# Prioritized Research Gaps Report for Selected Substance Use Disorder Topics Calendar Year 2017

## Psychological Health Center of Excellence

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Defense Health Agency
7700 Arlington Boulevard
Falls Church, VA 20042-5101

**Prepared by the Psychological Health Center of Excellence**

Erin H. Beech, MA, Senior Research Associate
Bradley Belsher, PhD, Chief, Research Translation and Integration
Nigel Bush, PhD, Director, Research, Outcomes and Investigations
Marjorie Campbell, PhD, Associate Director, Research
Daniel Evatt, PhD, Chief, Research Production and Investigation
Fuad Issa, MD, Psychiatrist, Chief, Implementation Section
Marija Kelber, PhD, Research Psychologist
Maria Morgan, PhD, Research Psychologist
Jean Otto, DrPH, MPH, Clinical Research Epidemiologist
Nancy Skopp, PhD, Clinical Research Psychologist
Amanda Edwards-Stewart, PhD, Clinical Research Psychologist
Abigail Wilson, PhD, Clinical Research Epidemiologist
Don Workman, PhD, Clinical Research Psychologist

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Questions or comments about this report may be sent to the point of contact for this report, Marjorie Campbell, PhD, Associate Director of Research, at marjorie.s.campbell.civ@mail.mil or by mail to 7700 Arlington Blvd, Suite 5101, Box #22 (Silver Spring Office), Falls Church, VA 22041.

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## Executive Summary

**Background.** Each year, the Psychological Health Center of Excellence (PHCoE) produces a prioritized research gaps report on selected psychological health topics. PHCoE utilizes a rigorous and efficient methodology that incorporates stakeholder input, comprehensive review of authoritative source reports, in-depth analyses of published research, and scans of in-progress research to generate a prioritized list of research gaps. In 2017, PHCoE identified key research gaps within the domain of substance use disorder (SUD). This report describes the methods used and the results of this effort. The aims of this report are to 1) describe the methodology used for identifying and prioritizing research gaps, and 2) provide stakeholders within the Department of Defense (DoD) with pertinent information that may help prioritize future SUD research investments.

**Methods.** PHCoE convened a Workgroup of 13 members with experience in military psychological health research and delivery of care, epidemiology, and research methodology. After consulting stakeholders for guidance on SUD topic selection, the following three SUD topics were selected: 1) alcohol use disorder (AUD), including co-morbid conditions; 2) prescription opioids; and 3) novel synthetic drugs (NSDs) to include synthetic cannabinoids, synthetic cathinones, novel synthetic opioids, and e-cigarette use. Thirty-six authoritative sources were identified and scanned for statements pertaining to identified research needs. This process produced 175 statements of research needs that were then refined into 97 potential research gaps, including 35 each for AUD and prescription opioids and 27 for NSDs. PHCoE identified the potential gaps most relevant to the military, further reducing the list to 32 (11 each for AUD and prescription opioids and 10 for NSDs). These gaps were assigned to individual Workgroup members, with each member conducting an independent review of the published scientific literature to evaluate the degree to which existing research addressed their gap. Members reconvened and decided to retain, revise, or remove each gap based upon reviews of the literature. This resulted in a final list of 18 gaps: nine for AUD, four for prescription opioids, and five for NSDs. Next, to determine whether any in-progress research investments may address identified gaps, members reviewed the following sources: 1) ongoing research obtained from major military, veteran, and civilian research portfolios; 2) ongoing research documented in www.clinicaltrials.org; and 3) other relevant information (e.g., research committees and conferences). Based upon this review, members discussed the level of ongoing research investment for each relevant gap. Finally, members independently rated each gap using predetermined metrics. The final set of research gaps was prioritized based upon average scores across these ratings.

**Results.** A full list of the prioritized gaps for each SUD topic is presented in Tables 2 to 4 (see pages 9–10) of the report. The following AUD gap received the highest mean rating: *Examine the effects of leadership attitudes, group characteristics, and group identification factors on drinking in the military*. Two prescription opioid gaps received the highest rating: 1) *Investigate treatments for chronic pain other than conventional opioids that reduce risk for prescription opioid use, abuse, and misuse*; and 2) *Investigate the effectiveness of abuse deterrent formulations (ADFs) for preventing/minimizing opioid abuse and misuse, with a focus on military-relevant outcomes (e.g., fitness for duty, medical board)*. The highest rated NSDs gap was: *Develop and/or evaluate interventions to improve provider knowledge and practices regarding screening, diagnosing, and management of patients using synthetic cathinones, synthetic cannabinoids, and novel synthetic opioids (NSOs).*

**Discussion.** Using systematic and transparent methodology, the prioritized research gaps report for selected SUD topics was developed for calendar year 2017. Such a comprehensive approach for identifying research gaps is critical, as the results can inform key decisions on SUD research investment in the DoD and ensure that the most important and relevant research is prioritized. Nonetheless, policy and funding planners should also consider other sources of information that might significantly contribute to funding priorities. The field of SUD research encompasses a broad range of topics, and even a strong effort to prioritize specific research gaps may exclude significant gaps across research domains. The prioritization scores reflect variability in the degree to which published and in-progress research addressed the gaps and the extent to which the gaps are relevant to the military population and to care provided in the Military Health System.

# 1.0 Background

## 1.1 Report Purpose

Health research priority setting — a process that involves experts and stakeholders identifying and prioritizing research gaps — ensures that resources are directed toward studies that have the greatest public health benefit and that maximize the impact of the investments made by funding agencies (Viergever, Olifson, Ghaffar, & Terry, 2010). In 2016, the Psychological Health Center of Excellence (PHCoE) piloted a process to prioritize research on selected psychological health topics relevant to the Department of Defense (DoD). The 2016 effort encompassed the prioritization of research gaps on posttraumatic stress disorder (PTSD) and depression (Psychological Health Center of Excellence, 2017).

In 2017, PHCoE focused the research gap prioritization effort on the broad domain of substance use disorder (SUD). Military Health System (MHS) stakeholder input was solicited with the goal of selecting three of the most relevant SUD topics for a targeted and comprehensive review. This report describes the methodology, results, and challenges of the 2017 effort. The aims of this report are to 1) describe the methodology used for identifying and prioritizing research gaps and 2) provide DoD stakeholders with pertinent information that may help prioritize future SUD research investments.

## 1.2 Selection of SUD Topic Areas

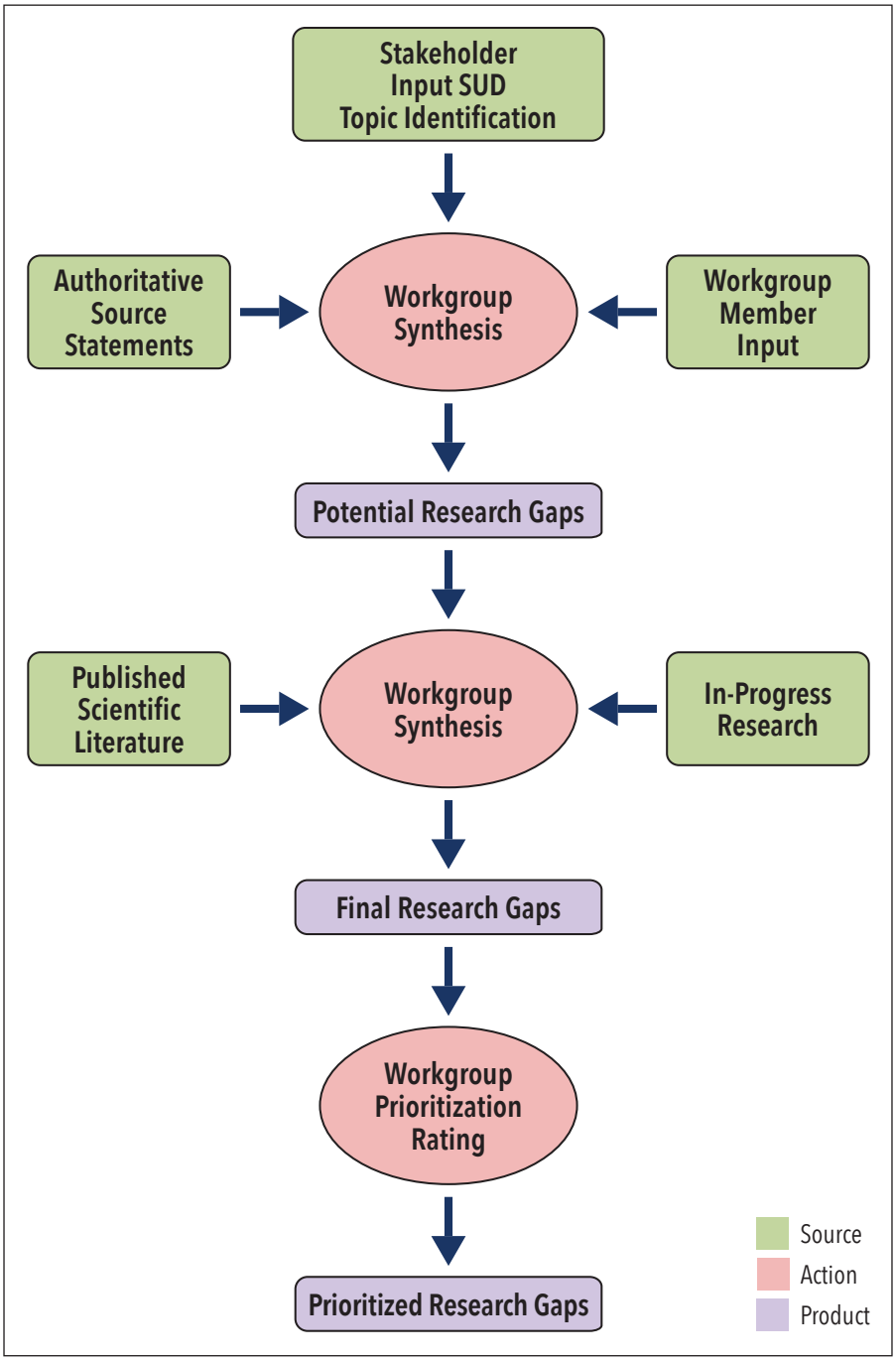
Research topics were selected by considering stakeholders' needs. For the 2017 report, the first task was to consult with the primary end-user of this effort, the Defense Health Agency (DHA) J-9 Research and Development Directorate leadership. PHCoE solicited feedback on the *2016 Research Recommendations Report for Posttraumatic Stress Disorder and Depression in the Military* (Psychological Health Center of Excellence, 2017) for input on methodology and strategy to inform the 2017 research gaps initiative. For guidance on SUD topic selection, stakeholders were consulted from the Addictive Substance Misuse Advisory Committee (ASMAC), which consists of senior subject-matter expert representatives from the Services, Health Affairs, and DHA. Subject-matter experts from the U.S. Army Medical Research and Materiel Command (USAMRMC) were also consulted. Stakeholders identified SUD areas that they perceived as most relevant to Service members' readiness and functioning. To obtain data about substance use and misuse by active-duty Service members (ADSMs), PHCoE also reviewed the preliminary results of the *2015 Department of Defense Health Related Behaviors Survey (HRBS) of Active-Duty Service Members*, as well as relevant PHCoE surveillance data. Based on these sources of information, PHCoE selected the following three SUD topics: 1) alcohol use disorder (AUD), including co-morbid conditions; 2) prescription opioids; and 3) novel synthetic drugs (NSDs) to include synthetic cannabinoids, synthetic cathinones, novel synthetic opioids, and e-cigarette use.

## 1.3 Approach

There are multiple approaches for identifying and prioritizing research gaps, but there is no established best practice. Historical approaches relied almost solely on expert or authoritative opinion collected by workgroups or panels. Recently, more systematic methodologies for prioritizing research involved using systematic reviews (Andrews, 2013; Carey, Yon, Beadles, & Wines, 2012; Robinson et al., 2013; Saldanha, Wilson, Bennett, Nicholson, & Robinson, 2013) and/or stakeholder input (Carey et al., 2010; Carey et al., 2012; Lindson, Richards-Doran, Heath, & Hartmann-Boyce, 2017). While these systematic approaches are optimal ways to inform health care decisions, the time and resources required to undertake such efforts are considerable. Incorporating elements of these prior approaches, PHCoE developed a rigorous yet efficient methodology that utilized stakeholder input to select topics, authoritative source reports to determine research needs, and subject-matter experts to review published and in-progress research in order to estimate the degree to which the research addressed the identified gaps. In 2016, PHCoE piloted these methods on the topics of PTSD and depression, resulting in the *2016 Research Recommendations Report for Posttraumatic Stress Disorder and Depression in the Military* (Psychological Health Center of Excellence, 2017). In 2017, PHCoE expanded on this methodology to synthesize and prioritize SUD research gaps. Specifically, the following steps were taken (see Figure 1 on page 5):

1. Solicited stakeholder input to select SUD topic areas
2. Scanned authoritative sources to identify statements of research needs and used subject-matter experts to refine research needs into potential research gaps
3. Reviewed published and in-progress research to revise or remove potential gaps
4. Derived a final list of gaps and applied metrics to prioritize them by importance to the MHS

**Figure 1. Overview of Research Gap Identification and Prioritization Process**



# 2.0 Method

## 2.1 Procedures

### 2.1.1 Convene the PHCoE Workgroup Members

PHCoE convened 13 Workgroup members who were experts in military psychological health research and health care delivery, psychological health matters, and research methodology. The multidisciplinary Workgroup was composed of clinical and research psychologists, epidemiologists, a psychiatrist, and neuroscientists.

