2016 Research Recommendations Report for Posttraumatic Stress Disorder and Depression in the Military

Prepared by the Psychological Health Research Work Group
Deployment Health Clinical Center
Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury

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DISCLAIMER

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Acronyms

AHRQ	Agency for Healthcare Research and Quality
APA	American Psychological Association
CPGs	Clinical Practice Guidelines
CRF	Corticotrophin Releasing Factor
DCoE	Defense Centers of Excellence
DHCC	Deployment Health Clinical Center
DoD	U.S. Department of Defense
IOM	Institute of Medicine
IPR	In-Progress Review
KT	Knowledge Translation
KTO	Knowledge Translation Office
MHS	Military Health System
MHSRS	Military Health System Research Symposium
MHWG	Mental Health Working Group
MOMRP	Military Operational Medicine Research Program
NCCOSC	Naval Center for Combat and Operational Stress Control
NDRI	National Defense Research Institute
NRAP	National Research Action Plan
PH	Psychological Health
PHCC	Psychological Health Clinical Care
PH KTWG	Psychological Health Knowledge Translation Work Group
PHP&A	Psychological Health Performance and Analytics
PHR	Psychological Health Research

PH RWG	Psychological Health Research Work Group
PTSD	Posttraumatic Stress Disorder
rTMS	Repetitive Transcranial Magnetic Stimulation
SMEs	Subject Matter Experts
SUD	Substance Use Disorder
TBI	Traumatic Brain Injury
T2	Telehealth and Technology
USUHS	Uniformed Services University of the Health Sciences
VA	Veterans Affairs

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Executive Summary

The Psychological Health Knowledge Translation Work Group of the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE) tasked the Psychological Health Research Work Group (PH RWG) of the Deployment Health Clinical Center (DHCC) to collate and prioritize identified gaps in Posttraumatic Stress Disorder (PTSD) and depression in the military. The methodology developed by PH RWG called for establishing an expert panel to take the following steps: scan authoritative sources for identified research gaps, review published scientific literature to assess them, examine available in-progress DoD research investments, and develop and apply metrics to prioritize the gaps by importance to the MHS.

The panel convened by the PH RWG consisted of six psychological health research subject matter experts (SMEs) from the DHCC Research Directorate. The PH RWG also tapped six additional SMEs from other DHCC Directorates and the Knowledge Translation Office as consultants, based on their specialized expertise in certain areas. After identifying authoritative sources (e.g., state of the science reports, policy documents), the panel reviewed them to collate identified research gaps in PTSD and depression in the military. By consolidating similar gaps and eliminating duplicative entries, the panel reduced its initial list of 236 gaps (Appendix A) to 32. Applying additional two criteria to reduce the list again— whether the gap could be addressed through relevant research and whether addressing the gap could improve and optimize clinical care in the military—yielded a list of 12 research gaps for PTSD and 9 for depression (Appendix C).

Each panel member then took responsibility for following a defined search process in order to gather more information about 2 or 3 of the 21 gaps, including the degree to which existing research had already closed them. After completing these deep dives, each panel member then presented his or her findings to the group. After extensive discussion, the panel reached full consensus on the 10 most critical gaps in PTSD and the 6 most critical in depression.

The panel's next step was to determine whether any of DoD's in-progress research investments in psychological health were already closing these identified gaps. As no comprehensive database of DoD-supported psychological research exists, the PH RWG requested summary information about current portfolios from Service branches and DoD agencies funding relevant psychological research, reviewed relevant information from research committees, meetings, and conferences, and synthesized this information and all available DoD PH portfolio information into spreadsheets to identify current studies, outcomes, and other study variables (Appendix E). Finally, consultants to the PH RWG searched www.clinicaltrials.gov—a database for in-progress research—for current PTSD and depression research, and reviewed summary information on DoD policies for PTSD and depression.

As no validated measures for prioritizing research gaps exist, the panel developed a set of metrics for a Likert scale assessment to prioritize these gaps. The top three recommendations for the PTSD gaps are the following: (1) conduct head-to-head comparative effectiveness trials of efficacious PTSD treatment that include better controls; (2) conduct well-controlled trials to examine integrated approaches to care for PTSD patients with multi-morbidities (e.g., PTSD and depression, PTSD and TBI) and psychosocial complexities (e.g. marital concerns, military transitions); and (3) examine the efficacy and/or effectiveness of modularized interventions based on components of evidence-based PTSD treatments in order both to overcome treatment barriers and limitations and also to improve reach and impact. The top three recommendations for addressing depression gaps are these: (1) conduct head-to-head comparative effectiveness trials of efficacious depression treatments that include better controls; (2) examine the effects of sex/gender and race/ethnicity on depression and related outcomes; and (3) conduct research to evaluate the effectiveness of widely used depression treatment programs with inconsistent or limited evidence.

This initiative is an important effort to apply a systematic approach to prioritizing research gaps. Such an approach is critical; however, policy and funding planners should not exclude other sources of information that might significantly contribute to funding priorities. Plans are underway to modify the PH RWG prioritization process based on lessons learned from this first initiative. Such lessons include two primary assertions: any comprehensive approach to identifying research gaps and priorities should include input from more than one source; and since the domains of PTSD and depression research are expansive, even a strong effort to prioritize specific research gaps will necessarily exclude many significant gaps across research domains.

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Background

The Psychological Health Knowledge Translation Work Group of the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE) tasked the Psychological Health Research Work Group (PH RWG) of the Deployment Health Clinical Center (DHCC) to collate and prioritize identified gaps in psychological health research relevant to the Department of Defense (DoD). In accordance with the priorities of DCoE's leadership, the PH RWG considered collating research gaps in the fields of Posttraumatic Stress Disorder (PTSD), depression, substance use disorder, women's issues, and suicide in the military. In order to meet resourcing constraints, the Knowledge Translation Steering Committee (KTSC) limited the scope to PTSD and depression in the military.

Developing a best practice for collating and prioritizing identified research gaps is essential for the Military Health System (MHS), as a systematic, transparent process can help inform and prioritize research funding and increases the likelihood that comprehensive research portfolios target relevant gaps. This initiative, the first of a planned annual process, focused on developing a replicable methodology. The following report summarizes that methodology, presents the work group's findings and recommendations, and highlights some of the challenges that the work group faced.

The PH RWG defined 'research gaps' as unanswered questions or unaddressed needs, as identified either by authoritative sources or by the professional opinion of its expert panel. Both the sources and panel are described below.

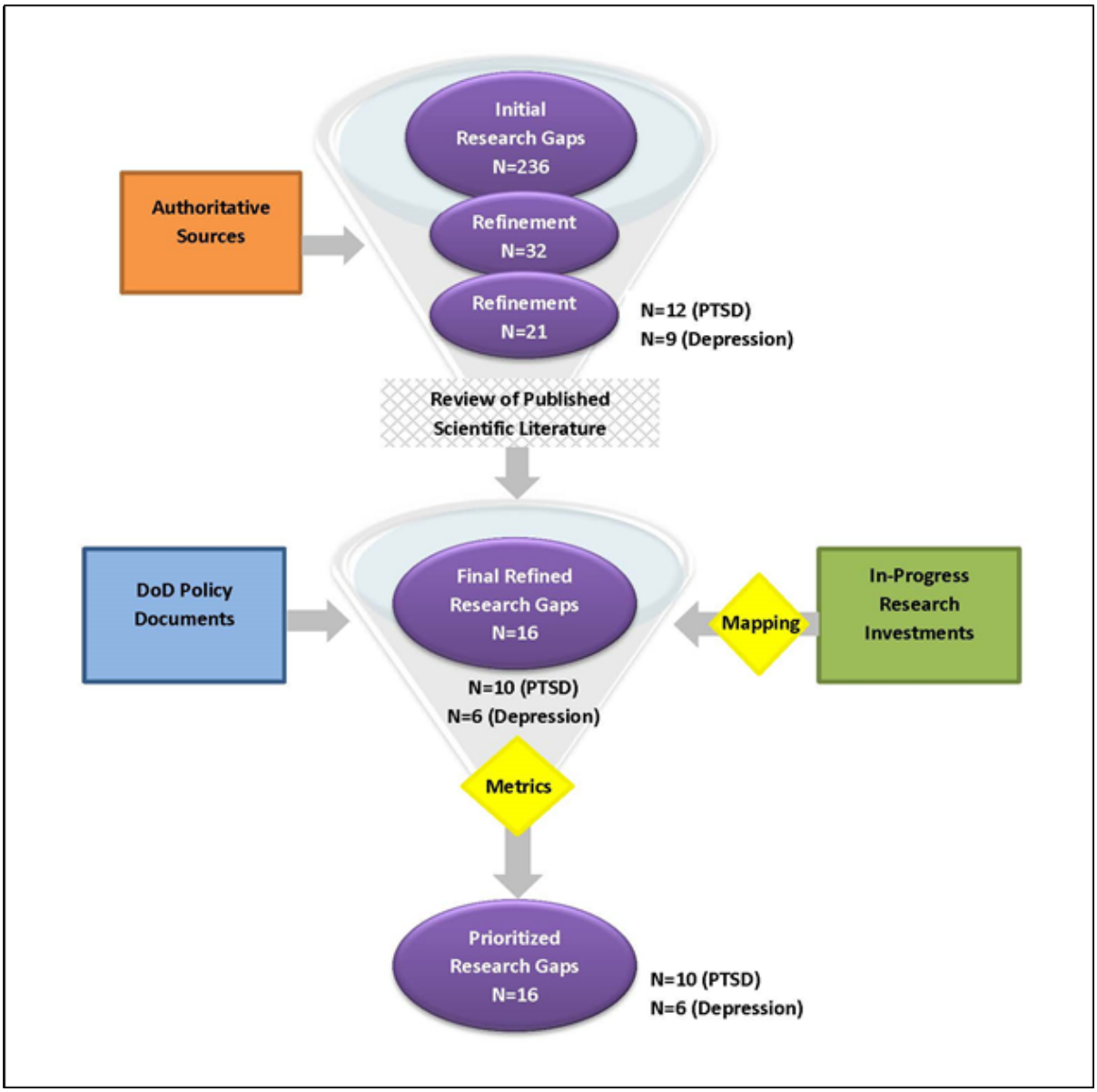
Methods

Establishing a methodology was the first and most challenging aspect of this project: there are multiple approaches across settings to identify and prioritize research gaps but no established best practice. Historical methods relied almost solely on expert or authoritative opinion collected by workgroups or panels. The primary weakness of this method is that experts may have personal biases regarding research preferences. Recent attempts to prioritize research have involved a variety of methodologies using systematic reviews (Andrews, 2013; Carey, Yon, Beadles, and Wines, 2012; Robinson et al., 2013; Saldanha, Wilson, Bennett, Nicholson, and Robinson, 2013). Although less biased than expert opinion, systematic reviews also have limitations: generally time intensive with focused research questions, they cannot be solely relied upon to fully inform prioritization of broad portfolios of research. In addition, novel research questions—those based on recently discovered evidence that may have high potential for impact—may not yet be mature enough to apply to a systematic review. More recently still, organizations such as the Agency for Healthcare Research and Quality (AHRQ) and the Patient-Centered Outcomes Research Institute (PCORI) have applied a systematic methodology to prioritize research gaps that includes stakeholder input for prioritization (Carey et al., 2010; Carey et al., 2012). While this

comprehensive approach is recognized as an optimal way to inform health care decisions, the time and resources required to undertake this effort are considerable.

The PH RWG therefore collaborated with the Knowledge Translation Office to develop a rigorous but manageable methodology, informed by these recent practices and relying on the PH RWG's subject matter expertise. Approved by the KTSC, this methodology called for establishing an expert panel to take the following steps: scan authoritative sources for identified research gaps, review published scientific literature to assess them, examine available in-progress DoD research investments, and develop and apply metrics to prioritize the gaps by importance to the MHS. The subsections below discuss each of these steps in detail.

Figure 1. PH RWG Methodology for Research Gap Identification and Prioritization



Establishment of an Expert Panel

The panel convened by the PH RWG consisted of six psychological health research subject matter experts (SMEs) from the DHCC Research Directorate, chosen for their experience in military psychological health care, psychological health matters, and research methodology. The PH RWG also tapped six additional SMEs from other DHCC Directorates and the KT Office as consultants, based on their specialized expertise in certain areas such as biomarkers. The resulting breadth of knowledge and experience ensured that the panel would be able to assess all necessary material for collating and prioritizing gaps.

Review Authoritative Sources to Determine Initial Research Gaps

The expert panel first identified authoritative sources as the basis for its work, such as the National Research Action Plan (NRAP), the National Defense Authorization Acts (assisted by consulting SMEs), AHRQ, American Psychological Association, Institute of Medicine, and Veterans Affairs/Department of Defense Clinical Practice Guidelines, as well as DoD Instructions and DoD Directives. By considering only those sources with scientific and military relevance and a focus on psychological health issues, the panel identified 25 to scan for information about identified research gaps in the treatment of PTSD and depression in the military (Appendix A). The panel members' independent review of these documents and group discussion about them yielded a list of 236 gaps. (The review and discussion also yielded a list of 60 related research priorities and recommendations, which appears in Appendix B.) After reducing that list to 32 by consolidating similar gaps and eliminating duplicative entries, the panel applied two criteria to reduce the list again: whether the gap could be addressed through relevant research and whether addressing the gap could improve and optimize clinical care in the military. Twelve research gaps for PTSD and nine for depression (Appendix C) received at least 80% consensus on 'yes' for each and so made the cut for further consideration. The panel decided on 80% consensus as the threshold for inclusion to ensure that one down vote would not exclude a gap from the list.

Conduct a Review of Published Scientific Literature to Refine Gaps

Each panel member then took responsibility for gathering more information about 2 or 3 of the 21 gaps, including the degree to which existing research had already closed them. Each panel member first searched PubMed for reviews of relevant scientific literature and then supplemented his or her findings with those from other sources, such as RAND Corporation, National Center for PTSD, AHRQ, Cochrane Collaboration, Trends Journal, and Google Scholar. The panel imposed three limitations on these searches. To reflect the current state of the science, it first confined the searches to reviews published within the last three years. Consistent with the practices of organizations such as Cochrane Collaboration, it also limited searches whenever possible to systematic reviews—evidence-based syntheses of primary research. (If fewer than three systematic reviews were available, a panel member could substitute published scholarly reviews.) Finally, it defined the parameters of available key words to use as search terms: each had to derive from the specific language of the authoritative sources or from a unique component of the gap. This search identified all relevant full text articles for each panel member to read on his or her assigned topics; he or she then synthesized the information to develop meaningful conclusions.

Figure 2 illustrates an example of a literature review methodology for the gap "novel psychological treatment approaches for PTSD based on established research."

Figure 2. Example of Literature Review Methodology

"Novel psychological treatment approaches for PTSD based on established research"

- Inclusion criteria: Systematic Review, 2013–2016
- Exclusion criteria: Treatments recommended by VA/DoD Clinical Practice Guidelines
- Searched PubMed for "PTSD Treatment" (MeSH) and publication type = "reviews" (n=2110)
- Identified 12 additional sources (RAND reports, IOM reports)
- Screened 2122 articles, 1522 excluded
- Reviewed 600 abstracts, 590 excluded
- Reviewed 20 full text articles

After extensive discussion, the panel reached full consensus on the 10 most critical gaps in PTSD and the 6 most critical in depression.

