimated # of RCTs** | **Existing high-quality reviews** | **Estimated new research** |
| --- | --- | --- | --- | --- | --- | --- |
|  | Collaborative care for the treatment of PTSD | 1.5 | See text | ~12 | RAND report in progress | NA |
|  | PTSD treatment dosing, duration, and sequencing | 3 | ptsd[ti] AND (dosing OR dose response OR "treatment duration" OR "treatment sequencing")  Filters Humans | ~49 | None identified | NA |
|  | Treatment of refractory PTSD | 2.25 | ("Stress Disorders, Post-Traumatic"[Mesh] OR PTSD[ti]) AND (refractory OR treatment resistant OR treatment-resistant OR non-remittent OR chronic[ti])  Filters Randomized Controlled Trial | ~79 | Cochrane review on psychological therapies16 | NC |
|  | Comparison among different trauma-focused psychotherapy interventions for PTSD | 2 | ptsd AND ("trauma-focused" OR "Prolonged Exposure" OR "Cognitive Processing Therapy" OR Eye-Movement Desensitization and Reprocessing OR Trauma-Focused Cognitive Behavioral Therapy OR Brief Eclectic Psychotherapy OR Narrative Exposure Therapy OR Written Narrative Exposure) NOT protocol[ti]  Filter: RCTs | ~ 256 RCTs | AHRQ report Jonas et al. (2013)17 | NC |
|  | Effectiveness of different sleep management interventions for PTSD | 2.75 | "Sleep"[Mesh]) AND "Stress Disorders, Post-Traumatic"[Mesh] AND (intervention OR management)  Filters Randomized Controlled Trial, English | ~49 | None identified | NA |
|  | Effects of PTSD interventions on non-clinical outcomes | 1.75 | ptsd[ti] AND (Cost OR employ\* OR work OR "physical function" OR cognitive function OR "psychological function" OR "emotional function" OR "social function" OR sexual OR "quality of life" OR interperson\* OR homeless\*)  Filters Randomized Controlled Trial, English, Adults | ~89 | Upcoming AHRQ report will address some non-clinical outcomes17 | NC |
|  | Use of technology-based modalities to augment/enhance PTSD treatments | 2 | (ptsd[ti] OR post-traumatic stress disorder[ti]) AND ("Telemedicine"[Mesh] OR telemedicine[tiab] OR telehealth[ti] OR email[tiab] OR internet[ti] OR video[tiab] OR videos[tiab] OR skype[tiab] OR computer-based OR phone-based OR telephone-based OR web-based[tiab] OR computerized OR smartphone OR virtual OR avatar OR "information and communication technology" OR ict OR cell phone\* OR mobile phone\* OR interactive voice response OR text message\* OR "digital communication" OR "e-health" OR "interactive video" OR web-cam\* OR webcam\* OR remote monitor\* OR remotely monitor\* OR two-way camera\* OR personal monitor\* OR web-based portal\* OR social network\* OR secure chat OR chatroom\* OR chat room\* OR online[tiab] OR online[ot] OR information technolog\*)  Filters Randomized Controlled Trial, English | ~55 | AHRQ report17 will likely include technology-augmented approaches (but not specifically focus on these) | NA |
|  | Interventions to treat dually diagnosed patients with PTSD and other mental health conditions | 2 | (("Stress Disorders, Post-Traumatic"[Mesh]) AND "Therapeutics"[Mesh]) AND "Diagnosis, Dual (Psychiatry)"[Mesh]  Filters Randomized Controlled Trial, English | ~10 | None identified | NA |
|  | Predictors of PTSD treatment retention and response | 3.5 | ((PTSD[ti] OR "Stress Disorders, Post-Traumatic"[Mesh]) AND (retention OR retain OR retaining OR dropout OR response OR "symptom improvement")) AND (predict\* OR correlat\* OR associat\*) | ~1,757 | See text | NA |
|  | Video teleconferencing for delivery of PTSD treatment  Changed to  Barriers and facilitators of video teleconferencing in PTSD treatment | 2.5 | (PTSD[ti] OR "Stress Disorders, Post-Traumatic"[Mesh]) AND video\*  Filter: Randomized Controlled Trial  (PTSD[ti] OR "Stress Disorders, Post-Traumatic"[Mesh]) AND video AND (barrier\* OR faciliat\* OR stigma) | ~22  ~9 | None identified | NA |