### 2.1.2 Obtain Stakeholder Guidance on Methodology

PHCoE first consulted with DHA J-9 Research and Development Directorate leadership, the primary stakeholder and end-user of the report, to obtain feedback on the *2016 Research Recommendations Report for Posttraumatic Stress Disorder and Depression in the Military* (Psychological Health Center of Excellence, 2017) and guidance on methodology and strategy for the current research gaps initiative. DHA J-9 leadership advised working closely and collaboratively with USAMRMC and considering their research portfolio. DHA J-9 leadership also recommended discussing and reporting on research gaps that recently published research had addressed, and thus were no longer considered gaps. This guidance was incorporated into the methodology discussed below.

### 2.1.3 Solicit Stakeholder Input to Select SUD Topic Areas

PHCoE consulted several diverse sources for guidance on SUD topic selection, including stakeholders from the ASMAC and USAMRMC. Stakeholders identified SUD research areas that they perceived as most relevant to Service members' readiness and functioning.

The ASMAC includes senior military addiction subject-matter experts representing the Services, Health Affairs, and DHA. The ASMAC provided suggestions for topic areas, including AUD as a priority (with an additional suggestion of comorbidities), prescription opioids abuse/misuse, cannabis, nicotine, and synthetic opioids. In addition, ASMAC members recommended reviewing the HRBS and examining public health approaches for SUD topics.

USAMRMC manages an SUD research portfolio for the DoD. USAMRMC suggested further research on opioids, nicotine, marijuana, and alcohol (including relationship to suicide and co-occurring disorders). Additional suggestions included exploring SUD as a cross-cutting disorder, investigating SUD and risky behaviors (including anger), and identifying gaps in research relevant to providers' needs, as driven by practice gaps.

As requested by the ASMAC, the preliminary results of the 2015 HRBS were used as a source of information about SUD patterns among ADSMs. The survey provided information on rates of self-reported prescription drug and substance use, abuse, and misuse, which were considered in subsequent gap analyses. In addition, surveillance results from the PHCoE Performance and Analytics team regarding AUD and prescription opioid use among ADSMs were considered.

The Workgroup members convened, discussed information gathered from these sources, and selected the SUD topics for the 2017 report. All stakeholders identified prescription opioid abuse/misuse and AUD as priority areas; in accordance with suggestions from several stakeholders, alcohol use comorbidities were also included with AUD. This decision aligned with the 2016 research gaps report (Psychological Health Center of Excellence, 2017), which excluded alcohol comorbidities from the PTSD and depression research gaps and recommended that this important topic be included in the SUD gap effort. Finally, NSDs were selected as a topic that captured multiple interests proposed by stakeholders (i.e., cannabis, nicotine, and synthetic opioids). While other potentially important topics were proposed, they were not included for CY 2017 based upon their military relevance, scope of the review, and/or availability of resources required to cover the SUD topics deemed most immediately significant.

### 2.1.4 Scan Authoritative Sources to Identify Statements of Research Needs and Refine them into Potential Research Gaps

PHCoE identified 36 reports from authoritative sources, including the Center for Substance Abuse Treatment, National Institute on Drug Abuse, U.S. Department of Health and Human Services, American Psychiatric Association, RAND Corporation, Centers for Disease Control and Prevention, Institute of Medicine, and U.S. Department of Veterans Affairs (VA)/DoD clinical practice guidelines. These reports were selected based on their SUD focus, scientific merit, and military relevance (see Appendix A on page 16).

PHCoE conducted a document review of these authoritative sources to identify statements of research needs. These statements identified SUD questions that remained unanswered or unknown. PHCoE scanned the authoritative source reports using search terms related to the three SUD topics and reviewed relevant sections for statements that identified

research needs. The review yielded a list of 175 statements of research needs (14 for AUD, 114 for prescription opioids, 12 for NSDs, and 35 for general SUD) (see Appendix B on page 18). Based on independent reviews of the literature and subject-matter expertise, members generated additional statements of research needs that the authoritative sources omitted. Members then discussed these statements, removed duplicate entries, consolidated overlapping constructs, and added relevant content to each statement. Very broad statements were divided into multiple, more specific statements, and very narrow statements were combined into broader statements when appropriate. This process resulted in 97 potential research gaps (35 gaps each for AUD and prescription opioids, and 27 for NSDs) (see Appendix C on page 34). A potential gap is one not yet verified as a gap via the subsequent methodological process.

Next, we selected a subset of potential gaps most relevant to the military by indicating support for inclusion of each of the 97 gaps on a four-point scale (0 = no support and 3 = full support). Each member rated the gaps independently while taking into consideration six criteria related to assessment of military importance (items 1–4, Armed Forces Health Surveillance Center, 2012; items 5–6, Psychological Health Center of Excellence, 2017). When expressing their support for each potential gap, members considered the following:

1. Costs to the MHS (e.g., bed days, clinic visits, and costs of prescriptions, procedures, disability, diagnostics, and prevention)
2. Military operations (e.g., lost duty time and fitness for duty, such as physically and psychologically unfit, medical evacuations, and training cancellations)
3. Compassion to Service members (i.e., responsibility of military leaders to protect the well-being of those they lead, e.g., avoiding preventable illnesses and deaths and considering adverse effects of countermeasures)
4. Political or public concern (i.e., increased public interest due to reports by Veterans, family members, news reporters, activists, politicians, physicians, scientists)
5. Feasibility (i.e., addressing the gap would be achievable in the military environment through relevant research)
6. Impact (i.e., addressing the gap would be important to improving and optimizing clinical care in the military setting)

In order to provide a comprehensive yet reasonable number of research areas, PHCoE agreed a priori to select ten gaps for each topic area. Therefore, we averaged the ratings across all raters to identify the ten top-rated gaps for each topic. Because two AUD and two prescription opioids gaps tied for tenth place, we selected 11 gaps each for AUD and prescription opioids, along with the 10 NSDs gaps (see Appendix D on page 38).

#### 2.1.5 Review Published Scientific Literature to Revise or Remove Potential Gaps

The 32 potential gaps were divided among the Workgroup members, and each member then conducted an independent review of the published scientific literature for their assigned gaps. The objectives of this task were to identify the degree to which existing research findings had sufficiently addressed the potential gap and to clarify and further refine the remaining research gaps. We accomplished this using the following approach for each potential gap: 1) Conducted comprehensive literature searches using key search terms. 2) Reviewed and synthesized the results of these literature searches and conducted additional searches when appropriate. 3) Presented the findings to other members and recommended removal or revision of the gaps. 4) Voted and reached full consensus on removal and revisions of gaps.

A search strategy was developed for each gap, employing a standardized methodology to conduct literature searches on each gap in MEDLINE and the Cochrane Library. Given that the authoritative reports that generated the potential gaps lists had already considered older research, the searches were limited to articles published beginning in 2014, reflecting the current state of the science. Deriving keyword search terms from specific components of each gap resulted in a comprehensive list of alternative search terms and inclusion and exclusion criteria for any phenomenon encompassed in the gap. PHCoE ran searches and reviewed search results, applied the inclusion and exclusion criteria, and generated a final list of relevant articles.

The articles were then reviewed. If the results of the original search were not sufficient, members were encouraged to conduct additional searches of the literature. For these searches, members could consider older research and they could draw on their knowledge of prior research when synthesizing recently published findings. Whenever possible, members limited their assigned full-text literature examinations to systematic reviews. If no systematic reviews were available, members reviewed narrative reviews and individual studies. Members then synthesized the reviewed literature and provided an expert opinion regarding removal or revision of the assigned gaps.

Next, the Workgroup reconvened and members presented the results of their independent review of the scientific literature for each assigned gap. Members summarized the evidence for their assigned potential gaps and recommended retaining, removing, or revising the potential gap. The group then discussed the evidence and recommendations. We decided, by consensus, whether to retain or remove the gap, depending on the existence of high-quality studies with consistent results and the relevance of future research efforts to military populations. Some gaps were revised based on the existing evidence,

and multiple similar gaps were consolidated. If revision had modified the gap sufficiently to render the original search insufficient, members conducted a follow-up literature search on the revised gap.

In the last step of the literature review process, members voted and reached full consensus on removal or revision of gaps. We removed 14 gaps at this stage, resulting in a final tally of 18: nine for AUD, four for prescription opioids, and five for NSDs. Thus, after review of the published literature, we reduced 32 potential gaps to 18 final gaps. Appendix E (see page 39) shows the potential gaps; the rationale for retaining, removing, or revising each potential gap; and the final gaps.

### 2.1.6 Examine In-Progress Research Investments

The next task in the systematic process was to determine whether any in-progress research investments—i.e., those not yet published or otherwise completed and reported—addressed the remaining 18 gaps. Three strategies were employed to obtain pertinent information for relevant in-progress research. First, agencies that fund SUD research were contacted for summary information about current research portfolios. We received research information from USAMRMC, VA, and National Institutes of Health (NIH). Additionally, members examined relevant information previously obtained from attending research committees and conferences, including the Military Operational Medicine Research Program Substance Use In-Progress Review (September 2017); the DoD, VA, and NIH Joint Review and Analysis Substance Abuse Research Portfolio (June 2017); and the Military Health System Research Symposium conference (August 2017). Finally, members searched www.clinicaltrials.gov, a database for in-progress research, and identified approximately 300 studies potentially relevant to the gaps. Each member scanned the findings for their assigned gap, reviewed each study, and determined the likelihood that it might potentially address or close a gap. Though many of the studies lacked detailed information about the methodology and results were not yet available, the information was sufficient to inform members about the extent of research investment in a particular gap area. The review of in-progress research provided no new significant information to recommend further removal of the gaps, but it did inform the prioritization process described below.

### 2.1.7 Prioritize Research Gaps and Develop Recommendations

Gaps were prioritized using metrics (see Table 1) adapted from those used in the *2016 Research Recommendations Report for Posttraumatic Stress Disorder and Depression in the Military* (Psychological Health Center of Excellence, 2017). The degree to which published and in-progress research addressed each gap varied. The first two of the four prioritization metrics assessed this variability. The metrics also assessed the degree to which gaps were considered important for the military population and to care provided in the MHS. Each member completed the ratings independently.

**Table 1. Research Gap Prioritization Metrics**

| | Very little | | 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 current research investment, how much does this remain a research gap? | 1 | 2 | 3 | 4 | 5 |
| 3. How much would addressing this research gap impact[1] the population? | 1 | 2 | 3 | 4 | 5 |
| | Not at all likely | | Somewhat likely | | Very likely |
| 4. What is the likelihood that closing the gap would improve care in the MHS? | 1 | 2 | 3 | 4 | 5 |

[1] "Impact" includes reach, severity, and alternative treatment options.

### 2.1.8 Map the Gaps to the National Research Action Plan Interagency Research Continuum Approach

To ensure alignment between research gaps and national strategic priorities, we mapped the prioritized gaps to the "Interagency Research Continuum Approach" outlined in the National Research Action Plan (NRAP) (DoD, VA, Department of Health and Human Services, & Department of Education, 2013). We categorized gaps into one or more of the following categories: foundational science, epidemiology, etiology, prevention and screening, treatment, follow-up care, and services research.

## 3.0 Results

Each gap was assigned a priority score by summing each member's ratings on the four metrics (range 4–20), and then calculating a mean score across all raters for each gap. Mean scores ranged from 13.54 to 16.85 for AUD, 13.00 to 15.92 for prescription opioids, and 13.77 to 15.92 for NSDs gaps. Gaps, prioritized from highest to lowest based on their ratings, are presented in Tables 2–4. Two prescription opioids gaps tied for first place and two NSDs gaps tied for fourth.
Tables 2–4 also present the NRAP categories for each gap. As Figure 2 (see page 10) shows, gaps ranged across almost the entire NRAP spectrum.