Examine In-Progress Research Investments

The panel's next step was to determine whether any of DoD's in-progress research investments in psychological health were already closing these identified gaps. As no comprehensive database of DoD-supported psychological research exists, the PH RWG employed three strategies to learn about relevant DoD research in progress.

The PH RWG first requested summary information about current portfolios from Service branches and DoD agencies funding relevant psychological research. The Naval Center for Combat and Operational Stress Control, RAND National Defense Research Institute, and DCoE's Telehealth and Technology Center (T2) responded; time limitations prevented responses from the U.S. Army Medical Research and Materiel Command and from the Center for Studies of Traumatic Stress (CSTS) at the Uniformed Services University of the Health Sciences (USUHS).

The PH RWG next reviewed relevant information from research committees, meetings, and conferences, including the MHS Research Symposium and the Military Operational Medicine Research Program (MOMRP) Resilience In-Progress Review (IPR), both in August 2016, and the Military MOMRP PTSD IPR and Naval Research Roundtable Symposium, both in September 2016. The PH RWG synthesized this information and all available DoD PH portfolio information into spreadsheets to identify current studies, outcomes, and other study variables (Appendix E).

Finally, consultants to the PH RWG searched www.clinicaltrials.gov, a database for in-progress research, for current PTSD and depression research. They mapped the resulting list of approximately 1,000 studies to each gap (Appendix F) by matching the study topic information with each relevant gap topic. The consultants also reviewed information on DoD policies for PTSD and depression to determine if any policy changes had rendered any gap irrelevant.

Panel members did not formally synthesize information they had gained either from attending scientific conferences or from working on grants and article reviews, but they took such information into consideration in their deliberations. Although too imprecise to categorize or to determine study quality, it informed the panel members' background information and added to their general knowledge of the state of the science.

The overall effect of these processes provided "due diligence" to ensure that the expert panel had considered as much ongoing research as possible; importantly, these steps demonstrated no significant new information to help close the 21 identified research gaps.

Prioritize Research Gaps and Develop Recommendations

The panel developed a set of metrics for a Likert scale assessment to prioritize these gaps. The five metrics were equally weighted at 20 percent; 4a and 4b, representing different ways to evaluate the same construct, each contributed 10 percent to the 20 allotted to question four. After collaborating on a uniform process for applying these metrics, each panel member applied them to assess the relevance and impact of the 16 gaps.

Figure 3. Research Gap Prioritization Metrics

	None		Some		Very much
1. Based on existing scientific evidence, how much does this remain a research gap?	1	2	3	4	5
2. Based on the current research investment, how much does this remain a gap?	1	2	3	4	5
3. How much would addressing this gap impact[1] the population?	1	2	3	4	5
4a. How much do developing programs or policies **reduce**[2] the relevance of the gap?[3]	1	2	3	4	5
4b. How much do developing programs or policies **increase**[4] the relevance of the gap?	1	2	3	4	5

[1] "Impact" includes reach, severity, and alternative treatment options.
[2] "Reduce" refers to programs or policies that create barriers.
[3] Item 4a was reverse scored.
[4] "Increase" refers to programs or policies that are facilitators.

	Not at all likely		Somewhat likely		Very likely
5. What is the likelihood that closing the gap would improve care in the MHS?	1	2	3	4	5

Results

The panel tallied and averaged all responses and assigned each gap a summary score. The panel then used those scores to rank the gaps highest to lowest, yielding a list of ten prioritized research gaps in the treatment of PTSD and six prioritized research gaps in the treatment of depression in the military. It then developed recommendations to address each of these gaps, listed in Table 1 and Table 2 below. The shaded rows in each table depict the four overlapping recommendations between PTSD and depression. Comments pertaining to a recommendation for a specific gap appear in the tables; comments relevant to recommendations for all gaps appear in the General Recommendations section.

The PH RWG also mapped the prioritized gaps to the "Interagency Research Continuum Approach" outlined in the NRAP (Figures 4 and 5). This approach aims to ensure alignment between research gaps and strategic priorities. At the same time, it organizes studies along the following progression: foundational science, epidemiology, etiology, prevention and screening, treatment (combined here with follow-up care), and implementation (services) research. It also facilitates strategic analysis of the gaps, helps identify future areas of focus, and indicates the key areas most immediately actionable.

Table 1. Prioritized List of Research Recommendations for Gaps in PTSD in the Military*

Rank	Score	Research Recommendation *(NRAP)*	Comments
1†	20.67	Conduct head-to-head comparative effectiveness trials of efficacious PTSD treatments that include better controls. ***(Treatment, Services Research)***	Trials may include comparisons within, between, or combination comparisons of psychotherapies and pharmacotherapies. Comparisons between pharmacotherapies and psychotherapies should include consistent measurements and outcomes (e.g., side effects and risks, long term outcomes, attrition). Secondary outcomes (e.g., military vs. nonmilitary, trauma type, clinical settings) should also be included when possible. Consider advanced methodologies (e.g., SMART trials) to incorporate these concerns into one design.

2†	20.67	Conduct well-controlled trials to examine integrated approaches to care for PTSD patients with multi-morbidities (e.g. PTSD and depression, PTSD and TBI) and psychosocial complexities (e.g., marital concerns, military transitions). ***(Treatment)***	While co-morbid PTSD and substance abuse disorder (SUD) were excluded for the purposes of this task, the PH RWG plans to address this specific PTSD co-morbidity when investigating SUD in future research gap prioritization efforts. Please note that current recommendations do not preclude considering co-morbid PTSD and SUD.
3	20.33	Examine the efficacy and/or effectiveness of modularized interventions based on components of evidence-based PTSD treatments in order to overcome treatment barriers and limitations and to improve reach and impact. ***(Treatment, Follow-up Care, Services Research)***	Modularized interventions refer to abbreviated or hybrid approaches based on components from established evidence-based interventions. Approaches should take into account diagnostic complexity and improve reach by overcoming barriers (e.g., attrition, geographical limitations, patient preferences).
4	20.25	Examine the effects of sex/gender and race/ethnicity on PTSD prevention, treatment, and other related outcomes. (***Epidemiology, Prevention and Screening, Treatment, Services Research***)	Relevant outcome variables include differential treatment trajectories, treatment access, diagnosis, stigma, patient preferences, impact of diagnosis on career path, and other pertinent issues. Consider differential effects of life events such as deployment and family issues.
5	20.17	Examine the efficacy of novel pharmacotherapies for PTSD based on emerging basic science. (***Foundational Science, Treatment***)	Interventions may include but are not limited to promising pharmacotherapies such as Orexin antagonists or Corticotrophin Releasing Factor (CRF1 and CRF2) antagonists.

6	18.75	Conduct research to evaluate the effectiveness of widely-used PTSD treatment programs in the MHS that currently have inconsistent or limited evidence. This gap specifically refers to large programs (not individual interventions, per se) designed to identify, prevent, or treat PTSD in the military that have not been substantiated by evidence. (***Prevention and Screening, Treatment, Services Research***)	Research should include common data elements that can be translated into program evaluation and serve as a bridge between research and subsequent evaluation efforts.
7	18.08	Improve understanding of possible PTSD biomarkers, taking into account limitations in specificity, or predisposing, or environmental factors. (***Foundational Science, Epidemiology, Etiology, Prevention and Screening***)	Studies should include very large cohort samples and take into account complex biological symptoms, early childhood trauma, and trauma type.
8	17.92	Conduct research to improve implementation, delivery, impact, and reach of telehealth and mobile health interventions for PTSD in the Active Duty (AD) population. (***Follow-up Care, Services Research***)	None
9	17.83	Conduct well-controlled trials for mindfulness-based approaches for PTSD. (***Treatment, Services Research***)	Examine the effectiveness of mindfulness based approaches as a monotherapy. Additionally, examine how adjunctive mindfulness based approaches fit into existing interventions and programs (e.g., effects on adherence, compliance, medication use).

10	16.67	Conduct well-controlled trials on emerging psychological treatments for PTSD that have not yet been substantiated by a complete evidence base. (***Foundational Science, Treatment***)	Novel psychotherapies should be examined along the continuum of research. When appropriate, basic science should be conducted to establish an evidence base. Once an evidence base is established, well controlled clinical trials should be conducted that include but are not limited to strong comparison conditions and large sample sizes.

*The shaded rows represent overlap with gaps identified for depression.
†The top two gaps were tied based on total score. To simplify ranking and to break the tie, the gap with the lower variation in score (as measured by lowest standard deviation) was ranked first.

Figure 4. PTSD Research Gaps Mapped to NRAP Research Continuum

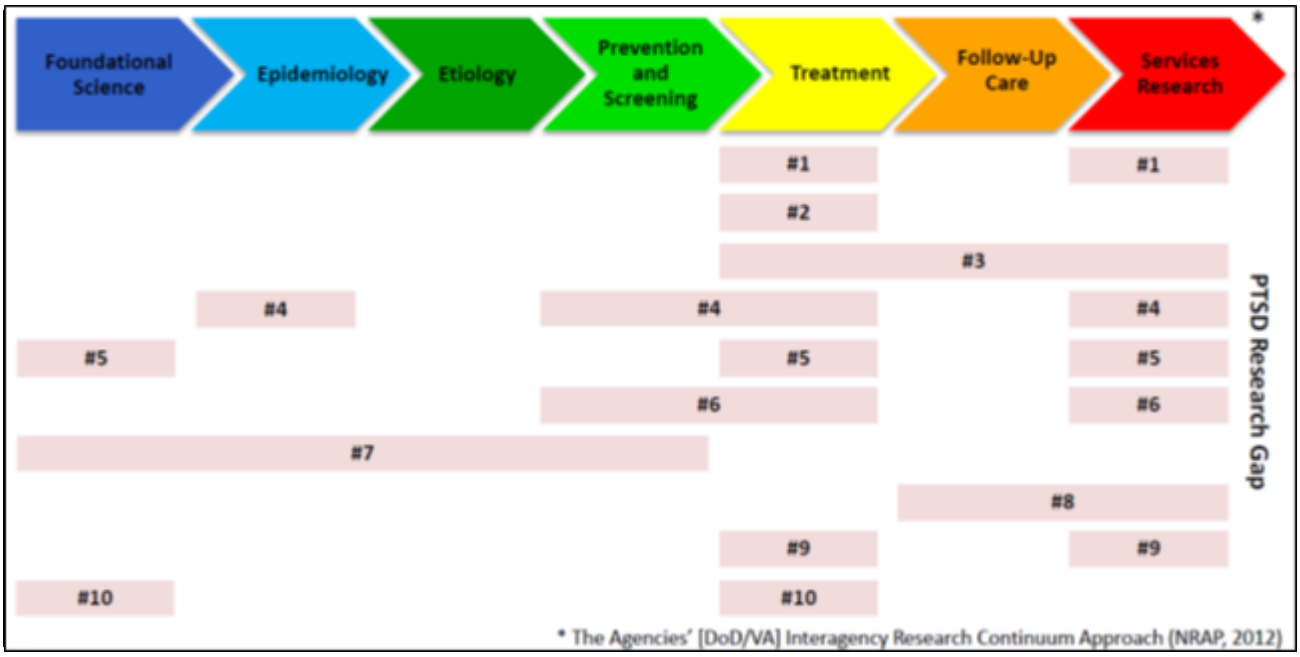


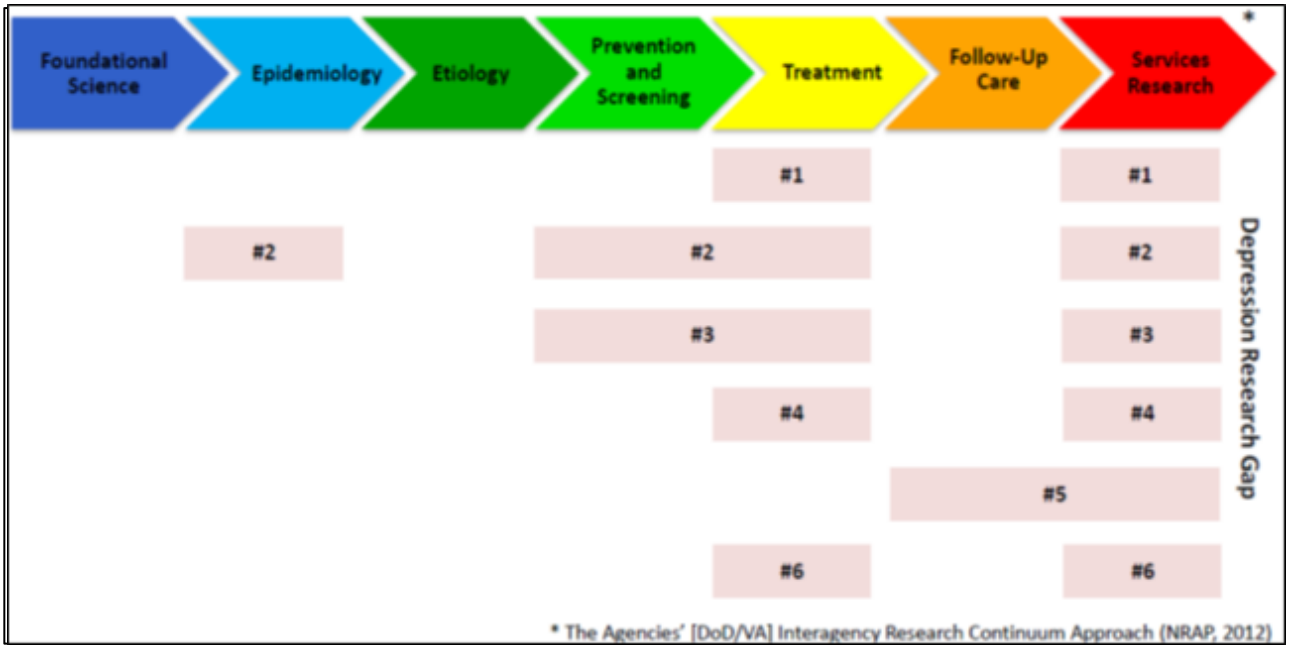
Table 2. Prioritized List of Research Recommendations for Gaps in Depression in the Military*

Rank	Score	Research Recommendation *(NRAP)*	Comments
1	20.67	Conduct head-to-head comparative effectiveness trials of efficacious depression treatments that include better controls***. (Treatment, Services Research)***	Trials may include comparisons within, between, or combination comparisons of psychotherapies and pharmacotherapies. Comparisons between pharmacotherapies and psychotherapies need to include consistent measurements and outcomes (e.g., side effects and risks, long term outcomes, attrition). Secondary outcomes (e.g., clinical settings, provider characteristics, patient preferences) should also be included. Consider differential effects of pharmacotherapy class on temporal treatment effects , as some are more effective for short term vs long term. Consider advanced methodologies (e.g., SMART trials) to incorporate these concerns into one design.
2	20.25	Examine the effects of sex/gender and race/ethnicity on depression prevention, treatment, and other related outcomes. (***Epidemiology, Prevention and Screening, Treatment, Services Research***)	Relevant outcome variables include potential differential treatment trajectories, treatment access, diagnosis, stigma, patient preference, impact of diagnosis on career path, and other pertinent issues. Consider differential effects of life events such as deployment and family issues. More focus is needed on perinatal depression.
3	18.75	Conduct research to evaluate the effectiveness of widely used depression treatment programs with inconsistent or limited evidence. (***Prevention and Screening, Treatment, Services Research***)	This topic refers to large programs designed to identify, prevent, or treat depression in the military that have not been substantiated by evidence. Research should include common data elements that can be translated into program evaluation and serve as a bridge between research and subsequent evaluation efforts.