|  | Comparison of different PTSD treatment modalities | 1.75 | See text | NA | See text | NA |
|  | Genomic and molecular effects on causal pathways that contribute to PTSD | 1.75 | ("Stress Disorders, Post-Traumatic" [Mesh] OR posttraumatic stress[ti] OR post-traumatic stress[ti] OR post traumatic stress[ti] OR ptsd[ti]) AND (gene OR genetic OR genomic OR molecular)  Filter: Humans | ~752 | None identified | NA |
|  | Evidence-based clinical and non-clinical early interventions for PTS and PTSD | NA | ("Stress Disorders, Post-Traumatic" [Mesh] OR posttraumatic stress[tiab] OR post-traumatic stress[tiab] OR post traumatic stress[tiab] OR ptsd[tiab]) AND ("prevention"[tiab] OR "prevent"[tiab] OR "preventive"[tiab] OR "preventative"[tiab] OR early intervention [tiab])  Filter: RCT | ~126 | AHRQ report18 Cochrane report19 | NC |
|  | Relative weights of known risk and protective factors for PTSD | NA | (PTSD[ti] OR "Stress Disorders, Post-Traumatic"[Mesh]) AND (prevalence OR (develop\* and diagnosis)) AND (predict\* OR associat\*) | ~6,140 | None identified | NA |
|  | Natural histories in service members | NA | ("Stress Disorders, Post-Traumatic" [Mesh] OR posttraumatic stress[ti] OR post-traumatic stress[ti] OR post traumatic stress[ti] OR ptsd[ti]) AND ("course of" OR longitudinal OR “natural history” OR "trajectory") AND (veteran OR combat OR military OR troop OR soldier OR army OR air force OR marine OR navy) | ~473 | None identified | NA |
|  | Predictors of military occupational fitness  Changed to  Functional outcomes in patients with PTSD | NA | ("Stress Disorders, Post-Traumatic" [Mesh] OR posttraumatic stress[ti] OR post-traumatic stress[ti] OR post traumatic stress[ti] OR ptsd[ti]) AND (cognitive[Tiab] OR neuropsychological[Tiab] OR memory[Tiab] OR attention[Tiab] OR concentration[Tiab] OR working memory[Tiab] OR executive function[Tiab] OR verbal fluency[Tiab] OR information processing[Tiab] OR neural processing[Tiab] OR psychomotor[Tiab] OR visuospatial[Tiab] OR employment OR "functional status" or "social function" OR "social functioning")  Filter: Humans | ~4,999 | None identified | NA |
|  | Prevalence of PTSD in service members and family | NA | ("Stress Disorders, Post-Traumatic" [Mesh] OR posttraumatic stress[ti] OR post-traumatic stress[ti] OR post traumatic stress[ti] OR ptsd[ti]) AND (prevalence[tiab] OR epidemiology[tiab] OR incidence[ti]) AND (veteran OR combat OR military OR troop OR soldier OR army OR air force OR marine OR navy)  Filter: Humans | ~683 | None identified | NA |
|  | Suicide aftercare | NA | "suicide aftercare" OR (care suicide attempt\*)  No filters | ~4476 | None identified | NA |

**Notes**

Abbreviations: # number, AHRQ: Agency for Healthcare Research and Quality, ESP: Evidence-based Synthesis Report, HTA: Health Technology Assessment, NA not applicable, NC not calculated due to additional considerations, PTSD post-traumatic stress disorder, RCT randomized controlled trial

Stakeholder impact rating: The stakeholders and the procedure are outlined in the main manuscript. The rating scale ranged from 0 (equivalent to “no impact”) to 4 (equivalent to “high impact”).

Search strategy: The search strategy is based on a PubMed search.

Estimated # of RCTs: The number is based on studies indexed as RCTs in PubMed.

Existing high-quality reviews: We reviewed Agency for Healthcare Research and Quality (AHRQ), Cochrane, Department of Veterans Affairs Evidence Synthesis Program (ESP), and Health Technology Assessment (HTA) systematic reviews and evidence reports indexed in PubMed and PubMed Health.

Estimated new research: Number of new RCTs indexed in PubMed that are not included in existing high quality systematic reviews and evidence reports.

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