**Table 2. Prioritized List of Research Gaps on Alcohol Use Disorder in the Military**

| Rank | Mean Score* | Research Recommendation *(NRAP)* |
|---|---|---|
| 1 | 16.85 | Examine the effects of leadership attitudes, group characteristics, and group identification factors on drinking in the military. ***(Etiology)*** |
| 2 | 16.62 | Examine the impact of relevant DoD- and Service-specific policies and procedures on Service member problem-drinking and Service member readiness (e.g., confidentiality, type of treatment services available, disciplinary consequences for infringement, and the cost of alcohol on base). ***(Etiology)*** |
| 3 | 16.46 | Develop effective public health interventions that address specific elements of military culture identified as being associated with increases in problem-drinking. ***(Prevention and Screening)*** |
| 4 | 16.15 | Examine the effects of hazardous alcohol use/AUD on Service member readiness and unit functioning. ***(Epidemiology)*** |
| 5 | 15.92 | Investigate the effectiveness of interventions for prevention of alcohol-related sexual assault/domestic violence in the military (both for victims and perpetrators). ***(Prevention and Screening)*** |
| 6 | 15.85 | Identify factors that improve effective implementation of evidence- and population-based approaches for the treatment and management of alcohol misuse/AUD in the MHS. ***(Services Research)*** |
| 7 | 15.38 | Examine the optimal integrative treatment approach for patients with AUD plus comorbid psychiatric conditions in the MHS (within and across settings). ***(Services Research)*** |
| 8 | 14.92 | Examine the effects of social identity characteristics (e.g., age, gender, race/ethnicity, sexual orientation) on AUD treatment-seeking, engagement, and retention. (Findings may inform military programs to improve treatment in minorities.) ***(Follow-up Care)*** |
| 9 | 13.54 | Develop and comparatively test multi-faceted (i.e., professional, organizational, and patient oriented) strategies to increase use of evidence based practices for the treatment of AUD in the MHS. ***(Services Research)*** |

*Score range, 4–20

**Table 3. Prioritized List of Research Gaps on Prescription Opioid Use in the Military**

| Rank | Mean Score* | Research Recommendation *(NRAP)* |
|---|---|---|
| 1† | 15.92 | Investigate treatments for chronic pain other than conventional opioids that reduce risk for prescription opioid use, abuse, and misuse. ***(Etiology, Treatment)*** |
| 1† | 15.92 | Investigate the effectiveness of abuse deterrent formulations (ADFs) for preventing/minimizing opioid abuse and misuse, with a focus on military-relevant outcomes (e.g., fitness for duty, medical board). ***(Etiology)*** |
| 3 | 15.23 | Investigate the effectiveness of opioid prescription drug misuse screening approaches within the context of existing MHS opioid misuse mitigation strategies (e.g., comprehensive screening approaches like the Stratification Tool for Opioid Risk Mitigation). ***(Prevention and Screening)*** |
| 4 | 13.00 | Apply and evaluate structured strategies that aim to increase uptake of current opioid CPG recommendations to prevent abuse/misuse. ***(Services Research)*** |

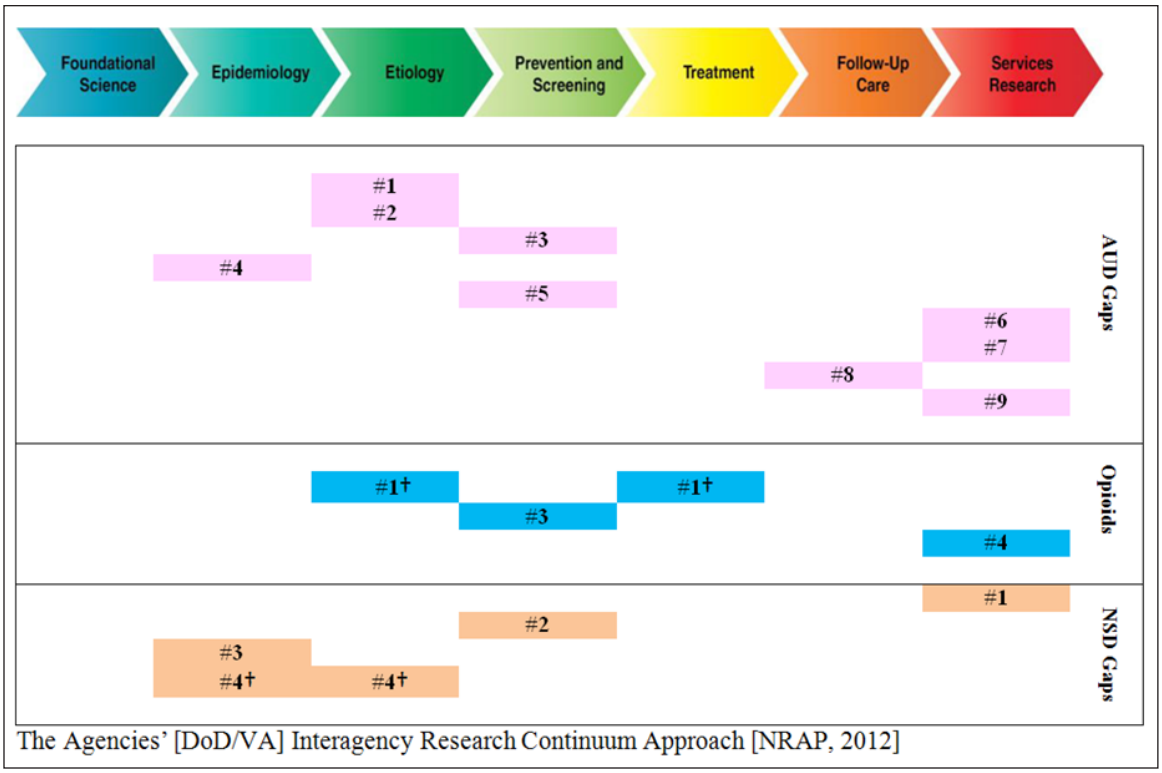
*Score range, 4–20
†The top two gaps were tied based on mean score.

**Table 4. Prioritized List of Research Gaps on Novel Synthetic Drugs in the Military**

| Rank | Mean Score* | Research Recommendation *(NRAP)* |
|---|---|---|
| 1 | 15.92 | Develop and/or evaluate interventions to improve provider knowledge and practices regarding screening, diagnosing, and management of patients using synthetic cathinones, synthetic cannabinoids, and novel synthetic opioids (NSOs). ***(Services Research)*** |
| 2 | 14.85 | Investigate public health and educational activities to prevent synthetic cathinone, synthetic cannabinoid, and NSO use in the military community. ***(Prevention and Screening)*** |
| 3 | 14.38 | Investigate the effects of synthetic cathinone, synthetic cannabinoid, NSO use on functioning (e.g., psychosocial, occupational, readiness) in ADSMs. ***(Epidemiology)*** |
| 4† | 13.77 | Examine the effects of social factors (e.g., social networks, social media, interpersonal relationships, military community) on awareness, initiation, cessation, and prevention of the use of synthetic cathinones, synthetic cannabinoids, and NSOs. ***(Etiology)*** |
| 4† | 13.77 | Examine prevalence and demographics of synthetic cathinone, synthetic cannabinoid, and NSO use in ADSMs across Services, including among the general active-duty population. ***(Epidemiology)*** |

*Score range, 4–20
†The bottom two gaps were tied based on mean score.

**Figure 2. Research Gaps Mapped to NRAP Research Continuum**




†Tied based on mean scores.

# 4.0 Discussion

Modifying the methodology developed and piloted in 2016 (Psychological Health Center of Excellence, 2017), PHCoE identified, refined, and prioritized gaps in SUD research for selected topic areas relevant to the military. After receiving end-user stakeholder guidance on the overall methodological approach, expert stakeholder input regarding the most relevant SUD topic areas was obtained. Authoritative sources and members' expertise specific to these topic areas were used to produce an initial list of 175 research needs, which were refined into 97 potential research gaps and reduced to 32 potential gaps most relevant to the military. Members conducted reviews of the published literature to ensure that the gaps reflected the current state of the science. Removing, combining, and revising the gaps based on these findings, a final list of 18 research gaps was produced (nine AUD gaps, four prescription opioids gaps, and five NSDs gaps). Next, a review of in-progress research informed the members of the current research investments for each gap. Last, the final 18 gaps were prioritized using predetermined metrics. The final SUD research gaps ranged across the research continuum described in the NRAP.

The following sections report methodological recommendations relevant to all the gaps, as well as the challenges and limitations related to this approach.

## 4.1 General Recommendations

PHCoE identified nine general recommendations pertaining to study design and methodology that researchers should consider when initiating any new research in DoD, when appropriate and feasible:

- Measure and report relevant secondary outcomes, such as functional impairment, quality of life, fitness for duty, and other military-relevant outcomes, as well as outcome measures that assess clinically relevant change
- Measure adverse events, harms, and occurrences of suicidal ideation in both pharmacological and psychotherapeutic trials
- Use standardized definitions of drug use, misuse, and abuse
- Use novel methodologies that incorporate sophisticated study designs
- 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 and include results (including lack of differences) in reports and publications
- Track longitudinal outcomes with at least one year of follow-up, and include active duty status to veteran status when appropriate
- Evaluate implementation and dissemination concerns, including cost-effectiveness of interventions, strategies, and models of continuing care
- Consider the potential of telehealth and mobile technologies to improve access and enhance quality of care

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

## 4.2 Challenges, Responses, and Way Forward

During the 2016 pilot, PHCoE identified challenges associated with research gap identification and prioritization. Table 5 (see page 12) lists these challenges, describes responses to these challenges when identifying and prioritizing SUD gaps, and recommends the way forward.

**Table 5. Challenges, Responses, and Way Forward**

| Challenges | Responses | Way Forward |
|---|---|---|
| 1. There are inherent limitations related to using experts to prioritize gaps, including subjectivity and potential bias. In addition, the Workgroup consisted of a relatively small number of individuals within the same organization | • Increased the number of members from 6 to 13<br>• Relied on consensus opinion for most decisions<br>• Independently applied the metrics to the research gaps, with independent members blind to others' ratings<br>• Required expert members to participate in the review of published scientific literature to inform their expert opinion<br>• Consulted with important external SUD stakeholders to inform the selection of topic gap areas (ASMAC, USAMRMC) | • Continue consulting with external stakeholders to inform gap selection<br>• Consider incorporating more members with expertise relevant to a particular topic<br>• Consider inviting members external to PHCoE to engage in the process or contribute in another fashion<br>• Consider inviting external stakeholders (rather than PHCoE) to rate and prioritize gaps |
| 2. Time and resource constraints limited the breadth and depth of this work | • Sought and received approval to narrow the scope of the research gaps to three SUD topic areas<br>• Requested and obtained resource and workload assistance from the contract support team for certain labor-intensive tasks | • Explore incorporating additional PHCoE organizational resources to support this work<br>• Consider focusing on one psychological health topic each year (for greater comprehensiveness and depth)<br>• Continue to plan ahead and consider utilizing project management expertise in developing and adhering to a reasonable timeline, and spreading workload into manageable sections |
| 3. Identification of research gaps relied heavily on review of authoritative sources, which were not comprehensive and may have resulted in omissions | • Ensured that all military-relevant sources were included<br>• Examined non-traditional sources, such as clinical practice guidelines (CPGs) from external professional organizations outside of the military (e.g., American Psychiatric Association CPGs)<br>• Added new process of requesting/ obtaining gaps derived from individual members to augment authoritative source gaps<br>• Obtained guidance from external stakeholder experts in the SUD field (ASMAC, MRMC) to inform selection of SUD topics<br>• Reviewed SUD-related ADSM responses to Health Related Behavior Survey<br>• Reviewed SUD-related surveillance data | • Continue to select authoritative sources based on relevance to the military<br>• Utilize Provider Needs Assessment Survey results (to be completed in 2018) to help address this challenge<br>• Utilize surveillance and practice gap findings<br>• Consider engaging with multiple stakeholders and sources of information to identify a more comprehensive list of potential gaps |
| 4. In-progress research review is inherently limited because the quality and outcomes of the work are difficult to ascertain at that stage | • Created spreadsheets to summarize and synthesize information as best as possible to assist in drawing conclusions<br>• Captured certain quality variables, such as design of trials | • Develop and strengthen relationships with relevant stakeholders and points of contact in order to obtain more complete information |
| 5. There are no known validated measures to prioritize research gaps | • Re-designed the metrics based on 2016 lessons learned<br>• Considered and applied metrics to evaluate "military importance" from a published report | • Conduct a comprehensive survey of relevant metrics literature and consult stakeholders to identify the most important metrics to incorporate |

## 4.3 Limitations

This initiative is an important effort that applied a systematic approach to prioritizing research gaps. Such an approach is critical because it ensures that the most important and most relevant research gaps are prioritized; however, policy and funding planners should consider multiple sources to inform their funding priorities. Though the reports by authoritative sources include thorough summaries and analyses of a particular topic, their goal is not necessarily to identify all relevant research needs and they may not have included some important statements of research needs. Furthermore, the subject-matter experts prioritizing research gaps were members of the same organization, which may have resulted in a limited perspective. Research topics not considered by PHCoE may also be worthy of funding and further research. This report intends to inform decisions regarding future research study selection and funding. Stakeholders should use it in conjunction with existing prioritization processes while continuing to rely on other experts and portfolio managers to identify research priorities. It is not likely any one program of research at this time can address or close all of these gaps.

Some of the research gaps were removed based on the volume, quality, and consistency of both published and ongoing research studies on the topic. However, the removal of a potential gap did not necessarily indicate that the gap was completely closed. Rather, removed gaps were not considered an immediate priority, based on published and ongoing research. Future developments could increase the priority of these potential gaps and necessitate further study.

It is not feasible to validate the metrics used to prioritize gaps and it is unclear what constitutes the smallest meaningful difference between scores. Moreover, all prioritized gaps made it through every step of the gap priority methodology, including synthesis of published studies and consideration of ongoing research. Thus, all of the final 18 gaps are considered a priority. Higher scores may reflect increased prioritization, but all gaps are worthy of funding and funding decisions may consider additional information that could alter the prioritization of these important gaps.