4	18.33	Conduct research to examine the best approach for delivering repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant depression in the military. (***Treatment, Services Research***)	The PH RWG recommends including measurements of utilization and cost-effectiveness, and provider and patient preferences. Examine if rTMS is best delivered as monotherapy or augmentation to treatment. Include measures of long-term safety. This recommendation does not refer to prioritizing efficacy trials as there is existing literature on rTMS efficacy.
5	17.92	Conduct research to improve implementation, delivery, and reach of telehealth and mobile health interventions for depression in the AD population. (***Follow-up Care, Services Research***)	None
6	17.75	Examine benefits and weaknesses of interventions for depression with a limited evidence base being used in the health care system, often as an adjunctive treatment. (***Treatment, Services Research***)	This refers to treatments that are not first line treatments but providers choose to deliver as monotherapies or adjunctive therapies, often based on patient preferences. Explore how interventions impact participation, utilization, adherence, functionality, and quality of life. Studies should also examine cost effectiveness.

*****The shaded rows represent overlap with gaps identified with PTSD.

Figure 5. Depression Research Gaps Mapped to NRAP Research Continuum



General Recommendations

The panel identified six general recommendations pertaining to study design and methodology. Each of these should be implemented only when appropriate and feasible.

- Measure relevant secondary outcomes, such as functional impairment, quality of life, and fitness for duty.
- Measure adverse events, harms and occurrences of suicidal ideation in both pharmacological and psychotherapeutic trials.
- Use common data elements and maintain individual subject-level data in order to facilitate retrospective meta-analytic studies
- Track sex/gender and racial/ethnic differences.
- Track longitudinal outcomes from active duty to veteran status.
- Evaluate implementation and dissemination concerns, including cost-effectiveness of interventions.

As studies incorporate these recommendations, researchers can make more direct comparisons across studies.

Challenges, Responses and Way Forward

After identifying challenges and engaging in ongoing quality improvement processes to ensure adequate mitigation of risks, the PH RWG drafted these recommendations regarding the way forward.

Table 3. Challenges Identified by the PH RWG, Their Responses, and Way Forward

Challenge	PH RWG s Response	Way Forward
1. There are inherent limitations related to using an expert panel to prioritize gaps, including subjectivity and potential bias. In addition, this panel consisted of a relatively small number of individuals within the same organization.	▪ Relied on consensus opinion for most decisions ▪ Independently applied the metrics to the research gaps, with independent panel members being blind to authorship of others' ratings ▪ Required every expert panel member to participate in the review of published scientific literature to inform his/her expert opinion ▪ Employed two consulting SMEs who advised the expert panel as needed	▪ Consider incorporating more members with expertise relevant to a particular topic. ▪ Consider inviting members external to DHCC. ▪ Consider briefing the Mental Health Workgroup (MHWG) as interim step to gain external expert input. ▪ Consider these challenges when developing new Work Plan in January 2017.

2. Due to a collapsed time period between receipt of tasking requirements and mandated deliverable completion date, time and resource constraints limited the breadth and depth of this work.	▪ Sought and received approval from the KT Steering Committee to narrow scope of the research gaps to two PH topics ▪ Requested and obtained resource and workload assistance from KTO	▪ Explore incorporating additional DCoE and/or DHCC organizational resources to support this work. ▪ Consider focusing on one PH topic each year for greater comprehensiveness and depth. ▪ More time will be available to accomplish work in the future; planning further ahead will spread workload into manageable sections.
3. Identification of research gaps relied primarily on review of authoritative sources, which were not comprehensive and may have resulted in omissions.	▪ Ensured that all military-relevant sources were included ▪ Examined non-traditional sources, such as CPGs from external professional organizations outside of military (e.g., APA CPGs)	▪ Use Provider Needs Assessment Survey results (to be completed in 2017) to help address this challenge. ▪ Use surveillance and practice gap findings. ▪ Consider engaging with multiple stakeholders and sources of information to identify a more comprehensive list of potential gaps. ▪ Continue to select authoritative sources based on relevance to the military. ▪ Consider briefing the Mental Health Workgroup (MHWG) as an interim step to gain external expert input.

4. No centralized database of DoD-supported research exists. The PH RWG was unable to obtain research portfolio information from some important sources. In addition, the panel received incomplete in-progress research investment information, which precluded formal assessment of quality.	▪ Reached out to as many contacts as possible ▪ Obtained assistance to organize all relevant trials from clinicaltrials.gov ▪ Organized information obtained from outside sources as well as information already held ▪ Included relevant information from professional meetings and conferences	▪ Continue to develop and strengthen relationships across the MHS. ▪ Begin the process to develop a centralized database of all DoD-supported PH research, which will likely be a long-term (i.e., multi-year) effort. ▪ Ensure comprehensive project management plan enables the PH RWG to request information far enough in advance to allow stakeholders to respond thoroughly.
5. In-progress research review is inherently limited because the quality of the work is difficult to ascertain at that stage.	▪ Created spreadsheets to summarize and synthesize information as best as possible to assist in drawing conclusions ▪ Captured certain quality variables such as design of trials	▪ Strive to obtain more complete information by developing and strengthening relationships with relevant stakeholders and points of contact (POCs).
6. There are no known validated measures to prioritize research gaps.	▪ Piloted and developed set of metrics to prioritize research gaps ▪ Made as few assumptions as possible in formulating the metrics. For example, instead of assuming that closure of a gap would automatically lead to improvement of care in the MHS, we considered that issue in the metrics	▪ Perform statistical analyses of the metrics and use the results to inform the next iteration of these metrics. ▪ Conduct a comprehensive survey of relevant metrics literature and consult stakeholders to identify most important metrics to incorporate.

Conclusion

This pilot initiative aimed to identify and prioritize research gaps in the military in the areas of PTSD and depression. The structured, systematic, and transparent methodology developed by the PH RWG for this effort relied on findings and statements from authoritative sources; it also incorporated and synthesized published scientific literature, DoD policies, and DoD in-progress research investments. As no validated measures exist to prioritize research gaps, the expert panel convened by the PH RWG developed a set of metrics to prioritize gaps. It then developed recommendations to address them.

This process identified 10 prioritized recommendations for addressing research gaps in PTSD and 6 for depression.

The top three recommendations for the PTSD gaps are the following: (1) conduct head-to-head comparative effectiveness trials of efficacious PTSD treatments that include better controls; (2) conduct well-controlled trials to examine integrated approaches to care for PTSD patients with multi-morbidities (e.g., PTSD and depression, PTSD and TBI) and psychosocial complexities (e.g. marital concerns, military transitions); and (3) examine the efficacy and/or effectiveness of modularized interventions based on components of evidence-based PTSD treatments in order both to overcome treatment barriers and limitations and also to improve reach and impact. The top three recommendations for addressing depression gaps are: (1) conduct head-to-head comparative effectiveness trials of efficacious depression treatments that include better controls; (2) examine the effects of sex/gender and race/ethnicity on depression and related outcomes; and (3) conduct research to evaluate the effectiveness of widely used depression treatment programs with inconsistent or limited evidence.

This initiative is an important effort to apply a systematic approach to prioritizing research gaps. Such an approach is critical; however, policy and funding planners should not exclude other sources of information that might significantly contribute to funding priorities. Plans are underway to modify the PH RWG prioritization process based on lessons learned from this first initiative. Such lessons include two primary assertions: any comprehensive approach to identifying research gaps and priorities should include input from more than one source; and because the domains of PTSD and depression research are expansive, even a strong effort to prioritize specific research gaps will necessarily exclude many significant gaps across research domains.

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Appendix A: Authoritative Source Research Gap Scan

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
Basic research- mechanisms, biomarkers, imaging, genomics, etc.				
1	NRAP	…a limited understanding of underlying mechanisms of PTSD, the long-term consequences of TBI, and warning signs for tragic outcomes such as suicide is hampering progress in prevention, diagnosis, and treatment.	3	P
2	NRAP	Improved techniques are needed to determine when and what symptoms are attributable to the traumatic (physical) event, to understand the brain events that give rise to the post-concussive syndrome concurrent with PTSD symptoms, and to elucidate the neural basis of the interaction between mTBI, PTSD, depression, and suicidality.	12	B
3	NRAP	…determine the neural basis of PTSD	12	P
4	NRAP	The mechanisms underlying the development of PTSD and comorbid conditions following traumatic exposure need to be better elucidated to enable the identification of individuals at risk	18	P
5	NRAP	As cognitive science evolves to reveal how dysfunction in memory, learning, and attention processes contribute to the development, prevention, and treatment of mental illness, researchers need to translate these findings into prediction models and novel prevention and treatment interventions.	18	P
6	NRAP	Research is needed to identify and characterize biomarkers that can predict increased vulnerability to the development of PTSD, indicate changes in the spectrum of symptoms associated with worsening function, and demonstrate at the biologic level a positive response to intervention.	18	P
7	IOM 2014	One important topic that has not been investigated extensively is how different types of memory systems interact. Given that PTSD is characterized by intrusive and habitual episodic memory retrieval accompanied by heightened learned threat responses and physiological arousal, this might be an important avenue for future research.	201	P
8	IOM 2014	Traditional research on learning and memory has focused on memory encoding and retrieval, not the storage process itself, which is a promising topic.	201	P
9	IOM 2014	…the committee identified relatively few ongoing studies of the mechanisms of fear resilience or fear-control techniques beyond extinction or cognitive regulation.	201	P

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
10	IOM 2014	…the committee found little research on the relationship between the stress–hypothalamic pituitary axis response and the mechanisms of emotion and fear control. Those mechanisms are inherently intertwined in PTSD, so understanding their interactions is important and research on this topic should be expanded.	201	P
11	IOM 2014	Although an understanding of basic general psychological and neurobiological principles underlying the development and persistence of PTSD is clinically important, this research cannot be adequately translated into treatment and prevention unless it is known how the mechanisms interact with individual characteristics.	201	P
12	IOM 2014	…relatively little is known about how sex differences may impact the underlying neurobiology and psychology of PTSD.	202	P
13	IOM 2014	The genomics of PTSD is in its infancy compared with the genomics of other common psychiatric disorders such as schizophrenia. There is a great deal of knowledge to be gained in this field, but whether it will translate into innovative interventions to prevent or ameliorate PTSD is unknown. The most promising research for translation appears to be prospective human studies that integrate multiple levels of biological data.	202	P
14	IOM 2014	Advances in basic science and PTSD genetics could help to identify social, psychological, or biological markers that might indicate vulnerability to PTSD either before or after trauma exposure.	204	P
15	IOM 2014	There is no research on overcoming barriers to translation of basic research to treatment and clinical practice.	212	P
16	VA/DoD MDD CPG	Additional research is required in the use of genetic testing to aid in the selection of the most appropriate medication for a specific patient. Currently, there is insufficient evidence to support the routine use of genetic testing for the selection of one antidepressant over another.	13	D
Treatment – Overall/Combination				
17	NRAP	Current PTSD pharmacotherapy and medications are inadequate, with somewhat limited success in treating individuals with PTSD.	12	P

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
18	IOM 2014	There are a limited number of studies that have investigated PTSD treatments in service member and veteran populations.	206	P
19	IOM 2014	The combination of various clinical approaches to address the complexity of PTSD issues (for example, concurrent treatment for PTSD and comorbidities or treatments that combine psychotherapies, pharmacotherapies, and complementary and alternative therapies) needs to be studied further in military and veteran populations.	206	P
20	IOM 2014	Once efficacy is established, primary treatments can be studied in combination with other treatments to determine the added value of combination treatments or how treatment-protocol modifications can improve benefits.	207	P
21	IOM 2014	The committee did not identify any studies of the value of combining cognitive training methods with traditional cognitive behavioral therapy (CBT) or exposure therapies, such as Cognitive Processing Therapy (CPT), Prolonged Exposure (PE) and Eye Movement Desensitization and Reprocessing (EMDR). That may constitute a research gap in as much as psychotherapy approaches may be more effective when combined to address both cognitive control of emotional regulation and extinction-based cognitive and behavioral concerns.	207	P
22	IOM 2014	Given the current and growing number of service members and veterans who have PTSD symptoms and the availability of effective treatments for PTSD, a topic of research that is often overlooked but would be beneficial in the short term is methods to overcome barriers that prevent the widespread use of effective treatments in DoD and VA health care systems. This may include research on health services, effective models for PTSD management, the establishment of evidence-based practice competencies, provider training, and the effective implementation and dissemination of evidence-based care.	222	P
23	APA 2016	Based on the evidence available to date from the systematic review, the panel was not able to recommend one treatment (psychotherapy or pharmacotherapy) versus another.	11	P
24	APA 2016	…gaps include the comparative effectiveness of psychological and pharmacological treatments and combinations of treatments, subgroup effects, applicability of findings to patients with comorbidities common among people with PTSD, impact of treatments on important patient-oriented outcomes such as quality of life, long-term treatment effects, adverse effects and harms, and patient preferences.	13	P

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
25	APA 2016	Clearly, head to head trials comparing psychological treatments to medications are desperately needed.	81	P
26	APA 2016	…the paucity of relevant treatment comparisons (i.e., comparative effectiveness trials) limits the ability of clinicians to make evidence-based recommendations for selecting one psychotherapy versus another or one medication versus another.	92	P
27	APA 2016	…there are few comparative effectiveness trials of efficacious psychotherapies compared to efficacious medications.	92	P
28	APA 2016	…it is not yet known if treatment combinations, particularly psychotherapy with pharmacotherapy, are more effective than their use alone.	92	P
29	APA 2016	…more research is needed regarding different mental health treatment combinations, sequences, and integration. Specifically, panel members recommend trials comparing efficacious psychotherapies to each other, efficacious medications to each other, and efficacious psychotherapies to efficacious medications.	92	P
30	APA 2016	…trials are needed to determine whether combined treatments enhance the effect of psychotherapies and medications that are effective alone.	92	P
31	AHRQ 2013	We found insufficient head-to-head evidence comparing efficacious treatments…	8	P
32	AHRQ 2013	…head-to-head evidence was insufficient to draw any firm conclusions about comparative effectiveness, primarily due to unknown consistency (with data from just one study) and lack of precision. [KQ 3- psychotherapy compared with pharmacotherapy)	29	P
33	AHRQ 2013	Overall, evidence was insufficient to determine whether combinations of psychological treatments and pharmacological treatments are better than either one alone when initiating treatment.	29	P

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
34	AHRQ 2013	Some guidelines identify psychological treatments over pharmacological treatments as the preferred first step and view medications as an adjunct or a next-line treatment. We found insufficient direct evidence (from head-to-head trials) to support this approach. Indirect evidence suggests that psychological treatments are more effective than pharmacological ones because effect sizes for reduction of PTSD symptoms are much larger in trials of the efficacious psychological treatments. However, conclusions based on naive indirect comparisons can be flawed, primarily because it is difficult to determine the similarity of populations across two somewhat different bodies of literature (i.e., studies of psychological treatments and those of pharmacological treatments).	30	P
35	VA/DoD MDD CPG	Specifically, it would be helpful to know how and when to combine psychotherapy and medications as initial therapy and whether there are particular combinations that are more effective than others for both complex and uncomplicated patients.	13	D
36	VA/DoD MDD CPG	…there are few trials comparing combination treatment to monotherapy, and the studies reflect a lack of consensus on the inclusion criteria for patients with severe, chronic and/or recurrent depression (although the studies have been limited to recurrent depression with three or more episodes).	38	D
37	VA/DoD MDD CPG	Determining the effectiveness and safety of combination treatment versus monotherapy alone should be a high research priority given the potential costs and other burden differences in the two treatment options versus the high burden of illness in patients with severe or recurrent or treatment-resistant depression.	39	D -
38	VA/DoD MDD CPG	The evidence does not support recommending any specific evidence-based psychotherapy over another.	43, 44	D
39	AHRQ 2015	Our confidence in the benefits and harms of SGAs compared with the remaining treatment options is low or insufficient, indicating that the bodies of evidence had major or unacceptable deficiencies.	8	D
40	AHRQ 2015	For second-step therapies (i.e., therapy for patients with MDD who did not achieve remission after a first treatment attempt with SGAs), comparative evidence is limited.	8	D
41	AHRQ 2015	The evidence was mixed with regard to response and remission, and was insufficient to draw conclusions about differences in response, remission [SGA vs. BA].	23	D

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
42	AHRQ 2015	Four trials yielded insufficient evidence to determine whether the comparative effectiveness of SGAs versus any psychological treatment changes as a function of MDD severity.	24	D
43	AHRQ 2015	One trial yielded insufficient evidence to determine whether the comparative effectiveness of SGAs versus SAMe changes as a function of MDD severity.	25	D
44	AHRQ 2015	Our confidence in findings from the comparisons of remaining treatment options was low or insufficient, indicating that these bodies of evidence had major or unacceptable deficiencies.	27	D
45	AHRQ 2015	Overall, data do not indicate differences in comparative effectiveness between SGAs and nonpharmacological interventions for patients with severe MDD. This important question concerning MDD severity, although raised by a few systematic reviews, remains without a clear answer.	28	D
46	AHRQ 2015	We found no eligible studies that compared SGAs with behavior therapy or behavior modification, humanistic therapies, yoga, or mindfulness interventions. Given the wide use of these types of psychotherapies in clinical practice, further research into their comparative effectiveness with SGAs in treating MDD patients is desirable.	29	D
47	S. 2410 (2015)	Sec. 733. Report on improvements in the identification and treatment of mental health conditions and traumatic brain injury among members of the Armed Forces.	213-217	B
Treatment – Psychological				
48	IOM 2013	VA has included Acceptance and Commitment Therapy for depression in its national rollout of evidenced-based treatments; however, there is not sufficient evidence to support its use as a first line intervention.	21	D
49	IOM 2013	Small RCTs and open trials of acceptance and commitment therapy have been conducted and warrants further review.	196	P
50	IOM 2013	Additional research with larger samples and more rigorous designs is needed before more definitive claims can be made about the effectiveness of ACT.	209	D

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
51	IOM 2013	…considered the evidence base for numerous other psychosocial therapies, including psychodynamic psychotherapy, brief eclectic psychotherapy, hypnosis, relaxation, stress inoculation training, interpersonal therapy, skills training in affect and interpersonal regulation, and group therapy. That committee found that, with the exception of CBT-based group therapy, the efficacy of the other psychosocial therapies is supported by only a few RCTs.	195-96	P
52	IOM 2013	…there is inadequate evidence to determine the effectiveness of brief (low intensity) interventions (such as mindfulness-based cognitive therapy) for the prevention of relapse or recurrence of depression.	209	D
53	IOM 2014	It is important to continue to develop and evaluate new psychotherapy options because there is currently no evidence-based treatment that is effective for everyone who has PTSD and no treatment that is so appealing, engaging, and pragmatically deliverable to patients that it breaks down all barriers to care. Thus, the rigorous study of new psychotherapies is essential for maximizing the treatment options to address each patient's unique needs and preferences…	207	P
54	APA 2016	For adult patients with PTSD, there is insufficient evidence to recommend for or against clinicians offering the following psychotherapies/interventions: relaxation, seeking safety.	18	P
55	APA 2016	For adult patients with PTSD, the panel concludes that the evidence is insufficient to recommend for or against clinicians offering Seeking Safety versus active controls.	18	P
56	APA 2016	There is insufficient/very low strength evidence of a benefit for the critical outcome of PTSD symptom reduction (relaxation).	55	P
57	APA 2016	There is insufficient/very low evidence that the critical outcome of PTSD symptom reduction is the same in exposure based therapy and relaxation therapy.	59	P
58	APA 2016	There is insufficient/very low evidence that the critical outcome of PTSD symptom reduction is the same in exposure and exposure plus cognitive restructuring.	59	P
59	AHRQ 2013	Evidence was insufficient to determine efficacy for achieving remission for any psychological treatments except CBT-mixed treatments (moderate SOE) because trials typically did not report remission as an outcome.	24	P

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
60	AHRQ 2013	Most of the direct head-to-head comparative evidence was insufficient to determine whether psychotherapies differ in effectiveness, with a few exceptions.	24	P
61	VA/DoD MDD CPG	Good quality research studies on the benefits, harms, and burdens of couples therapy compared with individual therapy for MDD is also limited. Additional studies with larger sample sizes and greater heterogeneity among study subjects should be research priorities for understanding this treatment intervention given the link between relationship distress and depression as well as the potential for benefit.	13	D
62	VA/DoD MDD CPG	…not aware of studies comparing couples therapy with combined treatment…	44	D
Treatment-CAM/Somatic Treatments				
63	IOM 2013	Guideline recommendations do not show strong evidence supporting the use of various innovative or alternative treatments for PTSD, such as couple and family therapy and complementary and alternative medicine (CAM), which includes yoga, contemplative treatments, and acupuncture…these treatments do not have a substantial evidence base; evidence of the effectiveness of these therapies for PTSD is based on small RCTs, case studies, or anecdotal reports.	196	P
64	IOM 2013	In addition to the required evidence-based treatments, VA offers a variety of treatments that fit into the CAM category and have almost no evidence base, such as spirituality group, relaxation group, relaxation yoga group, group ear acupuncture, socialization group, Tai-Chi group, and yoga nidra group.	206	D
65	IOM 2013	…insufficient data are available to determine the efficacy of VNS.	210	D
66	IOM 2013	There are few data on complementary and alternative treatments for MDD.	210	D
67	IOM 2013	…although the treatments [CAM] appear promising, more rigorous and larger studies are needed to determine whether any of them should be formally indicated for MDD.	211	D

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
68	IOM 2014	Complementary and alternative treatments for PTSD—such as yoga, acupuncture, and animal-assisted therapy—received particular consideration as required by the legislation, but the lack of evidence on their effectiveness made them difficult to assess.	34	P
69	IOM 2014	Although the evidence base to support the effectiveness of most of these [CAM] treatments is lacking, a few studies show positive results.	150	P
70	IOM 2014	The committee identified several current studies that are funded by DoD, VA, and others to investigate rTMS, cranial electrotherapy stimulation, stellate ganglion block, trigeminal nerve stimulation, and bright-light therapy (see Appendix E). Those and other stimulatory and somatic interventions are promising treatments for PTSD and clearly warrant further study.	209	P
71	IOM 2014	The more frequently studied complementary and alternative therapies are meditation, acupuncture, yoga, and biofeedback. Less studied therapies include animal-assisted therapy, mantram repetition, and music therapy. The former studies are being conducted in a variety of PTSD populations, including veterans, and they are being evaluated in combination with treatment as usual. Their value as stand-alone treatments for PTSD is unknown.	209	P
72	IOM 2014	There is a lack of well-controlled studies on animal-assisted therapy and on acupuncture for PTSD; more research is needed on both.	210	P
73	IOM 2014	The study of psychobiotics (for example, gut microbiota) is a new field of medicine that is relevant to stress and related psychological disorders. Some researchers have suggested that preclinical and clinical studies of psychobiotics could inform treatment for stress- related conditions.	210	P
74	VA/DoD MDD CPG	There are large gaps in knowledge related to somatic treatments (e.g., deep brain stimulation, electroconvulsive therapy) and newer treatments (e.g., ketamine) for depression for which there is evidence of benefit as well as significant risks.	17	D
75	VA/DoD MDD CPG	Much of the research on nutritional supplements, exercise and related behavioral interventions is sparse and poorly conducted.	17	D

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
76	VA/DoD MDD CPG	There is limited evidence in support of the use of bright light therapy for patients with depression that includes a seasonal component.	45	D
77	VA/DoD MDD CPG	…limited information regarding the degree of short-term cognitive impairment associated with ECT as well as evidence of the efficacy of ECT in specific subgroups, such as the elderly and patients with treatment-resistant illnesses.	48	D
78	VA/DoD MDD CPG	As rTMS is an emerging technology, additional research is needed. Most importantly, the duration of the treatment effect and the long- term safety profile of the intervention need to be demonstrated.	50	D
79	VA/DoD MDD CPG	More evidence is needed to determine the best approach to using rTMS for treatment-resistant depression and if TMS should be a standalone or augmentation therapy.	50	D
80	VA/DoD MDD CPG	Head-to-head studies comparing rTMS to pharmacotherapy or psychotherapy were not found in our literature search.	50	D
81	VA/DoD MDD CPG	Although vagus nerve stimulation is FDA approved for treatment- resistant depression, there is no current evidence that supports its routine use in the treatment of MDD.	50	D
82	VA/DoD MDD CPG	As there is a lack of evidence in support of the routine use of VNS for treatment-resistant depression, more research is needed. Specifically, VNS should be studied in patients with recurrent seizures and depression.	51	D
83	VA/DoD MDD CPG	Given the lack of evidence in support of its effectiveness, and its potential harms and burdens, there is no basis upon which to recommend the use of DBS, which should be considered experimental until further evidence becomes available.	52	D
84	VA/DoD MDD CPG	For patients with MDD, there is insufficient evidence to recommend for or against acupuncture either as monotherapy or as an adjunctive treatment to pharmacotherapy.	52	D
85	VA/DoD MDD CPG	More rigorous studies using specific active controls, blinding of outcome assessors, allocation concealment, and ITT analysis are needed to fully understand the effectiveness and value of acupuncture in the treatment of MDD.	53	D

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
86	VA/DoD MDD CPG	Because MDD is a common co-occurring condition among those with chronic pain, and acupuncture is a common treatment modality within integrative military health clinics, additional assessment of depression outcomes in that population should be specifically investigated.	53	D
87	VA/DoD MDD CPG	A future systematic review that includes only high-quality RCTs is necessary to provide more confidence in exercise efficacy as monotherapy.	54	D
88	VA/DoD MDD CPG	While the widespread practice of these mind-body modalities have demonstrated significant merit as adjunctive approaches in managing certain disease conditions and health risks, the current state of the evidence regarding their effectiveness in the treatment of MDD is weak.	55	D
89	VA/DoD MDD CPG	In reviewing the literature of yoga, tai chi, and qi gong as they relate to the treatment of MDD, the quality of the evidence was found to be very low.	55	D
90	VA/DoD MDD CPG	While the authors acknowledge that specific values and preferences of patients may strongly favor the use of these mind-body modalities as an adjunctive treatment to other care, there is currently insufficient evidence to guide clinical decision-making with regard to their role in treating MDD. More methodologically rigorous research, particularly studies of mind-body modalities for depression in more generalized populations, is needed.	55	D
91	VA/DoD MDD CPG	It should be noted that efficacy of SJW for MDD is established for standardized extracts only, and not for other preparations (e.g., tinctures, infusions, dry herb capsules).	56	D
92	VA/DoD MDD CPG	We suggest that practitioners and policymakers wait until future research in this field is conducted before recommending omega-3 fatty acids in treatment of MDD.	57	D
93	VA/DoD MDD CPG	Future well designed adequately powered double-blind RCTs in severely depressed patients with concurrent vitamin D deficiency that utilize allocation concealment and ITT analysis are needed to guide clinical decisions in this particular subpopulation.	57	D
94	VA/DoD MDD CPG	There is mixed evidence regarding the use of guided self-help (GSH) interventions, including bibliotherapy.	58	D

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
95	AHRQ 2015	We identified no eligible trial that compared an SGA with yoga or meditation.	25	D
96	AHRQ 2015	We did not find any eligible switch evidence comparing an SGA strategy with either CAM or exercise.	26	D
97	AHRQ 2015	For many psychotherapies and all CAM therapies that have been evaluated against an SGA, the data were insufficient because trials did not report important outcomes, most notably quality of life and functional capacity.	29	D
98	AHRQ 2015	For CAM interventions, we found that most studies did not include the full range of SGA doses for comparison, and many studies made comparisons with only the very lowest SGA doses. To truly compare any CAM intervention for MDD treatment, future studies will need to incorporate SGA dosing strategies that use the entire SGA dosage range.	29	D
99	AHRQ 2015	Finally, a major gap in the evidence is the lack of studies addressing different treatment options for patients who have not achieved remission with first-step therapy. No second-step therapy data at all exist that compare SGA with CAM or exercise treatments.	29	D
Treatment – Pharmacological				
100	NRAP	There are no medications developed specifically for the treatment of PTSD.	19	P
101	NRAP	Many medications are used "off-label" to treat PTSD symptoms but lack scientific evidence that they are beneficial.	19	P
102	IOM 2013	Controversy surrounds the utility of antidepressants for treatment for mild depression. Because of small effect sizes, several reviews and meta-analyses have raised questions about the interpretation of results of RCTs.	208	D
103	IOM 2014	New pharmacotherapies, such as endocannabinoids, are promising and important for research.	206	P
104	IOM 2014	The committee found research gaps in the study of preclinical pharmacotherapies, such as the use of oxytocin, to identify molecular markers of reconsolidation and of hippocampal adult neurogenesis as related to pattern separation and pattern completion.	206	P
105	IOM 2014	Particularly promising are the clinical investigation of low doses of anesthetic drugs, such as ketamine, and the increasing evidence base on prazosin.	206	P

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
106	IOM 2014	Studies of drug effects on brain structure and chemistry, such as effects of escitalopram on BDNF, are valuable, and more studies of this type are needed.	207	P
107	IOM 2014	…hydrocortisone holds promise both for the prevention of PTSD and the understanding of the neurobiology of PTSD…	207	P
108	IOM 2014	…further studies of antipsychotics as a treatment for PTSD are needed…	207	P
109	IOM 2014	…polypharmacy is a continuing concern…	207	P
110	APA 2016	There is insufficient evidence to recommend for or against clinicians offering risperidone for treatment of adults with PTSD.	18	P
111	APA 2016	There was insufficient/very low strength of evidence for all other benefit outcomes (Topiramate).	57	P
112	APA 2016	The current panel did not complete a decision table or make recommendations for tricyclic antidepressants because the strength of evidence was rated insufficient in the systematic review.	78	P
113	APA 2016	…insufficient/very low SOE for the critical outcome of PTSD symptom reduction and the important outcome of reduction of comorbid depression or anxiety for mirtazapine.	79	P
114	APA 2016	The SOE was rated insufficient/very low for PTSD symptom reduction, remission or loss of diagnosis for prazosin.	79	P
115	AHRQ 2013	Among pharmacological treatments, we found evidence of moderate strength supporting the efficacy of fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine for improving PTSD symptoms. Risperidone may also have some benefit for reduction of PTSD symptoms (low SOE). Evidence was insufficient to determine whether other medications are efficacious for improving PTSD symptoms.	27	P
116	AHRQ 2013	Little direct comparative evidence (i.e., head-to-head) was available to determine whether pharmacological treatments differ in effectiveness.	27	P
117	AHRQ 2013	Focusing on the medications with moderate SOE supporting efficacy—topiramate, venlafaxine, fluoxetine, paroxetine, and sertraline—most of the evidence was insufficient to determine whether risks were increased, often primarily due to lack of precision.	30	P