## 4.4 Conclusion

PHCoE applied a systematic and transparent methodology to identify, refine, and prioritize selected SUD research gaps relevant to the military for CY 2017. This effort incorporated stakeholder input to identify relevant research needs and it relied on military psychological health experts to review authoritative sources, synthesize published scientific literature and in-progress research investments, and apply a set of metrics to prioritize gaps. From this effort, a final prioritized list of 18 SUD gaps emerged: nine AUD gaps, four prescription opioids gaps, and five NSDs gaps. Also of importance, our findings highlighted areas where published or in-progress studies addressed an area previously identified as a research gap. The results of this effort can help inform policy makers, researchers, and funding agencies in prioritizing future SUD research activities.

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## 6.0 Acronyms

| | |
|---|---|
| ADF | Abuse Deterrent Formulation |
| ADHD | Attention-Deficit/Hyperactivity Disorder |
| ADSM | Active-Duty Service Member |
| ASMAC | Addictive Substance Misuse Advisory Committee |
| AUD | Alcohol Use Disorder |
| CAM | Complementary and Alternative Medicine |
| CPG | Clinical Practice Guideline |
| DATA 2000 | The Drug Addiction Treatment Act of 2000 |
| DHA | Defense Health Agency |
| DoD | Department of Defense |
| ER/LA | Extended-Release/Long-Acting |
| FDA | U.S. Food and Drug Administration |
| HHS | U.S. Department of Health and Human Services |
| HRBS | Department of Defense Health Related Behaviors Survey |
| LOT | Long-Term Opioid Therapy |
| MAT | Medication-Assisted Treatment |
| MHS | Military Health System |
| NDAA | National Defense Authorization Act |
| NIDA | National Institute on Drug Abuse |
| NIH | National Institutes of Health |
| NRAP | National Research Action Plan |
| NSD | Novel Synthetic Drug |
| NSO | Novel Synthetic Opioid |
| ORT | Opioid Risk Tool |
| OTSG | Office of the Surgeon General |
| OUD | Opioid Use Disorder |
| PDM | Prescription Drug Misuse |
| PDMP | Prescription Drug Monitoring Program |
| PHCoE | Psychological Health Center of Excellence |
| PTSD | Posttraumatic Stress Disorder |
| RCT | Randomized Controlled Trial |
| SUD | Substance Use Disorder |
| USAMRMC | U.S. Army Medical Research and Materiel Command |
| VA | U.S. Department of Veterans Affairs |
| VA/DoD | Veterans Affairs/Department of Defense |
| WHO | World Health Organization |

## 7.0 Appendix A: References for Reports by Authoritative Sources


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# 8.0 Appendix B: Statements of Research Needs Identified by Authoritative Sources

**Table B1. Authoritative Source Statements of Research Needs for Alcohol Use Disorder**

| # | Source | Page | Needs Statements |
|---|---|---|---|
| 1 | Dedert et al., 2014 | 10 | "We found limited evidence for small or no effects of e-interventions compared with controls on long-term (≥6 months) alcohol outcomes in participants who screened positive for alcohol misuse. Findings were even more limited for participants with alcohol use disorder (AUD) or comparisons of e-interventions to face-to-face treatment. Further research is needed to determine with higher confidence whether e-interventions can produce long-term benefits for alcohol-related outcomes. In particular, given the limited number and duration of intervention episodes in the studies reviewed, it is possible that these e-interventions were not designed to be robust enough to produce significant, enduring effects on alcohol misuse. As reported in previous reviews, brief in-person interventions produce sustained reductions in alcohol consumption in participants with alcohol misuse. Current evidence does not support substitution of e-interventions for brief, in-person treatment. Future research on e-interventions should include evaluations of more intensive or longer duration e-interventions for alcohol misuse." |
| 2 | U.S. Department of Health and Human Services (HHS) and Office of the Surgeon General (OTSG), 2016 | 84 | "Additional research on the mechanisms underlying gene by environment interactions is expected to provide insight into how substance use disorders (SUDs) develop and how they can be prevented and treated." |
| 3 | HHS & OTSG, 2016 | 84 | "Not all adolescents who experiment with alcohol, cigarettes, or other substances go on to develop an SUD, but research suggests that those who do progress to more harmful use may have pre-existing differences in their brains. Additional research can shed light on how these differences contribute to the progression from use to a disorder, as well as how changes caused by substance use affect brain function and behavior and whether they can be reversed." |
| 4 | HHS & OTSG, 2016 | 86 | "Research on the neurobiological factors contributing to differential rates of substance use and SUD in particular racial and ethnic groups is much more limited.…Additional research will help to clarify the interactions between race, ethnicity, and the neuroadaptations that underlie substance misuse and addiction. This work may inform the development of more precise preventive and treatment interventions." |
| 5 | Kleber et al., 2006 | 48 | "…[M]ore research is needed to determine if gabapentin is an effective treatment for sleep disturbances related to alcohol dependence. In addition, more research is needed to determine if trazodone and gabapentin, as well as other sedating psychotropic medications, can effectively treat sleep disturbances not only in individuals with alcohol dependence but also in those with other SUDs." |
| 6 | Kleber et al., 2006 | 98 | "There are insufficient studies of adequate research design regarding the use of group or individual psychodynamically oriented psychotherapies for the treatment of individuals with an AUD." |
| 7 | Kleber et al., 2006 | 157 | "Brief interventions generally delivered over one to three sessions include an abbreviated assessment of drinking severity and related problems and the provision of motivational feedback and advice.…Further research is needed to determine which patients are optimally served by receiving a brief intervention." |
| 8 | Kleber et al., 2006 | 179 | "In addition to learning about specific treatment settings, more information is needed on the specific treatments for intoxication and withdrawal. Even in the treatment of alcohol withdrawal, for which there is considerable evidence and consensus, questions remain about the most effective class(es) of agents, the most effective agent(s) within a particular class, the most effective dosing regimen(s), and the choice of specific agents for treating specific patient subgroups or specific symptoms of withdrawal." |

**Table B1. Continued**

| # | Source | Page | Needs Statements |
|---|---|---|---|
| 9 | National Defense Authorization Act (NDAA), 2016 | 875 | "General study on gambling and problem gambling behavior among members of the Armed Forces.<br>(a) In general.—The Comptroller General of the United States shall conduct a study on gambling among members of the Armed Forces.<br>(b) Matters included.—The study conducted under subsection (a) shall include the following:<br>(1) With respect to gaming facilities at military installations, disaggregated by each military department, the number, type, and location of such gaming facilities.<br>(2) An assessment of the prevalence of and particular risks for problem gambling among members of the Armed Forces, including such recommendations for policies and programs to be carried out by the Department to address problem gambling as the Comptroller General considers appropriate.<br>(3) An assessment of the ability and capacity of military health care personnel to adequately diagnose and provide dedicated treatment for problem gambling, including—<br>(A) a comparison of treatment programs of the Department for alcohol abuse, illegal substance abuse, and tobacco addiction with treatment programs of the Department for problem gambling; and<br>(B) an assessment of whether additional training for military health care personnel on providing treatment for problem gambling would be beneficial.<br>(4) An assessment of the financial counseling and related services that are available to members of the Armed Forces and dependents of such members who are affected by problem gambling.<br>(c) Report.—Not later than one year after the date of the enactment of this Act, the Comptroller General shall submit to the congressional defense committees a report on the results of the study conducted under subsection (a)." |
| 10 | Veterans Affairs/Department of Defense (VA/DoD), 2015 | 31 | "Although qualitative work reflects some reservations among providers about screening for unhealthy alcohol use, evidence does not support provider concerns that delivering brief intervention based on alcohol screening results adversely affects patients' perceptions of care. More research is needed on the optimal frequency of screening for unhealthy alcohol use and alternative methods to promote more efficient and accurate collection of screening data directly from patients." |
| 11 | VA/DoD, 2015 | 33 | "Identifying the appropriate level of care in SUD treatment is a challenge, and numerous variables, including patient preference, patient motivation, patient willingness, and available resources can be taken into consideration. However, there is a lack of clear evidence that any specific factor accurately predicts the optimal level or intensity of care. The American Society of Addiction Medicine Patient Placement Criteria have been widely promulgated as a system to determine level of care…but controlled trials evaluating placement outcomes based on standardized assessment of these dimensions are lacking. Future research is needed to evaluate whether recently developed software to conduct the multidimensional assessment and yield an algorithmically derived placement recommendation leads to better outcomes than clinical judgment that may rely more generally on the six assessment dimensions and placement principles." |
| 12 | VA/DoD, 2015 | 37–38 | "Finally, little is known about the effectiveness of some of these interventions within specific subgroups, most notably the effectiveness of behavioral couples therapy in women and lesbian, gay, bisexual, and transgender individuals." |

**Table B1. Continued**

| # | Source | Page | Needs Statements |
|---|---|---|---|
| 13 | World Health Organization (WHO) 2014 | 11 | "Studies showing differences in consumption or alcohol-related harm between different ethnicities within countries have underlined the importance of further research on culture-related vulnerabilities." |
| 14 | WHO, 2014 | 16 | "More work is necessary to quantify the effects of alcohol on others in a way similar to that used to quantify the effects of passive smoking." |

**Table B2. Authoritative Source Statements of Research Needs for Prescription Opioids**

| # | Source | Page | Needs Statements |
|---|---|---|---|
| 1 | Center for Substance Abuse Treatment, 2009 | 72 | "In more recent years, buprenorphine treatment has been examined as an alternative to maintenance therapy for opioid dependence during pregnancy. Nonetheless, research is limited and only two randomized, double-blind studies have been conducted comparing methadone with buprenorphine." |
| 2 | Chou et al., 2016 | 10 | "Key Informants noted that in many office-based settings there was not a high demand for naltrexone (due in part to its mechanism of action as a pure opioid antagonist) and the perception that it might not be the optimal therapy for most patients, in the context of limited empiric data regarding its use in primary care." |
| 3 | Chou et al., 2016 | 28 | "A number of trials have evaluated the comparative effectiveness of different psychosocial interventions given as a component of medication-assisted treatment (MAT). However, relatively few trials on psychosocial interventions have been conducted in office-based settings." |
| 4 | Chou et al., 2016 | 30 | "Trials of MAT in office-based settings primarily enrolled patients with opioid use disorder (OUD) due to heroin; we identified no systematic review or randomized trial on effectiveness of MAT in primary care settings, specifically patients with OUD related to prescription opioids." |
| 5 | Chou et al., 2016 | 30 | "One Cochrane review evaluated the effectiveness of MAT in pregnant women, but evidence on effectiveness of U.S. Food and Drug Administration-approved office-based treatments for MAT was extremely limited." |
| 6 | Chou et al., 2016 | 30 | "…[A]lthough three trials (sample sizes 18, 30, and 175) evaluated buprenorphine versus methadone maintenance treatment, none were conducted in primary care or community-based settings." |
| 7 | Chou et al., 2016 | 30 | "A Cochrane review evaluated effectiveness of oral agonist treatment for OUD in injecting drug users on risk behaviors and rates of human immunodeficiency virus, but did not focus on medications approved for use in office-based settings and only included two trials in which patients were managed in primary care settings." |
| 8 | Chou et al., 2016 | 40 | "Although evidence is lacking with regard to how one model of care performs compared with another, comparative effectiveness research may not be the most important determinant for informing further diffusion of MAT." |
| 9 | Chou et al., 2016 | 42 | "Research on effectiveness of MAT in patients with prescription OUD. Most research on MAT has focused on patients with heroin use disorder. Research would be helpful for determining the degree to which evidence on MAT for heroin use disorder can be extrapolated to those with prescription OUD." |
| 10 | Chou et al., 2016 | 42 | "Research [needs to be done] on effectiveness of peer-delivered support services as part of MAT in primary care settings." |
| 11 | Chou et al., 2016 | 42 | "Research [needs to be done] to identify patients more likely to benefit from more intensive psychosocial services, and methods for effectively targeting specific types of psychosocial services. The need for more intensive psychosocial services is likely to vary. Understanding which patients require which services would be very helpful for designing and implementing effective models of care." |