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
118	VA/DoD MDD CPG	…lack of evidence demonstrating distinct differences in clinical outcomes between different drug classes…	33	D
119	VA/DoD MDD CPG	Brexpiprazole is newly approved and was not included in the evidence review search strategy of the current CPG.	36	D
Comorbidity				
120	NRAP	…the relationships between PTSD, TBI, suicide, and co-occurring conditions are not well understood.	12	B
121	IOM 2013	Others have cautiously concluded that more research is needed— especially multidisciplinary research in psychiatry, neuropsychology, neurology, and other fields—to examine PTSD, TBI, and their interaction with the use of comprehensive definitions and language that spans different disciplines.	82	P
122	IOM 2013	…there are no empirically validated therapies for comorbid PTSD, MDD, and postconcussive disorders, which may be confounded by substance use.	247	B
123	IOM 2013	There is little evidence on the best approaches for the assessment and treatment of patients who have comorbidities.	250	B
124	IOM 2013	…findings from several studies demonstrate the lack of knowledge about whether evidence-based treatments for a single condition are effective when conditions co-occur or unique therapies are necessary for people who have multiple conditions.	250	B
125	IOM 2013	No published studies addressed the relative accuracy of diagnostic tests used for assessing mild TBI or PTSD when one condition co- occurs with the other.	251	P
126	IOM 2013	…no published studies evaluated treatments for the symptoms of mild TBI and PTSD together.	251	P
127	IOM 2013	There is little evidence that supports any particular treatments for co-occurring PTSD and SUD, but some treatments are available.	251	P
128	IOM 2013	…not possible to draw confident conclusions about the efficacy and safety of antidepressants for treatment for MDD in people who are dependent on opioids, because of clinical and methodologic differences between studies.	252	D
129	IOM 2013	…there is minimal evidence of the effectiveness of CBT either alone or in combination with antidepressant medication for treatment for co-occurring MDD and SUD.	252	D

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
130	IOM 2013	The current literature emphasizes the need for research to develop an evidence base and identify best practices for patients who have comorbid conditions. In addition to determining which interventions are efficacious in treating for comorbid conditions, research studies should examine facets of clinical effectiveness, such as treatment adherence, engagement, and tolerability.	253	B
131	IOM 2014	…there is no guideline on how to integrate treatment for PTSD with treatment for these co-occurring conditions [such as TBI, substance use disorders, depression, and chronic pain].	34	B
132	IOM 2014	…pharmacotherapy for PTSD comorbid with bipolar disorder, attention deficit disorder, and mild TBI is not well studied but should be…	207	P
133	APA 2016	Unfortunately, there are no data on PTSD treatment effect heterogeneity by substance abuse status.	88	P
134	APA 2016	Further, there are no data from meta-analyses on treatment effect heterogeneity by substance abuse among persons with depression.	88	D
135	APA 2016	…participants with other important comorbid conditions were frequently excluded. Specifically, a majority of the RCTs excluded patients with substance dependence or suicidality, an important limitation given that PTSD, substance dependence and self-harm are so often co-morbid.	92	P
136	APA 2016	…it was unclear or inconsistently reported whether individuals also had comorbid problems such as dissociation.	93	P
Effectiveness/Implementation/Health Services (will be some cross-over into program evaluation)				
137	IOM 2013	Numerous programs exist to respond to the needs of returning OEF and OIF active-duty personnel, veterans, and family members, but there is little evidence regarding their effectiveness.	19	B
138	IOM 2013	…the limited data that are available suggest that patients in need of evidence-based care might not be receiving it.	21	B
139	IOM 2013	…there are few data on whether screening, assessment, and treatment interventions in DOD and VA are being implemented according to clinical guidelines and VA and DOD policy.	22	B
140	IOM 2013	There is a dearth of data on which treatments patients receive and whether the treatments were appropriate, timely, and delivered at the recommended intensity level (for example, individual vs group format and frequency and duration of sessions).	22	B

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
141	IOM 2013	…most treatment interventions for family members have been developed and tested in civilian communities and lack evidence of their effectiveness for military families.	23	B
142	IOM 2013	There is a striking lack of data to inform conclusions about the extent to which PTSD treatments are offered, delivered, and completed and about whether they are leading to improved patient outcomes.	196	P
143	IOM 2013	There is a striking lack of data to inform questions about the extent to which depression treatments are offered, delivered, and completed and whether they are leading to improved patient outcomes.	211	D
144	IOM 2013	No evidence was found to support particular sequencing of treatments in implementing practice recommendations of individual guidelines.	247	B
145	IOM 2014	…there are no data on whether mental health care providers in either department use the PTSD guideline or whether they offer evidence-based treatments…	34	P
146	IOM 2014	…the proportion of service members and veterans who have PTSD and recover without intervention is unknown.	50	P
147	IOM 2014	…DoD and the service branches lack data on whether the guideline is being used by providers to inform treatment decisions.	149	P
148	IOM 2014	No DoD data on the use of evidence-based psychotherapy and patient outcomes were available because such data are not collected at the national or service branch level.	149	P
149	IOM 2014	There is a dearth of literature on approaches for matching patients who have PTSD to specific treatments and what, if any, patient characteristics might improve treatment acceptability and response.	182	P
150	APA 2016	Some research on the efficacy of measurement–based care for the treatment of depression exists, but there is little information on the use of detailed measurements across time with specified symptom severity scales in order to increase efficacy or quality of care for PTSD.	75	P
151	APA 2016	While the Department of Veterans Affairs (VA) recently developed a guideline and a mandate for measurement based care in mental health, including PTSD, there is not yet research data supporting this particular practice.	75	P

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
152	APA 2016	Although monitoring PTSD symptoms across the course of treatment likely provides insight into progress and highlights ongoing clinical targets, research is needed to determine whether monitoring of PTSD symptoms improves client outcomes.	75	P
153	VA/DoD MDD CPG	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.	13	D
154	VA/DoD MDD CPG	Trials that address how often to deploy assessment instruments (function, symptom, global) and determine the impact of assessment on outcomes are needed.	13	D
155	IOM 2014	…no studies have confirmed the efficacy or effectiveness of the embedded mental health programs in the service branches.	73	P
156	S. 1356 (2016)	Sec. 729. Plan for development of procedures to measure data on mental health care provided by the Department of Defense (1) Outcomes for mental health care (2) Variations in such outcomes (3) Barrier, if any, to the implementation by mental health care providers.	873-874	B
157	H.R. 4909 (2017)	Sec. 732. Requirement to review and monitor prescribing practices at military treatment facilities of pharmaceutical agents for treatment of post-traumatic stress.	303	P
158	S. 2943 (2017)	Sec. 761. Requirement to review and monitor prescribing practices at military treatment facilities of pharmaceutical agents for treatment of post-traumatic stress.	451-452	P
Screening/Diagnosis				
159	IOM 2013	Minimal data are readily available on the numbers of people who have been screened and the extent to which follow up is appropriate and timely for those who screen positive.	22	B
160	IOM 2013	A wide array of PTSD screening tools are available for identifying undiagnosed cases of PTSD, but there is little evidence to support recommending one PTSD screening tool over another.	186	P
161	IOM 2013	Although the PCL threshold recommended by VA is consistent with the thresholds reported in the literature, the committee is not aware of the evidence underlying the specific thresholds used in DOD's deployment health assessment and RESPECT-Mil programs.	191	P

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
162	IOM 2013	In reviewing evidence on the accuracy of screening instruments to identify depressed adults, USPSTF found little evidence to support recommending one screening tool over another.	201	D
163	IOM 2013	The sparse data suggest that there is room for improvement in DOD and VA screening practices for MDD.	201	D
164	IOM 2013	The literature is insufficient to determine whether diagnostic or even screening instruments commonly used for assessing the symptoms of a particular condition perform accurately when a person has more than one condition. Nor does the literature support any one instrument over others.	250	B
165	IOM 2014	Research is needed to move beyond the traditional questionnaire based screening methods to neurobiological and behavioral screening for PTSD.	205	P
166	IOM 2014	There is also a need for randomized controlled trials that prospectively assess whether large-scale screening results in greater benefits to the population than more traditional approaches.	205	P
167	IOM 2014	The committee identified a research gap in the area of diagnosis—one potentially useful approach that is not being studied is the use of advanced statistical procedures, such as random forest classification and functional magnetic resonance imaging, to develop a neurobiologically based approach to diagnosis PTSD and to evaluate it against standard (that is, clinically based) diagnostic predictors.	205	P
168	OTSG/ MEDCOM 14-094	Although it is expected that prevalence will be similar and the majority of individuals who meet the definition according to DSM-IV-TR will also meet the definition according to DSM-5, there is emerging evidence that a sizable percentage of individuals may have discordant results in either direction…analyses of research that supported the four cluster structure being used now in DSM-5 remains controversial.	8	P
169	OTSG/ MEDCOM 14-094	There is a lack of clarity with regard to which diagnostic code should be applied in cases where subthreshold PTSD requires treatment.	8	P
170	OTSG/ MEDCOM 14-094	No standardized screening or assessment tool is available that can replace a comprehensive clinical interview that assesses the full spectrum of both PTSD and non-PTSD symptoms within the broader bio-psycho-social context.	9	P

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
171	S. 2410 (2015)	Sec. 701. Annual mental health assessments for members of the armed forces (a) A description of the tools and processes used to provide such assessments, including: (i) whether such tools and processes are evidenced-based; and (ii) the process by which such tools and processes have been approved for use in providing mental health assessments.	182-186	B
172	S. 1356 (2016)	Sec. 593. Report on preliminary mental health screenings for individuals becoming members of the Armed Forces. (b.2.) Recommendations with respect to the composition of the mental health screening, evidenced-based best practices, and how to track changes in mental health screenings relating to traumatic brain injuries, post-traumatic stress disorder, and other conditions.	833	B
Specific populations, subgroups, and precision medicine (Context, setting , culture, gender, racial/ethnic minorities, trauma type)				
173	NRAP	Researchers must also evaluate the impact of context, including the population (e.g., active duty, Reserve/Guard, Veterans, and families) and setting (e.g., deployed austere environments versus medical centers) in their studies.	12	B
174	IOM 2013	Whether clinicians who have ethnic characteristics similar to those of their patients would alleviate those problems [cultural insensitivity to nonwhite service members] is unknown.	27	B
175	IOM 2013	Historically, research on the health of veterans has focused on the health consequences of combat service in men, and there has been little scientific research on or longitudinal study of the health consequences of military service in women who served.	129	B
176	IOM 2013	…need to conduct studies with larger samples of women to improve understanding of issues relevant specifically to women.	129	B
177	IOM 2013	There is a paucity of information regarding disparities in health care in the OEF and OIF active duty and veteran populations.	443	B
178	IOM 2013	Research that has examined gender differences is generally mixed, and a recent review highlighted the need to conduct studies with larger samples of women to understand issues relevant specifically for women.	443	B
179	IOM 2013	There is a paucity of literature on disparities in health care in racial and ethnic minorities in the OEF and OIF populations.	445	B

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
180	IOM 2014	No information was found in the published literature or DoD reports on the need for and availability of racial and ethnic-group-specific mental health treatment services in the military.	172	B
181	IOM 2014	The availability of culturally tailored treatments may enhance engagement by members of racial and ethnic minority groups, but empirical evidence on their reach and effectiveness is lacking.	182	P
182	IOM 2014	Research needs to evaluate which treatments can be delivered to which patients who have which health conditions to maximize safe access to evidence-based treatment for service members, veterans, and their significant others.	218	P
183	APA 2016	…research evidence was insufficient to determine treatment effect heterogeneity by many of the subgroups that were examined. Members of the current guideline development panel agreed that the randomized trials included in the review do not sufficiently address the important issue of which treatments are best for which patients and constitutes an important future research need.	11	P
184	APA 2016	…insufficient evidence "to determine whether the findings are applicable to all those with PTSD or whether they are applicable only to certain groups" and insufficient evidence about whether there were subgroup effects. Thus panel members did not reach consensus about the generalizability of the systematic review's findings, reflecting differences of opinion found in the literature about conditions required to demonstrate generalizability.	12	P
185	APA 2016	…examination of treatment effect heterogeneity with diverse samples should be prioritized for future research.	12	P
186	APA 2016	…insufficient evidence from the systematic review to know whether any of the psychological or pharmacological treatments have stronger or weaker effects across subgroups based on any of the following: demographic characteristics (e.g., sex, ethnoracial minority status, military veteran, refugee), type of trauma (e.g., sexual assault, combat, disaster), comorbidity (e.g., substance abuse, depression), duration of symptoms, exposure to childhood trauma, repeat victimization, and level of severity at presentation.	85	P
187	APA 2016	The panel is in complete agreement that evaluation of treatment effect heterogeneity and inclusion of diverse samples in randomized trials are important priorities for future research.	88	P

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
188	APA 2016	…a limited number of studies have investigated moderators of treatment effects (or "subgroup analyses") that evaluate whether treatments are more or less effective for certain groups, such as men or women, specific ethnic or racial groups, persons with acute or chronic/complex PTSD, persons with mild or severe PTSD, or persons exposed to a particular type of trauma (e.g., combat trauma, sexual assault).	92	P
189	APA 2016	…there is little research to indicate which efficacious treatments are most effective for which patients under which conditions.	92	P
190	APA 2016	…relatively little evidence on patient preferences for different psychotherapies or different medications or the impact of those preferences on treatment engagement, retention, and outcome.	94	P
191	AHRQ 2013	Insufficient evidence to verify whether any treatment approaches were more effective for victims of particular trauma types or to determine comparative risks of adverse effects.	8	P
192	AHRQ 2013	…evidence was insufficient to make definitive conclusions about whether any treatment approaches are more effective for victims of particular types of trauma.	29	P
193	AHRQ 2013	Evidence was insufficient to determine whether findings are applicable to all those with PTSD or whether they are applicable only to certain groups. Evidence was insufficient to determine whether any treatment approaches are more or less effective for specific subgroups, including victims of particular types of trauma.	32	P
194	AHRQ 2015	No trials were specifically designed to assess differences in our specified subgroups.	27	D
195	AHRQ 2015	We did not identify any trials assessing differences between men and women in effectiveness or harms.	27	D
196	AHRQ 2015	No trials at all addressed effectiveness or harms in selected subgroups of patients who did not achieve remission following an initial adequate trial with one SGA.	27	D
197	AHRQ 2015	We did not find evidence to confirm or refute whether treatments are more or less efficacious for various subgroups (i.e., patients characterized by sex, race, or ethnicity, or individuals with coexisting psychiatric conditions).	28	D