**Table B2. Continued**

| # | Source | Page | Needs Statements |
|---|---|---|---|
| 12 | Chou et al., 2016 | 42 | "Research [needs to be done] on effectiveness of methods for reducing diversion (e.g., use of extended-release medications, thrice weekly observed dispensing, or pharmacy-based dispensing). Pharmacy-based dispensing is done in Canada and Europe for buprenorphine and methadone prescribed in primary care and has been piloted in small studies in the United States. Key Informants noted that preventing diversion has been a major concern of some payers and policymakers." |
| 13 | Chou et al., 2016 | 42 | "Research [needs to be done] to identify factors associated with high-quality care and how to measure it. With improved access to MAT, it is also critical to insure that the quality of care that is delivered is high. This will require development of new quality of care indicators for use of MAT in primary care settings." |
| 14 | Chou et al., 2016 | 42 | "Research [needs to be done] on effectiveness and safety of mid-level prescribing of buprenorphine, such as by nurse practitioners and physician assistants. Currently, the Drug Addiction Treatment Act of 2000 (DATA 2000) only permits physicians to prescribe buprenorphine for OUD. Allowing mid-level providers to prescribe buprenorphine could help improve access in rural areas with few or no physicians." |
| 15 | Chou et al., 2016 | 42 | "Research [needs to be done] to better understand the costs and cost-effectiveness of implementing MAT models of care. Although long-term treatment with buprenorphine/naloxone in office-based settings appears to be cost-effective…there are relatively few cost- and cost-effectiveness studies and analyses have not compared different MAT models of care or evaluated the use of newer pharmacological therapies. Such research would be of particular importance for policymakers, and that such research should address societal outcomes impacted by OUD (e.g., ability to work, criminal activity) in addition to impacts on drug use." |
| 16 | Chou et al., 2016 | 42 | "Research [needs to be done] to understand optimal methods for coordination and integration of care. Although Key Informants consistently noted that this is a critical component of successful MAT models of care, methods for coordination and integration of care varied among models and no study evaluated the effectiveness of different coordination and integration methods." |
| 17 | Chou et al., 2016 | 42 | "Research [needs to be done] on management of patients with OUD and concomitant chronic noncancer or cancer pain, benzodiazepine use, and/or alcohol use disorder (e.g., use of buprenorphine/naloxone for transitioning off high doses of opioids in patients with chronic pain). Treatment of OUD in patients who also have pain is a major challenge given the high prevalence of opioid prescribing. A systematic review of 10 studies of limited quality evaluated the role of buprenorphine for management of chronic pain, but only one study was conducted in primary care." |
| 18 | Chou et al., 2016 | 43 | "Research [needs to be done] to better understand optimal duration and doses of treatment. This is particularly important because otherwise payers may (and sometimes do) impose arbitrary duration limits for MAT." |
| 19 | Chou et al., 2016 | 43 | "Research [needs to be done] on effectiveness of alternative medications or formulations (e.g., implantable and injectable buprenorphine preparations). Such formulations could reduce the frequency of follow-up, increase uptake and compliance, and mitigate barriers related to long travel distance. However, there is almost no evidence on injectable buprenorphine used in primary care settings." |
| 20 | Chou et al., 2016 | 43 | "Research [needs to be done] to better understand patients who are appropriate for office-based treatment versus those who require treatment in an opioid treatment program. Key Informants noted that current methods to determine who is appropriate for office-based treatment are largely based on anecdotal experience." |

**Table B2. Continued**

| # | Source | Page | Needs Statements |
|---|---|---|---|
| 21 | Chou et al., 2016 | 43 | "Research [needs to be done] to understand why buprenorphine waivered physicians don't prescribe, factors associated with prescribing, and methods to increase prescribing. The gap between the number of waivered physicians and the number prescribing indicates that that there is substantial untapped capacity to prescribe buprenorphine." |
| 22 | Chou et al., 2016 | 43 | "Research [needs to be done] on effective methods for implementation of MAT models of care in primary care settings and increasing uptake of MAT. Although some multicomponent implementation strategies appear to be effective for enhancing access, they have not yet been studies in primary care settings." |
| 23 | Chou et al., 2016 | 43 | "Research [needs to be done] on patients who are more likely to benefit from extended-release naltrexone, comparative effectiveness of buprenorphine/ naloxone versus extended-release naltrexone, and optimal models of care for provision of extended-release naltrexone. Most models of care have focused on provision of buprenorphine/naloxone, and there is very little evidence on use of extended-release naltrexone in primary care settings." |
| 24 | Chou et al., 2016 | 43 | "Research [needs to be done] on effectiveness of telehealth and Web-based training, mentoring, and educational resources. These would be particularly useful in rural and other settings where addiction and other expertise are not available locally." |
| 25 | Chou et al., 2016 | 44 | "Research [needs to be done] on effectiveness of methadone for office-based treatment. Methadone is not authorized under DATA 2000 but has been evaluated in office-based settings in some clinical trials and observational studies in the United States and is used in primary care settings in other countries. Primary care providers in Canada, parts of Europe, and some other countries prescribe methadone for directly observed daily dispensing in local pharmacies. This model has not been tested in the United States, but could expand access to OUD treatment while limiting diversion." |
| 26 | Chou et al., 2016 | 47 | "A challenge in understanding current MAT models of care is the limited published data on most models. No study has compared the effectiveness of one MAT model of care in primary care versus another; rather, most trials have focused on specific components, in particular which medication was used and the type of psychosocial services provided." |
| 27 | Dowel, Haegerich, & Chou, 2016 | 8 | "…evidence on long-term opioid therapy (LOT) for chronic pain outside of end-of-life care remains limited, with insufficient evidence to determine long-term benefits versus no opioid therapy, though evidence suggests risk for serious harms that appears to be dose-dependent." |
| 28 | Dowel, Haegerich, & Chou, 2016 | 10 | "Results for the Opioid Risk Tool (ORT) were extremely inconsistent; evidence for other risk assessment instruments was very sparse, and studies had serious methodological shortcomings." |
| 29 | Dowel, Haegerich, & Chou, 2016 | 10 | "Evidence on other comparisons related to opioid dosing strategies (extended-release/long-acting (ER/LA) versus immediate-release opioids; immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled continuous dosing versus as-needed dosing; or opioid rotation versus maintenance of current therapy; long-term effects of strategies for treating acute exacerbations of chronic pain) was not available or too limited to determine effects on long-term clinical outcomes." |
| 30 | Dowel, Haegerich, & Chou, 2016 | 11 | "No study evaluated the effectiveness of risk mitigation strategies (use of risk assessment instruments, opioid management plans, patient education, urine drug testing, use of prescription drug monitoring program (PDMP) data, use of monitoring instruments, more frequent monitoring intervals, pill counts, or use of abuse-deterrent formulations) for improving outcomes related to overdose, addiction, abuse, or misuse." |

**Table B2. Continued**

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| 31 | Dowel, Haegerich, & Chou, 2016 | 14 | "Although no studies were found to examine prescribing of naloxone with opioid pain medication in primary care settings, naloxone distribution through community-based programs providing prevention services for substance users has been demonstrated to be associated with decreased risk for opioid overdose death at the community level." |
| 32 | Dowel, Haegerich, & Chou, 2016 | 14 | "However, limited evaluation of PDMPs at the state level has revealed mixed effects on changes in prescribing and mortality outcomes." |
| 33 | Dowel, Haegerich, & Chou, 2016 | 14 | "Potential harms of risk stratification include underestimation of risks of opioid therapy (OT) when screening tools are not adequately sensitive, as well as potential overestimation of risk, which could lead to inappropriate clinical decisions. Regarding risk mitigation approaches, limited evidence was found regarding benefits and harms." |
| 34 | Dowel, Haegerich, & Chou, 2016 | 14 | "Regarding risk stratification approaches, limited evidence was found regarding benefits and harms." |
| 35 | Dowel, Haegerich, & Chou, 2016 | 15 | "Limited information was found on costs of strategies to decrease risks associated with opioid therapy; however, urine drug testing, including screening and confirmatory tests, has been estimated to cost $211–$363 per test." |
| 36 | Dowel, Haegerich, & Chou, 2016 | 18 | "Although opioids can reduce pain during short-term use, the clinical evidence review found insufficient evidence to determine whether pain relief is sustained and whether function or quality of life improves with LOT." |
| 37 | Dowel, Haegerich, & Chou, 2016 | 18–19 | "…evidence is limited or insufficient for improved pain or function with long-term use of opioids for several chronic pain conditions for which opioids are commonly prescribed, such as low back pain, headache, and fibromyalgia." |
| 38 | Dowel, Haegerich, & Chou, 2016 | 19 | "Although evidence on long-term benefits of nonopioid therapies is also limited, these therapies are also associated with short-term benefits, and risks are much lower." |
| 39 | Dowel, Haegerich, & Chou, 2016 | 19 | "The clinical evidence review found insufficient evidence to determine long-term benefits of opioid therapy for chronic pain and found an increased risk for serious harms related to LOT that appears to be dose-dependent." |
| 40 | Dowel, Haegerich, & Chou, 2016 | 20 | "The clinical evidence review did not find studies evaluating effectiveness of patient education or opioid treatment plans as risk-mitigation strategies." |
| 41 | Dowel, Haegerich, & Chou, 2016 | 21 | "The clinical evidence review did not find evidence that continuous, time-scheduled use of ER/LA opioids is more effective or safer than intermittent use of immediate-release opioids or that time-scheduled use of ER/LA opioids reduces risks for opioid misuse or addiction." |
| 42 | Dowel, Haegerich, & Chou, 2016 | 22 | "The clinical evidence review found only one study addressing effectiveness of dose titration for outcomes related to pain control, function, and quality of life." |
| 43 | Dowel, Haegerich, & Chou, 2016 | 22 | "No studies were found in the clinical evidence review assessing the effectiveness of abuse-deterrent technologies as a risk mitigation strategy for deterring or preventing abuse." |
| 44 | Dowel, Haegerich, & Chou, 2016 | 23 | "Although there is limited evidence to recommend specific intervals for dosage titration, a previous guideline recommended waiting at least five half-lives before increasing dosage and waiting at least a week before increasing dosage of methadone to make sure that full effects of the previous dosage are evident." |
| 45 | Dowel, Haegerich, & Chou, 2016 | 25 | "Although evidence is insufficient to determine at what point within the first 3 months of OT the risks for opioid use disorder increase, reassessment of pain and function within 1 month of initiating opioids provides an opportunity to minimize risks of long-term opioid use by discontinuing opioids among patients not receiving a clear benefit from these medications." |

**Table B2. Continued**

| # | Source | Page | Needs Statements |
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| 46 | Dowel, Haegerich, & Chou, 2016 | 25 | "Although the clinical evidence review did not find studies evaluating the effectiveness of more frequent monitoring intervals, it did find that continuing OT for 3 months substantially increases risk for OUD." |
| 47 | Dowel, Haegerich, & Chou, 2016 | 26 | "Although the clinical evidence review did not find high-quality studies comparing the effectiveness of different tapering protocols for use when opioid dosage is reduced or opioids are discontinued, tapers reducing weekly dosage by 10%–% of the original dosage have been recommended by other clinical guidelines, and a rapid taper over 2–weeks has been recommended in the case of a severe adverse event such as overdose." |
| 48 | Dowel, Haegerich, & Chou, 2016 | 26 | "The clinical evidence review found insufficient evidence to determine how harms of opioids differ depending on patient demographics or patient comorbidities." |
| 49 | Dowel, Haegerich, & Chou, 2016 | 28 | "The clinical evidence review found insufficient evidence to determine how harms of opioids differ depending on past or current substance use disorder, although a history of substance use disorder was associated with misuse." |
| 50 | Dowel, Haegerich, & Chou, 2016 | 29 | "The clinical evidence review did not find studies evaluating the effectiveness of PDMPs on outcomes related to overdose, addiction, abuse, or misuse." |
| 51 | Dowel, Haegerich, & Chou, 2016 | 30 | "The clinical evidence review did not find studies evaluating the effectiveness of urine drug screening for risk mitigation during opioid prescribing for pain." |
| 52 | Dowel, Haegerich, & Chou, 2016 | 34 | "The evidence reviews forming the basis of this guideline clearly illustrate that there is much yet to be learned about the effectiveness, safety, and economic efficiency of LOT." |
| 53 | Dowel, Haegerich, & Chou, 2016 | 34 | "The National Institutes of Health panel recommended that research is needed to improve our understanding of which types of pain, specific diseases, and patients are most likely to be associated with benefit and harm from opioid pain medications; evaluate multidisciplinary pain interventions; estimate cost-benefit; develop and validate tools for identification of patient risk and outcomes; assess the effectiveness and harms of opioid pain medications with alternative study designs; and investigate risk identification and mitigation strategies and their effects on patient and public health outcomes." |
| 54 | Dowel, Haegerich, & Chou, 2016 | 34 | "It is also important to obtain data to inform the cost feasibility and cost-effectiveness of recommended actions, such as use of nonpharmacologic therapy and urine drug testing." |
| 55 | Dowel, Haegerich, & Chou, 2016 | 34 | "Additional research can inform the development of future guidelines for special populations that could not be adequately addressed in this guideline, such as children and adolescents, where evidence and guidance is needed but currently lacking." |
| 56 | U.S. Department of Health and Human Services and Office of the Surgeon General, 2016 | 283 | "A number of states have passed legislation requiring prescribers to check their PDMP before prescribing controlled substances. Additional research is needed to identify best practices and policies to maximize the efficacy of these programs." |
| 57 | Kleber et al., 2006 | 166 | "Currently, there is no research database that provides information about the relative efficacy and safety of higher doses (i.e., ≥100 mg/day) of methadone." |
| 58 | Kleber et al., 2006 | 171 | "There has been some interest in and research on using buprenorphine as a bridging agent to treatment with naltrexone. Several reports of buprenorphine's use in opioid withdrawal are open studies describing clinicians' experience with buprenorphine. Although the outcomes noted in these reports are confounded by the lack of important features found in appropriately conducted clinical trials, they do provide important clinical evidence of buprenorphine's acceptability as a withdrawal medication." |