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
198	AHRQ 2015	Whether and how differences in ethnic or cultural backgrounds and health systems affect the applicability of results to U.S. populations remain uninvestigated and unanswered.	29	D
Methodology				
199	IOM 2013	The data on short-term outcomes (outcomes in 6 months or less) is extensive, but data on long-term outcomes (over years) is less extensive and both can be challenged on methodologic grounds.	20	B
200	IOM 2014	Longitudinal studies can advance the understanding of how aging affects PTSD and comorbidities and can help to elucidate whether some interventions are beneficial in altering the course of the disorder. Thus, long-term follow-up of large DoD and VA cohorts might shed light on the effectiveness of prevention programs, early screening, and a variety of treatment interventions for PTSD.	213	P
201	IOM 2014	New research models—for example, pragmatic trials, practical clinical trials, and hybrid effectiveness–implementation trials—may be useful for addressing the common translational gap between randomized controlled trials and clinical practice.	215	P
202	APA 2016	In addition to the research gaps noted, there are also methodological concerns with many of the current PTSD treatment trials that should be addressed in future trials. Specifically, the panel recommends that investigators design trials to minimize attrition, identify reasons for attrition, decrease missing data, and incorporate rigorous methods of handling missing data such as multiple imputation or maximum likelihood.	14	P
Delivery/Technology				
203	IOM 2013	Although controlled trials of technology-based delivery of PTSD treatments are under way, there are no definitive conclusions about its effectiveness.	192-93	P
204	IOM 2013	Until the results from the four ongoing RCTs are available, there is insufficient evidence for the efficacy of virtual reality exposure programs that integrate computer graphics and head-mounted visual displays as a tool to deliver PE to reduce PTSD symptoms.	196	P
205	IOM 2014	The committee identified a research gap with regard to the use of mobile communication devices and their applications. There appears to be little research to determine how much applications such as VA's PTSD Coach are used once installed and what effect they have on improving treatment outcomes and reducing barriers to care.	210	P

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
206	IOM 2014	More research is needed to determine the characteristics of patients who can benefit from treatment delivered in a group or from combinations of individual and group or conjoint treatment.	210	P
207	IOM 2014	More research is needed to determine the role of the family in different treatment settings and the benefits of family involvement.	211	P
208	IOM 2014	Research is also needed to determine whether providing more choices of treatment modalities for service members and veterans helps to reduce barriers to care.	211	P
209	IOM 2014	...research is necessary to understand whether a patient who has initial involvement in a group setting with a non-evidence based treatment (such as yoga or psychoeducation) is more likely to engage in an evidence-based treatment later.	211	P
210	IOM 2014	Considering the need for well-trained providers of evidence-based treatments and the ubiquitous penetration of high-bandwidth Internet connectivity, the absence of more studies on online clinical training appears to be a gap in research and practice.	214	P
211	IOM 2014	The research needs to be assessed to determine whether telehealth approaches for both screening and treatment offer a preferable and cost-effective approach to PTSD care.	216	P
212	IOM 2014	..the attraction and adoption of virtual-reality exposure therapy still requires controlled research to determine how and to what extent this approach may break down barriers to PTSD care and enhance treatment dissemination. It also requires research to determine best practices for training providers to use and to implement the technology in DoD and VA settings.	219	P
213	IOM 2014	Although much of the content in the new mobile applications is similar to that on existing informational webpages, such as AfterDeployment and the VA's National Center for PTSD, research on their use and effectiveness in a mobile format is still needed.	220	P
214	IOM 2014	As mentioned in the section on training, DoD and VA are funding a few studies to assess the use of virtual reality for training (see also Appendix E). Such prototype systems, designed for interacting with highly realistic and natural-language-capable virtual patients, do not yet have an evidence base for their effectiveness for training.	221	P

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
215	VA/DoD MDD CPG	Yet we know little about how best to augment clinical care and improve outcomes using technology, including smartphones, social media, or computerized therapies.	13	D
216	VA/DoD MDD CPG	As a larger body of evidence exists for group CBT compared to other group psychotherapies, there is a need for more evidence for other types of group therapies.	37	D
217	VA/DoD MDD CPG	The current findings warrant further research on physician-delivered behavioral prescriptions for depression that could be effective, and, therefore, be expanded in a number of ways to include interactive websites, DVDs, and other media.	58	D
218	H.R. 3304 (2014)	Sec. 704. Pilot program on investigational treatment of members of the Armed Forces for traumatic brain injury and post-traumatic stress disorder. "Establishes a process for randomized placebo- controlled clinical trials of investigational treatments of TBI or PTSD for service members in health care facilities other than military treatment facilities."	P 123 - 124	P
Adverse Events/Harms/Other Outcomes				
218	APA 2016	There was insufficient/very low strength of evidence for the critical outcome of serious harms. The panel found no other interpretable evidence of serious harms [For CBT, CPT, CT, EXP, BEP, EMDR, NET, relaxation, Topiramate, EXP vs. relaxation, EXP vs. cognitive restructuring, CBT vs. relaxation, Seeking Safety vs. Active Controls, Venlafaxine ER vs. Sertraline]	51-54	P
220	APA 2016	The panel is unable to evaluate benefits vs. harms/burdens (Relaxation).	55	P
221	APA 2016	…other important outcomes, such as PTSD remission (absence of symptoms) and loss of PTSD diagnosis, were not always measured or reported.	93	P
222	APA 2016	Important "patient-centered" outcomes, such as quality of life and functional impairment were also infrequently studied or reported.	93	P
223	APA 2016	…although the pharmacotherapy trials typically reported information on side effects and serious harms, the psychological intervention studies usually did not.	93	P
224	APA 2016	…psychometrically sound measures of adverse effects should be included in future RCTs and reported in subsequent reports. Such measures should include assessments of suicidal ideation, self-injurious behaviors, hospitalizations, and other important adverse outcomes.	93	P

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
225	APA 2016	…other important outcomes, such as PTSD remission (absence of symptoms) and loss of PTSD diagnosis, were not always measured or reported.	93	P
226	APA 2016	Important "patient-centered" outcomes, such as quality of life and functional impairment were also infrequently studied or reported.	93	P
227	AHRQ 2013	…evidence for improving other outcomes of interest—anxiety symptoms, quality of life, disability or functional impairment, or return to work or active duty—was generally insufficient (often with no trials reporting those outcomes).	24	P
228	AHRQ 2013	Evidence was insufficient for other outcomes of interest, usually because no trials making the comparison reported those outcomes.	24	P
229	AHRQ 2013	…evidence in these studies was insufficient to determine efficacy for achieving loss of PTSD diagnosis for any of the pharmacological treatments because studies generally did not report it as an outcome. Similarly, evidence for improving other outcomes of interest was usually insufficient (often with no trials reporting those outcomes).	27	P
230	AHRQ 2013	…evidence was insufficient to determine comparative rates of adverse events for various interventions.	29	P
231	AHRQ 2013	For psychological treatments, the vast majority of studies reported no information about adverse effects. With such a small proportion of trials reporting data, evidence was insufficient to draw conclusions about withdrawals due to adverse events, mortality, suicide, suicidal ideation, self-harmful behaviors, or other specific adverse events.	29-30	P
232	AHRQ 2013	For pharmacological treatments, very few studies reported any information about mortality, suicide, suicidal ideation, or self-harmful behaviors (insufficient SOE). For most other adverse effects, risk of bias of included studies, inconsistency or unknown consistency, and lack of precision all contributed to the insufficient SOE determinations.	30	P
233	AHRQ 2015	Across all comparisons of interventions, major research gaps pertain to information about the comparative risk of harms and patient- relevant outcomes such as functional capacity and quality of life.	8	D

No.	Source	Identified Gap	Page No.	PTSD (P), Depression (D), or Both (B)
234	AHRQ 2015	The evidence is insufficient to form conclusions about differences in serious adverse events, such as suicidal ideas and behavior.	9	D
235	AHRQ 2015	The evidence was insufficient to draw conclusions about differences in functional capacity, quality of life, overall risk of adverse events, suicidal ideas or behaviors, or overall risk of serious adverse events.	23	D
236	AHRQ 2015	Across all comparisons of interventions, major research gaps pertain to information about patient-centered outcomes, such as functional capacity and quality of life, and the comparative risk of harms.	29	D
237	AHRQ 2015	Future studies should assess remission, response to treatment, quality of life, functional capacity, suicidal ideas and behaviors, and adverse events using standardized measures to allow for more direct comparisons across studies using the same or similar SGAs and psychological interventions. These same deficiencies in the literature extend to the comparative effectiveness of SGAs and both psychological and CAM interventions for treating MDD as a function of depression severity.	29	D
238	S. 2410 (2015)	Sec. 524. Comptroller General of the United States report on the impact of certain mental and physical trauma on discharges from military service for misconduct	P 104-105	B

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Appendix B: Authoritative Source Research Priorities Scan

Source	Identified Priorities/Recommendations	Page No.	PTSD (P), Depression (D), or Both (B)
Basic research- mechanisms, biomarkers, imaging, genomics, etc.			
NRAP	…accelerate discovery of underlying mechanisms and rapidly translate this understanding into actionable tools for prevention, early diagnosis, and better treatment.	3	P
NRAP	Build new tools and technologies to understand the underlying mechanisms of PTSD, TBI, suicide, and other conditions.	3	B
NRAP	Replicate and confirm emerging data on promising biomarker candidates and other diagnostic tools for PTSD, including genome- wide associations, plasma molecules, and methylation patterns.	6	P
NRAP	Optimize risk and resilience screening tools and test new PTSD prevention and treatment interventions that target underlying mechanisms and causal pathways.	6	P
NRAP	…establishing surrogate and clinically actionable biomarkers for early PTSD diagnosis and treatment effectiveness.	19	P
NRAP	…pursue the development of therapeutics targeting biomarkers and mechanisms uncovered in the course of research as well as assess the utility of repurposed or off-label treatments.	20	P
NRAP	…new partnerships will be pursued to aid in the identification of potential pharmacological targets for the prevention and treatment of PTSD.	20	P
NRAP	Fund new exploratory research on structural and/or functional changes in the brain immediately following trauma exposure to identify early changes indicative of the future development of PTSD and comorbidities.	22	P
NRAP	Review emerging genomic and molecular findings on causal pathways and changes that contribute to PTSD and perform critical replication of preliminary findings.	22	P
NRAP	Establish preliminary sex-specific risk allele biomarkers for PTSD to enrich and enhance risk prediction measures. This will aid in the identification of new targets for the development of prevention and treatment interventions.	22	P
NRAP	Disseminate findings (e.g., peer-reviewed publications, conferences, and briefings) from at least three genome-wide association studies with military, Veteran, or other high-risk cohorts to determine genetic patterns associated with PTSD and comorbidities.	23	P

Source	Identified Priorities/Recommendations	Page No.	PTSD (P), Depression (D), or Both (B)
NRAP	Identify and confirm whether potential biomarkers have clinical value for PTSD by utilizing studies that contain phenotypic and genetic data.	23	P
NRAP	Establish a validated PTSD assay from the DoD's systems biology effort for objective diagnosis and monitoring of treatment response.	23	P
NRAP	Identify brain circuitry changes related to treatment response and disseminate findings (e.g., peer-reviewed publications, conferences, and briefings) from at least two translational trials.	23	P
NRAP	Leverage results from biomarker research (e.g., data emanating from CAP-funded projects) and embed follow-on biomarker studies in select clinical trials to explore biological changes or markers that are associated with treatment response to better match individuals to treatments.	23	P
IOM 2013	Studies to determine whether biologic markers can help in predicting outcomes?	138	B
IOM 2013	Studies to elucidate how brain imaging can provide information about outcomes?	138	B
IOM 2013	Studies to determine if specific symptomatic markers predict the outcome of PTSD?	138	P
IOM 2013	Comparative-effectiveness trials to determine the effectiveness of group vs individual treatments, duration of psychotherapies, dose and duration in the use of SSRIs, and combination treatments.	254	B
IOM 2013	Studies of the effectiveness and efficacy of treatment interventions in producing improved desired outcomes in veterans and service personnel.	254	B
IOM 2014	Increasing understanding of basic biological, physiological, psychological, and psychosocial processes that lead to the development of more and better treatments for PTSD.	29, 245	P
IOM 2014	Developing markers to identify better approaches for PTSD prevention, diagnosis, and treatment.	29, 245	P
IOM 2014	Support neurobiology research that might help translate current knowledge of the neurobiology of PTSD to screening, diagnosis, and treatment approaches and might increase understanding of the biologic basis of evidence-based therapies.	36	P

Source	Identified Priorities/Recommendations	Page No.	PTSD (P), Depression (D), or Both (B)
Treatment – Overall/Combination			
NRAP	Continue research on the safety and efficacy of medications, psychotherapeutics, and combination treatments targeting underlying mechanisms of PTSD and comorbidities.	23	P
NRAP	Disseminate findings (e.g., peer-reviewed publications, conferences, and briefings) from translational trials that are targeting either (1) a putative mechanism in PTSD with the novel use of medications (e.g., CRF [corticotropin releasing factor] antagonist and mifepristone) or (2) comorbidities with PTSD.	23	P
NRAP	Disseminate findings (e.g., peer-reviewed publications, conferences, and briefings) from randomized controlled trials aimed at improving and optimizing PTSD treatment (e.g., psychotherapeutic and combination psychotherapeutic and pharmacological treatment protocols, including those for comorbid conditions).	23	P
IOM 2013	RCTs to determine the efficacy of interventions that do not yet have a strong evidence base, including telehealth mental-health care delivery, Internet-based clinician training and treatment interventions, complementary medicine approaches (such as yoga), staged and stepped care, and TBI treatments recommended by VHA guidelines.	254	B
IOM 2014	Developing and rigorously assessing new interventions and delivery methods (pharmacological, psychological, somatic, technological, and psychosocial) for both PTSD and comorbidities.	29, 245	B
IOM 2014	Study the efficacy of treatment.	35	P
Treatment – Psychological			
Treatment-CAM/Somatic Treatments			
Treatment – Pharmacological			
Comorbidity			
NRAP	…examine ways to optimally treat comorbid conditions (e.g., integrative versus sequential treatments).	19	B
IOM 2013	Studies with better exposure data, and objective diagnostic tests or biomarkers for mild TBI and PTSD are needed to improve our understanding of those highly comorbid conditions.	138	P

Source	Identified Priorities/Recommendations	Page No.	PTSD (P), Depression (D), or Both (B)
IOM 2013	Studies to identify what modifications, if any, need to be made in the current evidence-based treatment recommendations for each condition for the management of comorbid conditions.	254	B
IOM 2014	Encourage research to create an evidence base to guide the integration of treatment for comorbidities with treatment for PTSD. PTSD treatment trials should incorporate assessment of comorbid conditions and the value of concurrent and sequential care.	36	P
Effectiveness/Implementation/Health Services (will be some cross-over into program evaluation)			
NRAP	…facilitate the development of more personalized treatments; that is, individually tailored interventions with measurable responses.	19	P
NRAP	Continue research to improve and optimize the effectiveness and delivery of current evidence-based prevention and treatment interventions (including psychotherapies, combination therapies, and adjunctive treatments) and available medications for PTSD and comorbidities.	22	P
NRAP	Conduct research to optimize psychotherapeutic intervention approaches (e.g., repackaging, shortening, or integrating them) to achieve more rapid and long-lasting benefit.	23	P
NRAP	…determining how to enhance treatment-seeking behavior and reduce barriers to care, as well as utilizing standardized training procedures for professionals to implement evidence-based interventions with fidelity in health care systems and evaluate on an ongoing basis.	24	P
IOM 2013	The committee also recommends that the two departments ensure that treatment offerings are aligned with the evidence base, particularly before national rollouts, and that all patients consistently receive first-line treatments as indicated.	22, 255	B
NRAP	Enhance current PTSD evidence-based treatment delivery to be more brief, durable, and efficacious in treating service members, Veterans, and their family members, including individuals with multimorbidites, including substance abuse.	6	P

Source	Identified Priorities/Recommendations	Page No.	PTSD (P), Depression (D), or Both (B)
IOM 2013	The committee recommends that the DoD and the VA conduct systematic assessments to determine whether screening and treatment interventions are being implemented according to clinical guidelines and department policy. Data systems should be developed to assess treatment outcomes, variations among treatment facilities, and barriers to the use of evidence-based treatment.	23, 256	B
IOM 2013	The committee recommends that the DoD continue to promote an environment that reduces stigma and encourages treatment for mental-health and substance-use disorders. The committee recommends that the department undertake a systematic review of its policies regarding mental-health and substance-abuse treatment with regard to issues of confidentiality and the relation between treatment-seeking and military advancement. The committee recommends that the department regularly issue reports describing actions taken with regard to its policies and procedures to determine progress in this area.	26	B
IOM 2013	The committee recommends that the DoD, the VA, and other federal agencies fund research to determine whether culturally sensitive clinicians and treatment approaches improve retention in care and improve clinical outcomes.	27	B
IOM 2013	The committee recommends that the DoD and the VA consider ways to remove barriers and improve women's access to and use of health care in their systems. The two departments should examine issues related to women's circumstances and stressors—such as military workplace stress, sexual harassment and assault, posttraumatic stress disorder, and premilitary trauma—in an effort to reduce disparities and to provide health care that is sensitive to their needs and preferences.	27	B
IOM 2013	Research to assess consumer (patient and family) preferences for educational materials that explain the different evidence-based treatments that are available; such studies should determine the most effective formats for facilitating informed decision making.	254	B
IOM 2014	As innovative programs and services are developed and piloted, they should include an evaluation process to establish the evidence base on their efficacy and effectiveness.	27	B

Source	Identified Priorities/Recommendations	Page No.	PTSD (P), Depression (D), or Both (B)
IOM 2014	Increasing knowledge of how to overcome barriers to implementation, dissemination, and use of evidence- based treatments to improve their accessibility, availability, and acceptability for patients and their families.	29, 245	B
IOM 2014	Identifying effective care models, establishing evidence-based practice competences, and developing methods to enhance effective training in and implementation and dissemination of them.	29	B
IOM 2014	Institute programs of research to evaluate the efficacy, effectiveness, and implementation of all PTSD screening, treatment, and rehabilitation services, including research in different populations of active-duty personnel and veterans; the effectiveness of DoD prevention services should also be assessed.	35	P
IOM 2014	Improving the quality of mental health services, identifying effective care models, establishing evidence-based practice competences, and developing methods to enhance effective training in and implementation and dissemination of those competencies.	245	P
Screening/Diagnosis			
IOM 2013	The committee recommends that the DoD and the VA select instruments and their thresholds for mental health screening and assessment in a standardized way on the basis of the best available evidence.	22, 255	B
IOM 2013	Studies to determine how the current distinction between diagnosis and symptoms might predict outcome? The line between a diagnosis of PTSD and PTSD symptoms is not well validated. Can longitudinal studies determine a threshold and a constellation of symptoms that point clearly to a diagnosis?	139	P
IOM 2013	Studies of the psychometric properties of screening and assessment instruments to determine appropriate screening and diagnostic thresholds specifically for VA and DOD populations…	254	B
S. 1356 (2016)	Sec. 593. Report on preliminary mental health screenings for individuals becoming members of the Armed Forces. (b.1.) Recommendations with respect to establishing a secure, electronically-based preliminary mental health screening of new members of the Armed Forces.	833	B

Source	Identified Priorities/Recommendations	Page No.	PTSD (P), Depression (D), or Both (B)
Specific populations, subgroups, and precision medicine (Context, setting , culture, gender, racial/ethnic minorities, trauma type)			
IOM 2014	Understanding the heterogeneity of PTSD presentations and predicting responses to treatment for them in different populations and at different times in the course of the disorder.	29, 245	P
Methodology			
Delivery/Technology			
NRAP	Continue research to improve and optimize the effectiveness and delivery of service modalities for PTSD and comorbidities (e.g., telemedicine and web-based).	23	P
IOM 2014	The use of telehealth may improve access to care for service members and veterans, but pilot programs and studies need to be conducted to support their effectiveness and optimal use.	27	B
IOM 2014	Support research in both DoD and VA that investigates emerging technologic approaches (mobile, telehealth, Internet-based, and virtual reality) that may help to overcome barriers to awareness and to the accessibility, availability, and acceptability of and adherence to evidence-based treatments; disseminate the outcomes to a wide audience.	36	P
H.R. 3304 (2014)	Sec. 702. Mental health care treatment through telemedicine. Includes "a report on the use of telemedicine to improve the diagnosis and treatment of post-traumatic stress disorder, traumatic brain injuries, and mental health conditions."	121-122	B
S. 2943 (2017)	Sec. 705. Enhancement of use of telehealth services in military health system. (A) to improve access to primary care, urgent care, behavioral health care, and specialty care.	348-350	B
Adverse Events/Harms/Other Outcomes			
IOM 2013	Studies on cost-effectiveness focusing on the signature wounds of TBI, PTSD, and major depression should continue to be funded and conducted; the implications of prior cost effectiveness studies, where knowledge is sufficiently developed, guide the evolution of policy inside the VA and elsewhere.	423	B

Appendix C: Initial Refined List of Research Gaps

Initial Refined List of Research Gaps

PTSD (n=12)

- Combination treatments/common components of treatments for PTSD
- Frequently used interventions for PTSD with inconsistent or small evidence base
- PTSD treatment mechanisms
- PTSD biomarkers
- Comparative effectiveness of treatments for PTSD
- Treatment of PTSD in women and minorities: needs and access
- Impact of patient preferences on treatment outcomes/adherence for PTSD
- Technology solutions for improving care for PTSD
- Alternative delivery of established treatments for PTSD
- Novel psychosocial treatment approaches for PTSD
- Effectiveness of existing treatment programs for PTSD
- Integrating treatments for PTSD comorbidities and complex patients

Depression (n=9)

- Combination treatments/common components of treatments for depression
- Frequently used interventions for depression with inconsistent or small evidence base
- Comparative effectiveness of treatments for depression
- Treatment of depression in women and minorities: needs and access
- Impact of patient preferences on treatment outcomes/adherence for depression
- Technology solutions for improving care for depression
- Alternative delivery of established treatments for depression
- Somatic treatments for depression: feasibility and safety
- Effectiveness of existing treatment programs for depression

Appendix D: Final Refined List of Research Gaps

Final Refined List of Research Gaps

PTSD (n=10)

- Conduct head-to-head comparative effectiveness trials for PTSD that include better controls (20.67)
- Conduct well-controlled trials to examine integrated approaches to care for PTSD patients with multi-morbidity and psychosocial complexities (20.67)
- Examine the efficacy or effectiveness of combined treatment components for PTSD (20.33)
- Determine how sex and racial differences impact on prevalence of PTSD and impact on treatment (20.25)
- Examine efficacy of novel pharmacotherapies for PTSD based on emerging basic science. (20.17)
- Conduct research to evaluate the effectiveness of widely-used PTSD treatment programs with inconsistent or limited evidence. (18.75)
- Improve understanding of possible PTSD biomarkers, taking into account limitations in specificity, or predisposing or environmental factors such as early childhood trauma. (18.08)
- Conduct research to improve implementation, delivery, and reach of tele- and mobile health interventions for PTSD in the AD population. (17.92)
- Conduct well controlled trials for mindfulness based approaches for PTSD. (17.83)
- Conduct well controlled trials on non-standard psychological treatments for PTSD (16.67)

Depression (n=6)

- Conduct head-to-head comparative effectiveness trials for depression that include better controls (20.67)
- Determine how sex and racial differences impact prevalence of depression and impact on treatment (20.25)
- Conduct research to evaluate the effectiveness of widely-used depression treatment programs with inconsistent or limited evidence. (18.75)
- Conduct research to examine the best approach for delivering repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant depression in the military. (18.33)
- Conduct research to improve implementation, delivery, and reach of tele- and mobile health interventions for depression in the AD population. (17.92)
- Examine benefits and weaknesses of interventions for depression with a limited evidence base being used in the health care system. (17.75)

Appendix E: In-Progress Research Investments

Study Title	PI	Sponsor Institution	Populations	Interventions	Comparators	Outcomes	Objectives	Period of Performance	Study Status/Progress

Protected Information: 116 Entries

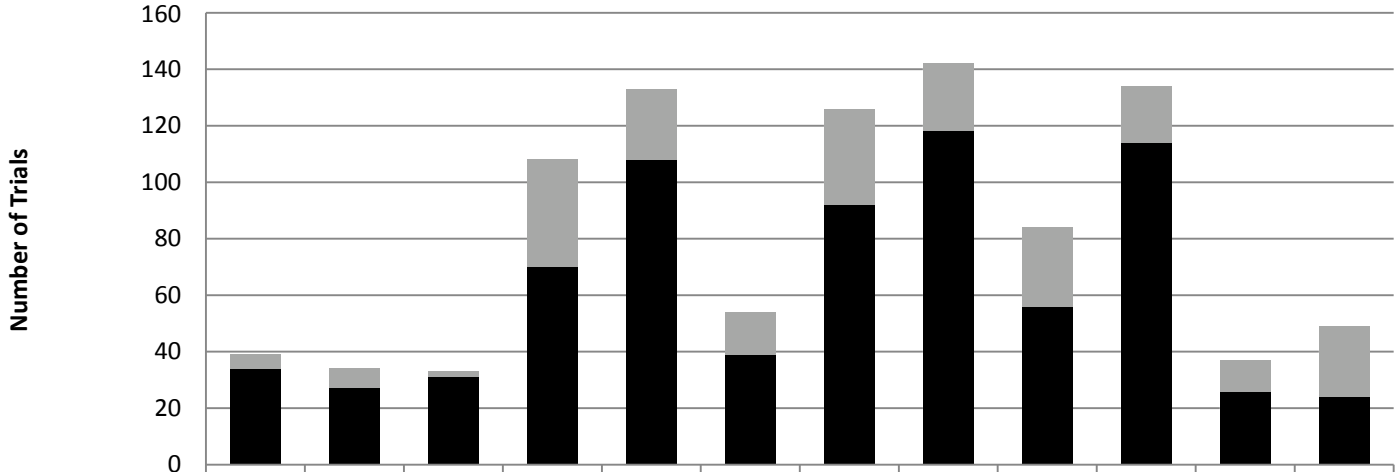
Appendix F: Current PTSD and Depression Research from clinicaltrials.gov

Clinical Trials that Address Posttraumatic Stress Disorder (PTSD) and Depression Research Gaps: Summary of Findings

EXSUM: The KT PH Work Group identified 12 broad research gaps (across PTSD and depression) and requested an assessment of how current research aligns to gaps (KT Element 1: Needs and Gaps Assessment). This report summarizes the results of this assessment using the National Institutes of Health's (NIH) clinicaltrials.gov website.

Subject matter experts in the fields of psychology, public health, medicine, and epidemiology abstracted and reviewed 186 PTSD and 841 depression studies. Subject matter experts reviewed studies against key variables (e.g., co-morbid, combination, modular) that align to domains within the pre-determined research gaps. 166 PTSD and 462 depression studies aligned to at least one of the pre-specified research gaps. Investments varied across gaps, with some gaps producing as many as 140 studies, while others as few as 30. See Table 1.

Table 1: Randomized Clinical Trials Across the 12 Pre-identified Research Gaps



	1. PTSD: Combined Tx	2. PTSD: CAM	3. PTSD: Comp Effectiveness	4. All: Women and Minorities	5. All: Telehealth	6. PTSD: Comorbidities	7: Depression: CAM	8. PTSD: Novel Tx	9. All: Implementation	10: Depression: Comp Effectiveness	11: Depression: Somatic	12. All: Biomarkers and Mechanisms
Other clinical trials	5	7	2	38	25	15	34	24	28	20	11	25
RCTs	34	27	31	70	108	39	92	118	56	114	26	24

Findings provide an indicator of the nature of research investments according to the pre-determined gap. For example, pre-identified gaps that have numerous investments addressing the gap, may not be as wide a gap as initially hypothesized; whereas pre-identified gaps that have few investments may continue to be a gap that needs to be addressed. The annotated database generated to produce this report formalizes an approach for informing the mapping of research investments to known gaps and may serve as an enduring updatable resource for executing this task in the future.

Task: To identify ongoing research catalogued in U.S. National Institutes of Health's (NIH) ClinicalTrials.gov database to determine alignment to 12 pre-specified (by the PH KT Workgroup) posttraumatic stress disorder (PTSD) and depression research gaps.

Method

- An advanced search was performed to identify PTSD and depression studies registered in ClinicalTrials from January 1, 2015 to November 15, 2016.
  - PTSD: Conditions = "PTSD" and First Received From = "01/01/2015"
  - Depression: Conditions = "depression" and First Received from = "01/01/2015"
- Studies (186 = PTSD, 841 = depression) were downloaded into an excel database and additional variables (e.g., Co-Morbid; Combination, Modular) were added to facilitate additional abstractions and review. To ensure that our methods were sound, a test abstraction and review were conducted for 5 studies. The test abstraction and review produced several observations and insights that informed variable revisions related to improving the efficiency of the analysis. Additionally, guidelines for abstraction as well as operational definitions were developed to facilitate review reliability. Note. The team iteratively modified some operational definitions throughout the course of abstraction and review.
- Seven subject matter experts (education: masters-level and above) in the fields of psychology, public health, medicine, and epidemiology were trained in task execution. Subject matter experts conducted abstractions and completed reviews for a pre-determined number of assigned studies.
- An eighth subject matter expert conducted reliability checks (to ensure coding was consistent and met operational definitions) at the completion of each day's work. Additionally, the subject matter expert compiled, aggregated, and analyzed data. Note. During data compilation and aggregation, several studies were removed based on the following decisions:
  - Studies classified as terminated, withdrawn or suspended. Reasoning: These studies do not represent current/actual investments.
  - Studies referencing conditions that are not mental health (e.g. Respiratory Depression, Cardiovascular Depression)
  - Studies examining disease conditions, such as pain, seizures, neonatal asphyxia, respiratory tract infections, down syndrome, or mental health/depression among providers of medical support, etc without a co-morbid mental health condition.

Note. Key search words queried (e.g., biomarkers, Orexin, adverse events) to facilitate assessment of pre-determined gaps and produce findings at a granular level, key search words were used.