**Table B2. Continued**

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| 59 | National Institute on Drug Abuse (NIDA), 2015 | 3 | "Additional analyses are needed to better characterize the population that abuses prescription opioids who transition to heroin use, including demographic criteria, what other drugs they use, and whether or not they are injection drug users." |
| 60 | NIDA, 2015 | 5 | "It is not clear whether the increased availability of heroin is causing the upsurge in use or if the increased accessibility of heroin has been caused by increased demand." |
| 61 | NIDA, 2016 | 15 | "The potential risks involved with LOT, such as the development of drug tolerance, hyperalgesia, and addiction, present doctors with a dilemma, as there is limited research on alternative treatments for chronic pain." |
| 62 | NIDA, 2016 | 21 | "While research regarding the impact of these programs is currently mixed, the use of PDMPs in some states has been associated with lower rates of opioid prescribing and overdose, though issues of best practices, ease of use, and interoperability remain to be resolved." |
| 63 | NIDA, 2016 | 24 | "Researchers are exploring alternative treatment approaches that target other signaling systems.…More research is also needed to better understand effective chronic pain management, including identifying factors that predispose some patients to SUD and developing measures to prevent the nonmedical use of prescription medications." |
| 64 | Pacula et al., 2016 | xi | "Most guidelines note the lack of strong research evidence for many of the current care recommendations that address the prevention of misuse of prescription opioids." |
| 65 | Pacula et al., 2016 | xi–xii | "Guidelines provide consistent support for conducting a comprehensive assessment of a patient medical history, including history of substance abuse and comorbid psychiatric and medical history, before initiating therapy.…However, there is little supporting evidence concerning the effectiveness of approaches, such as screening exams, to predict patient characteristics for misuse." |
| 66 | Pacula et al., 2016 | xii | "Many guidelines recommend written management plans and urine drug screens when there is a high risk of prescription drug misuse (PDM) despite limited evidence of these tools' effectiveness." |
| 67 | Pacula et al., 2016 | xii | "There is also a paucity of studies addressing the specific problem of prescription opioid abuse in the broader literature, and few empirical studies specifically address the prevention or treatment of PDM." |
| 68 | Pacula et al., 2016 | xii | "However, as this systematic review shows, more evidence is needed to help guide proper implementation of task-force recommendations with respect to alternatives to writing prescriptions." |
| 69 | Pacula et al., 2016 | xxiii | "In particular, there was limited evidence of effective strategies at the time in which we conducted our systematic review of the literature, but substantial attention given to the problem of PDM in the civilian sector in the past year might have generated some new evidence." |
| 70 | Pacula et al., 2016 | 9 | "For example, all clinical practice guidelines (CPGs) we identified, both military and civilian, support an initial assessment to evaluate risk of PDM at the time a provider is considering prescribing an opioid.…However, there was little supporting evidence concerning the effectiveness of this approach in predicting misuse." |
| 71 | Pacula et al., 2016 | 9 | "There was also no strong evidence for the utility of chronic opioid-management plans in curbing misuse." |
| 72 | Pacula et al., 2016 | 10 | "These reviews were consistent with the recommendations found in the aforementioned guidelines regarding lack of evidence supporting any particular screening instruments or the use of urine drug testing for identifying patients with PDM." |
| 73 | Pacula et al., 2016 | 13 | "The majority of current guidelines, consensus statements, and published literature focus on heroin abuse, rather than prescription misuse, and note a general lack of evidence of many of the approaches commonly used in practice to predict misuse." |

**Table B2. Continued**

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| 74 | Pacula et al., 2016 | 13 | "Given the general lack of evidence base supporting any clear guidelines in the prevention or treatment of PDM, it might be more useful to identify current prevention, identification, and treatment practices in medical treatment facilities than to adhere to specific CPGs." |
| 75 | Pacula et al., 2016 | 74 | "Many providers with whom we spoke called for a more standardized approach to identifying, managing, and treating PDM given the inconsistency across military treatment facilities and clinics. However, without a strong evidence base, it is not possible to definitively say which standardized approach the military should take." |
| 76 | Pacula et al., 2016 | 75 | "A common theme…is that the vast majority of people who are diagnosed as having a PDM had medically indicated use before they started misusing the drug. However, we cannot know, based on existing information, the extent to which this perception is true, particularly given that nonmedical use of any substance is taken very seriously in the military and hence unlikely to be reported." |
| 77 | Pacula et al., 2016 | 82 | "Of course, the insights from this study need to be considered in light of the study limitations…including the lack of extensive evidence about effective strategies for preventing and identifying PDM…" |
| 78 | National Defense Authorization Act (NDAA), 2017 | 1084 | "Sec. 746. Department of Defense study on preventing the diversion of opioid medications. (a) Study.—The Secretary of Defense shall conduct a study on the feasibility and effectiveness in preventing the diversion of opioid medications of the following measures:<br>(1) Requiring that, in appropriate cases, opioid medications be dispensed in vials using affordable technologies designed to prevent access to the medications by anyone other than the intended patient, such as a vial with a locking-cap closure mechanism.<br>(2) Providing education on the risks of opioid medications to individuals for whom such medications are prescribed, and to their families, with special consideration given to raising awareness among adolescents on such risks." |
| 79 | Veterans Affairs/Department of Defense (VA/DoD), 2015 | 43,63 | "While strong evidence supports opioid agonist therapy and moderate evidence supports extended-release injectable naltrexone, some patients may prefer oral naltrexone despite its lack of demonstrated effectiveness. Further research is needed to determine whether additional measures to improve treatment retention and medication adherence (e.g., Contingency Management) would reduce opioid consumption in patients taking oral naltrexone. Further research is needed to determine risks and benefits of buprenorphine/naloxone versus buprenorphine mono-product versus methadone for long-term outcome for children born to women with OUD." |
| 80 | VA/DoD, 2017 | 9 | "There is insufficient evidence to recommend for or against specific tapering strategies and schedules." |
| 81 | VA/DoD, 2017 | 15 | "There has been limited research on the effectiveness of LOT for non-end-of-life pain." |
| 82 | VA/DoD, 2017 | 21 | "Given the insufficient evidence of benefit for LOT, the clinician must carefully weigh harms and benefits and educate the patient as well as his or her family or caregiver prior to proceeding with treatment." |
| 83 | VA/DoD, 2017 | 21 | "Future studies examining the results of OT CPG implementation may lead to the development of new evidence particularly relevant to clinical practice." |
| 84 | VA/DoD, 2017 | 37 | "The Stratification Tool for Opioid Risk Mitigation…provides suggestions as to what alternative treatments have not been tried and what risk mitigation strategies need to be applied. Evidence supporting their use is poor but they facilitate providers 'determination of current, past and potential therapies and strategies.'" |

**Table B2. Continued**

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| 85 | VA/DoD, 2017 | 38 | "The literature review conducted for this CPG identified no studies evaluating the effectiveness of LOT for outcomes lasting longer than 16 weeks. Given the lack of evidence showing sustained functional benefit of LOT and moderate evidence outlining harms, non-opioid treatments are preferred for chronic pain." |
| 86 | VA/DoD, 2017 | 39 | "…[T]here is a lack of high quality evidence that LOT improves pain, function, and/or quality of life." |
| 87 | VA/DoD, 2017 | 40 | "In light of the low harms associated with exercise and psychological therapies when compared with LOT these treatments are preferred over LOT, and should be offered to all patients with chronic pain including those currently receiving LOT. There is insufficient evidence to recommend psychological over physical therapies or vice versa; the choice of which to try first should be individualized based on patient assessment and a shared decision making process." |
| 88 | VA/DoD, 2017 | 40 | "Further studies may help determine earlier in the course of treatment which patients are most likely to benefit from a specific non-pharmacologic therapy (physical, psychological, and pain rehabilitation) or non-opioid pharmacologic therapies alone or as part of a multimodal approach." |
| 89 | VA/DoD, 2017 | 42 | "The lack of evidence of efficacy of LOT and considerable evidence of significant harms of overdose, death from overdose, and increased risk of suicide outweigh any potential modest benefit of prescribing LOT in this population." |
| 90 | VA/DoD, 2017 | 43 | "Furthermore, there is a lack of evidence in favor of long-term therapy with benzodiazepines and opioids for chronic pain." |
| 91 | VA/DoD, 2017 | 43 | "Finally, further research is needed on the efficacy of alternative treatments for pain and ways to mitigate risks of opioid-related adverse events in patients with SUD and pain." |
| 92 | VA/DoD, 2017 | 43 | "Given the increasing use of cannabis among patients with chronic pain and the lack of randomized controlled trials (RCTs) comparing outcomes of prescribing LOT versus other therapies for patients with and without cannabis use and cannabis use disorder, future research is needed to optimize care for these patients." |
| 93 | VA/DoD, 2017 | 43 | "Research is also needed to determine which subpopulations of patients with active SUD are at greatest risk of OUD, overdose, and death." |
| 94 | VA/DoD, 2017 | 44 | "While the evidence for harm associated with the combination of opioids and Z-drugs (e.g., zolpidem, eszopiclone) is not as strong as the evidence for harm associated with the combination of opioids and benzodiazepines, we suggest not prescribing Z-drugs to patients who are on LOT, as moderate quality evidence demonstrates that the combination of zolpidem and opioids increases the adjusted odds ratio of overdose." |
| 95 | VA/DoD, 2017 | 45 | "Toward augmenting this evidence base, we recommend that future observational research examine age as a continuous predictor of adverse outcomes. Additionally, we recommend that future trials examine which risk mitigation strategies can reduce the additional risk of OUD and overdose in younger patients on LOT. Lastly, a deeper understanding of the mechanisms for addiction to opioids in young brains is needed." |
| 96 | VA/DoD, 2017 | 48 | "Distribution of naloxone for reversal is supported by the Substance Abuse and Mental Health Services Administration the American Medical Association and other medical societies, and is facilitated through the VA via Pharmacy Benefits Management. Clinical efficacy has been established for its use on short-acting opioids, but not for its use on long-acting opioids such as methadone or exceptionally potent opioids." |
| 97 | VA/DoD, 2017 | 50 | "Further research is needed to identify strategies for safely managing patients at elevated risk of suicide who demand opioid medications or become further destabilized during tapering." |

**Table B2. Continued**

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| 98 | VA/DoD, 2017 | 53 | "Recognizing the lack of evidence of long-term benefit associated with LOT used alone and the risks of harms with use of opioids without risk mitigation, dosing determinations should be individualized based upon patient characteristics and preferences…" |
| 99 | VA/DoD, 2017 | 54 | "Future research is needed to better determine the impact of systematic reductions in Morphine Equivalent Daily Dose in terms of pain relief, specific pain and medical conditions, overdose morbidity and mortality as well as potential adverse outcomes (e.g., the incidence of associated OUD, infectious diseases related to intravenous drug use disorder, and drug-related crime and diversion) and to determine whether/which conditions may be appropriately treated with LOT. Research is also needed to determine how frequency of monitoring should be impacted by dose." |
| 100 | VA/DoD, 2017 | 55 | "There was insufficient evidence to recommend for or against any specific opioid or opioid formulation, specifically the following: Short-acting versus long-acting opioids (for LOT for chronic pain), Route of administration/ delivery among alternatives such as transdermal, buccal, sublingual, or pumps, Abuse deterrent formulations (ADFs) of opioids compared to non-abuse deterrent formulations, Tramadol and other dual-mechanism opioids, Buprenorphine for pain (compared to other opioids), Methadone (with QT monitoring)." |
| 101 | VA/DoD, 2017 | 55 | "There is very low quality evidence to recommend for or against short-acting versus long-acting opioids for maintenance of OT." |
| 102 | VA/DoD, 2017 | 56–57 | "Our searches identified two RCTs in which the benefits of co-prescribing of naloxone with opioids were examined. However, both RCTs were rated as low to very low quality with short-term follow-up." |
| 103 | VA/DoD, 2017 | 57 | "There is low quality evidence that tramadol may be more effective than placebo for pain relief.…There is no long-term evidence of the comparative efficacy of tramadol versus another opioid or a non-opioid comparison such as non-steroidal anti-inflammatory drugs or acetaminophen." |
| 104 | VA/DoD, 2017 | 57 | "In long-term studies, compared to placebo, low quality evidence indicates that tapentadol is more effective for pain-related primary and secondary outcomes, but results were mixed for several different self-reported quality of life measures in these studies." |
| 105 | VA/DoD, 2017 | 57 | "Future research is needed to ascertain whether ADFs actually reduce OUD when used for chronic pain, and whether said formulations differ across clinical outcomes such as pain, function, and adverse events." |
| 106 | VA/DoD, 2017 | 58 | "In short-term studies, there is overall low to very low quality evidence that, when compared to placebo, patients receiving tapentadol experience more adverse events (e.g., vomiting, tiredness, dry mouth, dizziness, sweating, constipation, nausea) and drop out of treatment more often than the placebo groups." |
| 107 | VA/DoD, 2017 | 58 | "There is insufficient evidence to recommend buprenorphine over other opioids for the treatment of chronic pain." |
| 108 | VA/DoD, 2017 | 60 | "There is insufficient evidence to recommend methadone over other opioids for the treatment of chronic pain." |
| 109 | VA/DoD, 2017 | 67 | "Additional research is needed to identify the opioid tapering processes that are associated with the best patient outcomes among a broad range of domains including general functioning, psychosocial functioning, mood, pain related disability, and adverse outcomes assessed in the short, medium, and long-term." |
| 110 | VA/DoD, 2017 | 67 | "Low quality evidence supports the benefits of providing brief behavioral interventions and close monitoring to patients at high risk for prescription opioid misuse." |