- Findings for each pre-determined gap were summarized.

Assumptions

1. **Clinicaltrials.gov may not include all research investments for a particular condition.** Although researchers are encouraged to register their studies on this website, it is not a funding requirement. Consequently, the website may not capture all clinical trial research investments.
2. **Studies that use less rigorous experimental designs may not provide evidence in support of addressing a gap.** Different study designs (ranging from uncontrolled observational studies to tightly controlled, blinded, randomized) are registered, providing wide variability in research investments across PTSD and depression. Given the costs and time needed to execute Randomized Controlled Studies (RCTs), it could be hypothesized that the more RCTs per gap, the greater the investment. Therefore, the total number of RCTs have been presented for each research gap in addition to total numbers of studies.
3. **Some entries may not be unique.** Each study is treated as a unique registration for the purposes of our analysis. However, certain studies are registered multiple times, and thus may inflate the perceived investment of a research gap. It should be noted that these observations were infrequent and we expect their potential to skew findings to be minimal.
4. **The initial data query may not account for all PTSD and Depression studies.** The initial query was conducted to identify all clinical trials matching the condition "PTSD" or "Depression" (Time frame: January 1, 2015-November 15, 2016). Although we believe this was a comprehensive approach to identify studies, the query may miss studies examining PTSD and Depression in which the "Condition" field was not completed.
5. **Interrater variability may impact findings.** The report was generated through an exercise where individual reviewers read each trial and determined whether the trial met certain standards. Each reviewer was highly educated (Masters level of higher) and provided with clear operational definitions (Appendix A). Despite these efforts, some subjectivity may occur due to two reviewers interpreting different standards for mapping trials into categories.

Findings: The following sub-sections provide descriptive data for each of the pre-identified topics.

1. **Combined or modified treatment components for PTSD (39 Clinical Trials)**
   - 87% (n=34/39) of the studies identified represented RCTs
   - 79% (n=31/39) studies represented some sort of Combined Intervention
   - 20% (n=8/39) studies represented a Modular component
   - There were no studies that indicated a transdiagnostic approach

2. **Complementary and Alternative Medicine (CAM) approach for PTSD (34 Clinical Trials)**
   - Nearly 79% (n=27/34) of all studies were RCTs
   - A military population was involved in 20% (n=7/34) of the studies. Veterans populations participated in 35% (n=12/34) of the studies.
   - 20% (n=7/34) studies reported some sort of co-occurrence/comorbidity with PTSD
     - 28% (n=2/7) of these were comorbidities with mild TBI

  - 42% (n=3/7) of these were co-occurrences with Depression
- The CAM approaches focused on the following approaches:
  - 17% (n=6/34) studies on Mindfulness
  - 20% (n=7/34) studies on using Yoga (typically Sudarshan Kriya Yoga)
  - 9% (n=3/34) studies on Acupuncture
  - 6% (n=2/34) studies on Music
  - 6% (n=2/34) studies using Equine (Equine Assisted Therapies or Equine Assisted Activities)
    - Only 3 of the studies had a drug component in addition to CAM
  - 66% (n=2/3)of these studies involved use of some form of Cannabis
  - 33% (n=1/3) Remaining study involved Ketamine

3. **Comparative Effectiveness Studies for PTSD Treatment (33 Clinical Trials).** Note. Comparative Effectiveness Operational Definition: The direct comparison of existing interventions (intervention vs intervention) to determine which intervention has a larger effect. Studies that compare an intervention to general education, treatment as usual, or placebo will not be endorsed as comparative effectiveness. An example of Comparative Effectiveness for PTSD is: Prolonged Exposure Therapy vs Cognitive Processing Therapy.
   - 96.6% (n =28/29) of RCTs for PTSD Comparative Effectiveness studies
     - Of the RCTs for PTSD Comparative Effectiveness studies, 32.1%% (n=9/28) studies are combination studies
     - Of the RCTs for PTSD Comparative Effectiveness studies, 3.6%% (n=1/28) studies compare a pharmacological intervention to a psychosocial treatment
       - Of the RCTs for PTSD Comparative Effectiveness studies comparing a pharmacological intervention to a psychosocial treatment, 3.6% (n=1/28) assessed side effects as a primary/secondary outcome
       - Of the RCTs for PTSD Comparative Effectiveness studies comparing a pharmacological intervention to a psychosocial treatment, 3.6% (n=1/28) assessed adverse events as a primary/secondary outcome
   - 10.3% (n=3/29) of PTSD Comparative Effectiveness studies include a pharmacological intervention
     - Of PTSD Comparative Effectiveness studies that include a pharmacological intervention, 33.3%% (n=1/3) assessed differential effects of long term treatment as a primary/secondary outcome
   - 24.1%% (n=7/29) of PTSD Comparative Effectiveness studies include military populations
   - 37.9%% (n=11/29) of PTSD Comparative Effectiveness studies include veteran populations
     - Of PTSD Comparative Effectiveness studies, 0% (n=0 or unspecified/29) include military and veteran populations that assess different types of trauma as a primary/secondary outcome
   - 50% (n=14/28) of PTSD Comparative Effectiveness studies do not include military or veteran populations

- 24.1%% (n=7/29) of PTSD Comparative Effectiveness studies focus on co-morbid populations
  - Of PTSD Comparative Effectiveness studies that focus on co-morbid populations, 57.1% (n=4/7) are conducted with military and veteran populations
  - Of PTSD Comparative Effectiveness studies that focus on co-morbid populations, 14.3%(n=1/7) include PTSD and Depression
    - Of PTSD Comparative Effectiveness studies for PTSD, 6.9%% (n=2/29) use a SMART Trial Methodology

4. Women and minorities (108 Clinical Trials)

- 7% (n=12)of PTSD studies focus on women; 4% (n=7)of PTSD studies focus on minorities 12/186
  - Of PTSD studies that focus on women, 25% (n=3/12) of studies were conducted with a military and/or veteran population
  - Of PTSD studies that focus on minorities, 29% (n=2/7)of studies were conducted with a military and/or veteran population
  - Of depression studies that focus on women, 8% (n=1/12) of studies were conducted with a military and/or veteran population
  - Of depression studies that focus on minorities, 0% of studies were conducted with a military and/or veteran population
- 32% (n=31) of depression studies focus on post-partum and/or perinatal conditions (note-when searching look to see if this is condition or primary/secondary outcome)
- 0% (n=0) of PTSD and depression studies that focus on women assess deployment as a primary or secondary outcome

5. Telehealth (133 Clinical Trials)

- 14.0% (n=133/953)of PTSD and depression studies include a telehealth component; 11.3% (n=21/186) of PTSD studies include a telehealth component; 14.2% (n=115/807) of Depression studies include a telehealth component
  - Of the PTSD and depression studies that include a telehealth component, 4%(n=6/133) focus on military populations, 6.8% (n=9/133) focus on veteran populations
  - Of the PTSD and depression studies that include a telehealth component, 56.4%(n=75/133) focus on mobile and/or web applications

6. Comorbidities for PTSD (54 Clinical Trials)

- 29.0% (n=54/186)of PTSD studies focus on comorbid conditions
  - Of the PTSD studies that focus on comorbid conditions, 7.4%(n=4/54) assess combination treatments
  - Of the PTSD studies that focus on comorbid conditions, 5.6%(n=3/54) assess modular treatments
  - Of the PTSD studies that focus on comorbid conditions, 31.5%(n=17/54) include a military and/or veteran population

7. **Complementary and Alternative Medicine (CAM) approach for Depression (126 Clinical Trials)**
   - 15.6%(n=126/807) of depression studies that examine CAM treatments
     - Of the depression studies that examine CAM treatments, 13.5%(n=17/126) include combination treatments
     - Of the depression studies that examine CAM treatments, 5.6%(n=7/126) include modular treatments
     - Of the depression studies that examine CAM treatments, 3.2%(n=4/126) of CAM treatments were identified as augmentation treatments
     - 26.2%(n=33/126) of depression studies that examine CAM treatments assess quality of life as a primary/secondary outcome
     - 6.3%(n=8/126) of depression studies that examine CAM treatments assess treatment adherence as a primary/secondary outcome

8. **Novel Therapeutics based on established research for PTSD (142 Clinical Trials)**
   - 76 %(n=142/186) of PTSD studies that assess novel treatments (note. Key word is novel- this will not be an easy thing to search-and novel is in the eye of the beholder)
   - 6%(n=8/142) of PTSD studies that assess adjunctive treatments
   - 22% (n=31/142) of PTSD studies that assess combination treatments
     - Of PTSD studies that assess combination treatments, 26%(n=8) examine an adjunctive treatment

9. **Implementation (84 Clinical Trials)**
   - 66% (n=56/84) of these studies are RCTs
   - Looking broadly at all studies, 11%(n=21/186) of PTSD and 8% (n=68/807) depression studies that focus on Implementation and dissemination
   - 4% (n=3/84) of implementation and dissemination contain key words ("system", "health services") and upon review, suggest assessment of a system of care

10. **Comparative effectiveness for depression treatment (134 Clinical Trials)**
    - 85.1% (n =114/134) of RCTs for Depression Comparative Effectiveness studies
      - Of the RCTs for Depression Comparative Effectiveness studies, X% (n=66/134) studies are combination studies
      - Of the RCTs for Depression Comparative Effectiveness studies comparing a pharmacological intervention to a psychosocial treatment, 0% (n=0/134) assessed side effects as a primary/secondary outcome
      - Of the RCTs for Depression Comparative Effectiveness studies, 0% (n=0/134) studies compare a pharmacological intervention to a psychosocial treatment
    - RCTs for Depression Comparative Effectiveness studies assessing a pharmacological intervention (n=36)
      - Of the RCTs for Depression Comparative Effectiveness studies assessing pharmacological, 14% (n=5/36) assessed side effects as a primary/secondary outcome

  - Of the RCTs for Depression Comparative Effectiveness studies assessing a pharmacological intervention, 8% (n=3/36) assessed adverse events as a primary/secondary outcome
  - Of the RCTs for Depression Comparative Effectiveness studies assessing a pharmacological treatment, 0% (n=0) assessed second generation antidepressants as a primary/secondary outcome
  - Of the RCTs for Depression Comparative Effectiveness studies assessing a pharmacological intervention, 14% (n=5/36) assessed remission as a primary/secondary outcome
  - Of the RCTs for Depression Comparative Effectiveness studies assessing a pharmacological intervention, 3% (n=1) assessed responses to treatment as a primary/secondary outcome
  - Of the RCTs for Depression Comparative Effectiveness studies assessing a pharmacological intervention, 8% (n=3) assessed quality of life as a primary/secondary outcome
  - Of the RCTs for Depression Comparative Effectiveness studies assessing a pharmacological intervention, 8% (n=3) assessed suicide behavior as a primary/secondary outcome
  - Of the RCTs for Depression Comparative Effectiveness studies assessing a pharmacological intervention, 0% (n=0) assessed functional capacity as a primary/secondary outcome
- 29.9% (n=40/134) of Depression Comparative Effectiveness studies include a pharmacological intervention
- 0.75% (n=1/134) of Depression Comparative Effectiveness studies include military populations
- 0.75% (n=1/134) of Depression Comparative Effectiveness studies include veteran populations
- 98.5% (n=133/134) of Depression Comparative Effectiveness studies do not include military or veteran populations
- 42.5% (n=57/134) of Depression Comparative Effectiveness studies that focus on co-morbid populations
  - Of Depression Comparative Effectiveness studies that focus on co-morbid populations, 1.5% (n=2/134) are conducted with military and veteran populations
  - Of Depression Comparative Effectiveness studies that focus on co-morbid populations, 0%(n=0/134) include PTSD and Depression
  - Of Depression Comparative Effectiveness studies for PTSD, 3.7% (n=5/134) use a SMART Trial Methodology

11. Somatic therapeutics for depression (37 Clinical Trials)

- 5% (n=37) of depression studies that assess rTMS

- Of the depression studies that focus on rTMS, 8%(n=3) assess safety profile
- Of the depression studies that assess rTMS, 0%(n=0) are conducted with military populations
- Of the depression studies that focus on rTMs for comorbid conditions, 24%(n=9), 0%(n=0) are conducted with treatment resistant depression patients

12. Biomarkers and Mechanisms (49 Clinical Trials)

- 5 %(n=45) of PTSD and Depression studies assess at least 1 biomarker; 1%(n=7) of PTSD and Depression studies assess 2 or more biomarkers
  - Of the PTSD and Depressions studies that assess at least 1 biomarker, 7%(n=3) include cardiovascular risk as a primary/secondary outcome
  - Of the PTSD and Depressions studies that assess at least 1 biomarker, 4%(n=2) include HPA axis as a primary/secondary outcome
  - Of the PTSD and Depressions studies that assess at least 1 biomarker, 9%(n=4) include cortisol as a primary/secondary outcome
  - Of the PTSD and Depressions studies that assess at least 1 biomarker, 18%(n=8) include genetic factors as a primary/secondary outcome
  - Of the PTSD and Depressions studies that assess at least 1 biomarker, 16%(n=7) include life stress as a primary/secondary outcome
  - Of the PTSD and Depressions studies that assess at least 1 biomarker, 9%(n=4) include trauma as a primary/secondary outcome
  - Of the PTSD studies that assess at least 1 biomarker, 4%(n=2) also assess environmental factors
  - Of the PTSD studies that assess at least 1 biomarker, 8% (n=4) map onto the following mechanisms:
    - 50% (n=2) of these studies involve using the drug Suvorexant to suppress the Orexin system.
    - 25% (n=1) of these studies examines the effect of the HPA Axis
    - 25% (n=1) of these studies examines the effect of probiotic supplementation in addition to antidepressants

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Appendix G: DoD Policies Related to PTSD and Depression

ASD (HA) Current Policies that contain PTSD/Depression

#	Effective Date	Policy #	Policy Title	Terms Found
1	9/30/2011	6490.03	Deployment Health	Director, DHCC
2	10/2/2013	6490.12	Mental Health Assessments for Service Members Deployed in Connection with a Contingency Operation	PTSD, Depression
3	10/28/2015	6490.1	Continuity of Behavioral Health Care for Transferring and Transitioning Service Members	Behavioral Health
4	11/20/2014	6490.15	Integration of Behavioral Health Personnel (BHP) Services Into Patient-Centered Medical Home (PCMH) Primary Care and Other Primary Care Service Settings	PTSD, Depression
5	3/4/2013	6490.04	Mental Health Evaluations of the Military of Service Members	Mental Health, Psychiatric
6	2/27/2012	6490.09	DoD Directors of Psychological Health	Psychological Health, Mental Health
7	10/2/2013	6490.05	Maintenance of Psychological Health in Military Operations	Psychological Health
8	8/17/2011	6490.08	Command Notification Requirements to Dispel Stigma in Providing Mental Health Care to Service Members	Mental Health Care, Drug, Alcohol
9	10/2/2013	6025.2	Medical Management (MM) Programs in the Direct Care System (DCS) and Remote Areas	PTSD
10	2/5/2010	6490.07	Deployment-Limiting Medical Conditions for Service Members and DoD Civilian Employees	Mental Health, Psychological Antipsychotics
11	9/11/2015	6490.13	Comprehensive Policy on Traumatic Brain Injury-Related Neurocognitive Assessments by the Military Services	DCoE