**Table B2. Continued**

| # | Source | Page | Needs Statements |
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| 111 | VA/DoD, 2017 | 68 | "Research is needed to identify the efficacy and feasibility of providing multidisciplinary care to patients demonstrating significant high-risk medication-related behaviors when prescribed LOT in primary care settings." |
| 112 | VA/DoD, 2017 | 102 | "The lack of prospective and comparative studies concerning methadone dosing strategies highlights the need to carefully individualize the dosing regimen of methadone." |
| 113 | VA/DoD, 2017 | 154 | "Insufficient data exists to recommend routine laboratory screening for endocrinopathy in asymptomatic patients on OT." |
| 114 | VA/DoD, 2017 | 154 | "There is insufficient evidence to make recommendations regarding OT and immune dysfunction." |

**Table B3. Authoritative Source Statements of Research Needs for Novel Synthetic Drugs**

| # | Source | Page | Needs Statements |
|---|---|---|---|
| 1 | Gulf Coast High Intensity Drug Trafficking Areas Program, 2017 | 1 | "It is unknown at this time how U-47700 interacts with either fentanyl or heroin within the body." |
| 2 | National Institute on Drug Abuse (NIDA), 2015 | 2 | "So far, there have been few scientific studies of the effects of synthetic cannabinoids on the human brain, but researchers do know that some of them bind more strongly than marijuana to the cell receptors affected by Tetrahyrdocannabinol, and may produce much stronger effects. The resulting health effects can be unpredictable." |
| 3 | NIDA, 2015 | 3 | "Behavioral therapies and medications have not specifically been tested for treatment of addiction to [synthetic cannabinoids]." |
| 4 | NIDA, 2016 | 2 | "Much is still unknown about how synthetic cathinones affect the human brain." |
| 5 | NIDA, 2016 | 4 | "Much is still unknown about how all of the chemicals in synthetic cathinones affect the human brain." |
| 6 | NIDA, 2016 | 4 | "No medications are currently available to treat addiction to synthetic cathinones." |
| 7 | NIDA, 2017 | 2 | "More research is needed on the risks of [dripping]." |
| 8 | NIDA, 2017 | 2 | "…[M]ore research is needed to understand if experimenting with e-cigarettes leads to regular use of smokable tobacco." |
| 9 | NIDA, 2017 | 3 | "More research is needed on the health consequences of repeated exposure to these chemicals [in vapor]." |
| 10 | NIDA, 2017 | 3 | "E-cigarettes haven't been thoroughly evaluated in scientific studies. For now, not enough data exists on the safety of e-cigarettes, how the health effects compare to traditional cigarettes, and if they are helpful for people trying to quit smoking." |
| 11 | NIDA, 2017 | 3 | "…[E]-cigarettes are not a U.S. Food & Drug Administration (FDA)-approved quit aid, and there is no conclusive scientific evidence on the effectiveness of e-cigarettes for long-term smoking cessation." |
| 12 | NIDA, 2017 | 4 | "More research is needed to determine if e-cigarettes may be as effective as smoking cessation aids already approved by the FDA." |

**Table B4. Authoritative Source Statements of Research Needs for Substance Use Disorder**

| # | Source | Page | Needs Statements |
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| 1 | Center for Substance Abuse Treatment, 2009 | 40 | "However, on the whole, the evidence for genetic influence on the development of alcohol use disorders (AUD) in women is less consistent than for men. Interpretation of the literature is complicated by methodological issues, such as small sample sizes." |
| 2 | Center for Substance Abuse Treatment, 2009 | 156 | "While more research is needed to pinpoint the specific factors that lead to lower retention rates among ethnically diverse women, a key variable appears to be economic resources." |
| 3 | Center for Substance Abuse Treatment, 2009 | 170 | "Research findings are inconsistent in demonstrating the effectiveness of behavioral parenting programs for improving the parent-child relationship and children's psychological adjustment among mothers who have substance use disorders (SUDs).…More research is needed to evaluate the most effective parenting approaches and to address research methodological issues surrounding parenting program evaluations." |
| 4 | Center for Substance Abuse Treatment, 2009 | 181–182 | "More research is needed in evaluating outcome and the role of posttraumatic stress disorder and relapse." |
| 5 | Center for Substance Abuse Treatment, 2015 | 64–65 | "Research focused on case management in the substance abuse field is limited and offers many opportunities for local substance abuse programs to make significant contributions to the field. Suggested directions for future research include the following:<br>–Key ingredients of successful programs, especially for hard-to-reach populations<br>–Relative cost-effectiveness of particular case management models, including cost outcome results within systems incorporating full parity of substance abuse with other health care, outcome results when a full continuum of care is available to patients, and outcome results associated with use of standardized guidelines for placement, continued stay, and discharge for substance abuse patients<br>–Improved methodology to investigate research questions in "real world" settings<br>–Development of brief versions of valid and reliable research outcome instrumentation<br>–The effect of particular forms of case management on societal costs of substance abuse and its treatment" |
| 6 | Center for Substance Abuse Treatment, 2015 | 86 | "What is needed now is more research on case management. Several promising lines of research, presented in Chapter 4, suggest that certain forms of case management activities improved client outcomes, resulting in fewer employment problems, increased income, longer treatment retention, and diminished drug use. Other studies focusing on a criminal justice population suggest far-ranging benefits. However, the applicability of those studies to the population outside prison and jail has yet to be established." |
| 7 | Grant et al., 2015b | 65 | "Overall, the available evidence suggests no consistent effect of acupuncture versus comparator interventions on substance use outcomes, though we observed some positive effects for improving withdrawal/craving symptoms and decreasing anxiety.…The body of evidence underlying these analyses, however, is of low or very low quality due to attrition bias, high heterogeneity, and/or wide confidence intervals." |
| 8 | Grant et al., 2015b | 72 | "Moreover, much like the current review, these reviews indicated that most included studies were hampered by poor methodological quality and loss-to-follow-up, weakening the conclusions that can be drawn from this body of evidence." |
| 9 | Grant et al., 2015b | 73 | "As no included study focused on active military or veteran populations, future randomized controlled trials (RCTs) incorporating military-related eligibility criteria could provide more-applicable evidence to decision makers in military and veteran health systems. Researchers should also consider the potential effect of participant expectancies about acupuncture on intervention outcomes." |

**Table B4. Continued**

| # | Source | Page | Needs Statements |
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| 10 | Grant et al., 2015a | 44–45 | "To provide firmer conclusions about the efficacy and safety of mindfulness-based relapse prevention, future RCTs on this intervention are needed." |
| 11 | U.S. Department of Health and Human Services (HHS) and Office of the Surgeon General (OTSG), 2016 | 39–41 | "The clear implications of these data are that a comprehensive approach to reducing the misuse of alcohol and drugs—one that includes the implementation of effective prevention programs and policy strategies as well as high-quality treatment services—is needed to reduce the problems and costs of substance misuse in the United States." |
| 12 | HHS & OTSG, 2016 | 81 | "Additional research is needed to understand how using more than one substance affects the brain and the development and progression of addiction, as well as how use of one substance affects the use of others." |
| 13 | HHS & OTSG, 2016 | 86 | "Continued research is necessary to more thoroughly explain how substance use affects the brain at the molecular, cellular, and circuit levels. Such research has the potential to identify common neurobiological mechanisms underlying substance use disorders, as well as other related mental disorders." |
| 14 | HHS & OTSG, 2016 | 87 | "Little is known about the factors that facilitate or inhibit long-term recovery from SUDs or how the brain changes over the course of recovery. Developing a better understanding of the recovery process, and the neurobiological mechanisms that enable people to maintain changes in their substance use behavior and promote resilience to relapse, will inform the development of additional effective treatment and recovery support interventions. Therefore, an investigation of the neurobiological processes that underlie recovery and contribute to improvements in social, educational, and professional functioning is necessary." |
| 15 | HHS & OTSG, 2016 | 88 | "Prospective, longitudinal studies are needed to investigate whether pre-existing neurobiological factors contribute to adolescent substance use and the development of substance use disorders, how adolescent substance use affects brain structure and function, and whether the changes in brain structure and function that accompany chronic substance use can recover over time. Studies that follow groups of adolescents over time to learn about the developing human brain should be conducted. These studies should investigate how pre-existing neurobiological factors contribute to substance use, misuse, and addiction, and how adolescent substance use affects brain function and behavior." |
| 16 | HHS & OTSG, 2016 | 88 | "Patterns of alcohol and drug use change over time. New drugs or drug combinations, delivery systems, and routes of administration emerge, and with them new questions for public health. For example, concern is growing that increasing use of marijuana extracts with extremely high amounts of tetrahydocannabinol could lead to higher rates of addiction among marijuana users. Concerns also are emerging about how new products about which little is known, such as synthetic cannabinoids and synthetic cathinone's affect the brain. Additional research is needed to better understand how such products — as well as emerging addictive substances — affect brain function and behavior, and contribute to addiction." |
| 17 | HHS & OTSG, 2016 | 164 | "…[A]dditional research is needed to validate that outreach efforts geared at identifying individuals who need treatment are successful at increasing substance use treatment enrollment and subsequent outcomes." |
| 18 | Institute of Medicine, 2013 | 216 | "The present committee notes that to improve implementation of treatment regimens, the U.S. Department of Veterans Affairs (VA) has made extensive efforts to train clinicians in specialty substance-use care to deliver evidence-based therapies, such as cognitive-behavioral therapy and contingency management; however, there have been relatively few efforts to evaluate outcomes or to document the quality of implementation of treatment." |

**Table B4. Continued**

| # | Source | Page | Needs Statements |
|---|---|---|---|
| 19 | Kleber et al., 2006 | 47 | "Despite this clear evidence for an increased risk of suicidal behaviors in individuals with an SUD, few controlled studies are available to assist in guiding the treatment of such patients." |
| 20 | Kleber et al., 2006 | 48 | "As with the pharmacological treatments for sleep disturbances, more research is needed to determine if these strategies will help improve insomnia in individuals with other SUDs as well." |
| 21 | Kleber et al., 2006 | 59 | "Only a few pilot studies have been published that evaluate trauma exploration therapies (e.g., exposure therapy) in substance-abusing patients.…Future research is needed to define which patients may benefit from this type of treatment." |
| 22 | Kleber et al., 2006 | 60 | "Attention-deficit/hyperactivity disorder (ADHD) symptoms often interfere with a patient's adherence to substance use treatment, and therefore integrated psychosocial and pharmacotherapy treatment is recommended for patients with ADHD and an SUD. Although integrated psychosocial interventions for this population are recommended, research to support their use is limited." |
| 23 | Kleber et al., 2006 | 156 | "…[T]here was little empirical evidence from controlled studies that insight-oriented psychotherapy or counseling is an effective treatment for an AUD.…Empirical research on the efficacy of psychodynamic treatment for substance abuse is limited by the long-term nature of this approach and difficulties in developing representative training manuals." |
| 24 | Kleber et al., 2006 | 178 | "One broad area involves delineating the multiple factors that alter the development, manifestations, clinical course, and prognosis of SUD. Such factors may include developmental, biological, cognitive, and sociocultural factors, as well as the impact of early experiences with substances of abuse and the effects of co-occurring psychiatric or general medical conditions." |
| 25 | Kleber et al., 2006 | 178 | "Research on the modifying factors and underlying causes of SUD is inextricably linked to a need for studies of the gene or genes that influence the heritability of abuse and dependence on specific substances (e.g., alcohol, opioids) as well as the heritability of SUD in general." |
| 26 | Kleber et al., 2006 | 178 | "Another topic that requires further research relates to the acute and chronic effects of abused substances. This includes the effects of substances on a variety of organ systems as well as the pathogenesis of substance-induced fetal abnormalities after in utero exposure to substances of abuse." |
| 27 | Kleber et al., 2006 | 179 | "Virtually every aspect of SUD treatment provides an opportunity for further study and improvements in clinical care. More information is needed about the selection of treatment settings according to the unique needs of the individual patient." |
| 28 | Kleber et al., 2006 | 179 | "For children, adolescents, and adults at risk for an SUD, research is needed on the long-term efficacy of behavioral, psychosocial, and family-based interventions." |
| 29 | Kleber et al., 2006 | 179 | "The utility of a particular treatment setting for specific disorders may also be worthy of further study." |
| 30 | Kleber et al., 2006 | 179–180 | "Equally essential is additional research on psychosocial therapies for SUD. With each of the psychosocial therapies, research should determine the impact of sociodemographic, psychiatric, and general medical characteristics and patient treatment preferences on treatment participation and outcome." |
| 31 | Marquis et al., 2017 | 114 | "Finally, the fact that we have identified few academic studies that examine the relationships across multiple problematic behaviors suggests the need for the Office of the Secretary of Defense to take the lead in conducting such research to provide an evidentiary basis for its organizational approach to enhancing the health and well-being of service members and their families." |

**Table B4. Continued**

| # | Source | Page | Needs Statements |
|---|---|---|---|
| 32 | Marquis et al., 2017 | 115 | "The scientific knowledge base on risk and protective factors is still growing, and greater understanding is needed with respect to the full set of unique and overlapping factors that can reliably predict problematic behavior." |
| 33 | Marquis et al., 2017 | 117 | "As a priority, evaluate the effects of prevention and response strategies that the Department of Defense (DoD) is currently using to cope with individual problematic behaviors on other behaviors. Although there are issues with current methods of evaluating the impact that such strategies can have on problematic behavior, it nevertheless makes logical and financial sense-if DoD decides to evaluate a prevention program for a particular problematic behavior, such as hazing-that DoD also measure how it might influence other behaviors, such as sexual assaults." |
| 34 | Veterans Affairs/Department of Defense (VA/DoD), 2015 | 64 | "Further research is needed to determine models for effective and cost-effective continuing care. While there is expert consensus based on observational studies that the benefits of engagement in continuing SUD care outweigh risks when patients relapse or continue to use substances, we have found no randomized controlled trials, automatic "disciplinary" discharge from treatment continues in practice. Further research may be needed to compare the risks and benefits of automatic discharge from care and of various models of adjusting care based on response to treatment." |
| 35 | VA/DoD, 2015 | 64 | "Additional research on the use of telehealth in SUD may be beneficial, as evidence-based psychosocial interventions are not currently offered in all locations. Telehealth may help address barriers to care that contribute to low engagement in treatment in the SUD patient population." |

# 9.0 Appendix C: Initial Refined Lists of Potential Research Gaps

**Table C1. Initial Refined List of Potential Alcohol Use Disorder Gaps**

| | |
|---|---|
| **A. Treatment matching and precision medicine for alcohol use disorder (AUD)** | |
| 1 | Treatment matching and precision medicine for AUD (e.g., using Brief Alcohol Interventions), including the effects of treatment setting , and effects of age, ethnicity, and gender |
| 2 | Use of informatics to optimize treatment matching for AUD |
| **B. Pharmacotherapy for AUD** | |
| 3 | The effectiveness of pharmacotherapy for AUD intoxication and withdrawal |
| 4 | Moderators, such as medication dose and level of alcohol dependence, in the use of pharmacotherapy for AUD |
| 5 | Effectiveness of novel drug candidates and the novel use of off-label drugs as pharmacotherapy for AUD |
| 6 | Effectiveness of long-acting injectables as pharmacotherapy for AUD |
| **C. Psychotherapy (Psychosocial interventions; includes complementary and alternative medicine (CAM) + group/individual therapy, telehealth)** | |
| 7 | Effectiveness of Exercise as an adjunct treatment for AUD |
| 8 | Effectiveness of Peer support interventions for AUD |
| 9 | Comparative effectiveness of psychotherapy, including CAM, for AUD (with/without pharmacotherapy, group/individual, setting) |
| 10 | Effectiveness of telehealth interventions for AUD treatment |
| **D. Treating sleep disorders in AUD** | |
| 11 | Effectiveness of treatments for AUD-related sleep disturbance, including cognitive-behavioral therapy and pharmacotherapy (gabapentin) |
| **E. Biomarkers for AUD** | |
| 12 | Neurobiological precursors of AUD |
| 13 | Effects of alcohol dependence and addiction, treatment, and recovery on neurobiology |
| 14 | Mechanisms underlying gene x environment interactions in AUD |
| 15 | Moderating effects of gender on neurobiology in AUD |
| **F. Treatments for comorbid alcohol + psychological health (specified below)** | |
| 16 | Individual and group treatments for comorbid alcohol + posttraumatic stress disorder, major depressive disorder, attention-deficit/hyperactivity disorder, suicide |
| 17 | Optimal sequencing of treatment delivery for AUD and comorbid psychological health disorders (i.e., sequential for each disorder, or combined, coordinated care for both) |
| **G. Effects of gender, ethnicity, and culture on development of AUD and treatment** | |
| 18 | The effect of being lesbian, gay, bisexual, and transgender on development of AUD and treatment outcomes |
| 19 | Effects of military culture issues (e.g., installation policies, drinking norms) on development of AUD and treatment outcomes |
| 20 | Access to care, engagement in care, and treatment retention of women and minorities for AUD treatment |
| **H. Effects of family and military units on alcohol consumption** | |
| 21 | Effects of military leadership behaviors, norms and attitudes on unit drinking |
| 22 | Effects of individual drinking on family or other social unit (e.g., peer) functioning |
| 23 | Effects of alcohol on domestic violence and sexual assault |
| 24 | Effects of alcohol on child abuse and neglect |
| **I. Improve access, engagement, and continuity to care for AUD treatment** | |
| 25 | Strategies to improve access to care, engagement, and continuity of care (e.g., care management) for AUD |
| 26 | Effect of patient preferences on engagement and treatment outcomes |
| **J. Identification and management of alcohol problems in the military** | |
| 27 | Validity screening and assessment for AUD in the military health system |
| 28 | Impact of policies and procedures (e.g., confidentiality) on alcohol management and readiness |

**Table C1. Continued**

| | |
|---|---|
| **K. Improving alcohol-related provider + clinic behaviors** | |
| 29 | Increased use of evidence-based interventions and improved pharmacotherapy uptake by providers and clinics for AUD |
| 30 | Improved coordination of care for alcohol and comorbid psychological health conditions |
| **L. Identify effective prevention strategies and policies** | |
| 31 | Identify events across military career (e.g., deployment, attrition) associated with development of AUD |
| 32 | Examine sequence of development of AUD and comorbidities |
| **M. Alcohol epidemiology in the military** | |
| 33 | Epidemiology of AUD and comorbid psychological health conditions (gender, ethnicity, and age effects) |
| 34 | Prospective risk factors for VA alcohol and psychological health incidence |
| 35 | Cumulative effect of AUD and psychological health comorbidity mortality |

**Table C2. Initial Refined List of Potential Prescription Opioids Gaps**

| | |
|---|---|
| **A. Prevention** | |
| 1 | Effectiveness of screening measures, risk assessments (e.g., opioid risk tool, Stratification Tool for Opioid Risk Mitigation), and other strategies to predict opioid prescription drug misuse (PDM) |
| 2 | Investigate manner in which opioid use is initiated (e.g., via legitimate medical use), risk factors associated with opioid use disorder (OUD) (e.g., age, pain characteristics, user behaviors; substance use disorder (SUD)), timing and trajectory of increased opioid misuse, and other predictors of opioid PDM (and adverse events) |
| 3 | Effectiveness of abuse deterrent formulations (ADFs) (e.g., naloxone) and brief interventions for patients at high risk for OUD for preventing opioid PDM |
| 4 | Effectiveness of current care recommendations, including current practice guidelines, written management plans, patient education, patient monitoring, and informed consent in preventing opioid PDM |
| 5 | Identify biomarkers which indicate high risk for opioid addiction and OUD relapse. |
| **B. Screening/Diagnosis** | |
| 6 | Effectiveness of urine tests and screening instruments to identify opioid PDM |
| 7 | Identify predictors of opioid PDM leading to illicit opioid use (e.g., heroin) |
| **C. Treatment/Management of Chronic Pain** | |
| 8 | Effectiveness and long-term benefits of novel treatments for chronic pain (including treatments as an adjunct to long term opioid therapy (LOT)) |
| 9 | Comparative effectiveness of other treatments of chronic pain (e.g., exercise and psychological therapies) vs. LOT |
| 10 | Investigate timing, dosing, release schedule (extended-release/long-acting), and optimal conditions to decrease Morphine Equivalent Daily Dose) |
| 11 | Benefits, harms, and costs of LOT for non-end-of-life pain (outcomes lasting longer than 16 weeks) |
| 12 | Effectiveness of multidisciplinary pain interventions (e.g., combinations of behavioral health, pharmacological, physical therapy) |
| **D. Treatment/Management of Prescription Opioid Misuse/OUD** | |
| 13 | Effectiveness of Medication Assisted Treatment (MAT) for patients with OUD (in primary care)(gabapentin) |
| 14 | Comparative effectiveness of different types of MAT for patients with OUD |
| 15 | There is a lack of evidence regarding duration, doses, and titration of MAT for patients with OUD |
| 16 | Effectiveness of psychosocial and/or peer interventions as component of MAT for patients with OUD |
| 17 | Effectiveness and safety of mid-level providers (nurse practitioners, physician assistants) prescribing MAT for patients with OUD |
| 18 | Effectiveness of treatments informed by role of social attachment and oxytocin for patients with OUD |
| 19 | Further research is needed on the efficacy of alternative treatments for pain and ways to mitigate risks of opioid-related adverse events, including in patients with SUD and pain |
| 20 | Identify strategies for safely managing patients at elevated risk of suicide who demand opioid medications or become further destabilized during tapering |

**Table C2. Continued**

| | |
|---|---|
| **E. Pharmacological Treatments** | |
| 21 | Effectiveness of measures to improve adherence (e.g., contingency management) and retention for patients taking naltrexone in reducing opioid consumption |
| 22 | Comparative effectiveness and safety profile of MAT for prenatal patients |
| 23 | Comparative effectiveness of pharmacological agents for treatment of chronic pain, including administration, formulation, delivery, and different combinations (e.g., methadone vs. opioids; tramadol; non-steroidal anti-inflammatory drugs; buprenorphine) |
| 24 | Efficacy of novel drugs (e.g., tapentadol) and delivery methods for treating OUD |
| 25 | Effectiveness of buprenorphine as withdrawal medication |
| 26 | Adverse effects of polypharmacy that includes opioids |
| **F. Health Services** | |
| 27 | Effectiveness of treatment matching for all types of treatments (including multimodal, setting, psychosocial (e.g., pain management clinics)) |
| 28 | Effectiveness of prescription drug monitoring programs, including ease of use, inter-operability, effect of system of care, treatment related outcomes (e.g., abuse, addiction, overdose, misuse) in reducing diversion and misuse |
| 29 | Effectiveness of methods for reducing diversions (e.g., ADFs, technologies, and education) |
| 30 | Effective implementation of best practices (e.g., setting, care delivery) for the use of MAT and interventions to improve MAT prescribing practices, e.g., concordant with guidelines |
| 31 | Coordination and integration of care for patients with OUD |
| 32 | Effectiveness of telehealth interventions in treating OUD |
| **G. Special Populations** | |
| 33 | Benefits and harms of opioid use and symptom differences in opioid addiction depending on patient demographics (including understudied populations) |
| **H. Other** | |
| 34 | Identify biological mechanisms responsible for stress-induced vulnerability to opioid misuse and relapse |
| 35 | Effect of MAT on deployment readiness |

**Table C3. Initial Refined List of Potential Novel Synthetic Drugs Gaps**

| | |
|---|---|
| **A. Risk** | |
| 1 | Investigate risk factors for transitioning from recreational use to problem use of synthetic cathinones, synthetic cannabinoids, and novel synthetic opioids (NSOs), including demographics, psychological health comorbidities, substance use disorder (SUD), psychosocial/military stressors, and substance availability |
| 2 | Investigate normative perceptions and their impact on synthetic cathinone, synthetic cannabinoid, and NSO use among active-duty Service members (ADSMs) |
| **B. Epidemiology** | |
| 3 | Rates and demographics of synthetic cathinone, synthetic cannabinoid, and NSO use in ADSMs |
| 4 | Social network/geographic factors associated with synthetic cathinone, synthetic cannabinoid, and NSO use |
| **C. Prevention** | |
| 5 | Effect of public health and education campaigns and of interventions (e.g., Primed for Life) on prevention of synthetic cathinone, synthetic cannabinoid, and NSO use |
| **D. Screener** | |
| 6 | Develop, improve, and validate effective screening methods for synthetic cathinone, synthetic cannabinoid, and NSO use |
| **E. Treatment** | |
| 7 | Effectiveness of medications and psychosocial therapies (e.g., motivational enhancement therapies) to treat synthetic cathinone and NSO use |
| 8 | Identify potential medications to treat synthetic cathinone, synthetic cannabinoid, and NSO use |
| 9 | Effectiveness of e-cigarette intervention for cessation of tobacco smoking |
| 10 | Evaluate effectiveness of traditional nicotine cessation therapy vs. e-cigarette cessation intervention |
| 11 | Comparative effectiveness of e-cigarette interventions vs traditional interventions for tobacco cessation |

**Table C3. Continued**

| | |
|---|---|
| **F. Health Services** | |
| 12 | Develop and/or evaluate interventions to improve provider knowledge and practices regarding screening, diagnosing and management of patients using synthetic cathinones, synthetic cannabinoids, and NSOs |
| **G. Basic Research** | |
| 13 | Effects of synthetic cathinones, synthetic cannabinoids, and NSOs on structure and functioning of the brain |
| 14 | Biomarkers to identify individuals at risk for synthetic cathinone, synthetic cannabinoid, and NSO use |
| 15 | Neurobiological correlates of transition from synthetic cathinone, synthetic cannabinoid, and NSO recreational use to abuse/dependence |
| 16 | Develop and/or evaluate new or novel-use-of-existing overdose reversal and withdrawal medications for synthetic cathinones, synthetic cannabinoids, and NSOs |
| 17 | Investigate potential of synthetic cathinone, synthetic cannabinoid, and NSO use for addiction and dependency |
| 18 | Determine clinical presentation associated with synthetic cathinone, synthetic cannabinoid, and NSO use and addiction |
| 19 | Research on synthetic cathinone, synthetic cannabinoid, and NSO drug-drug interactions, including other drugs of abuse and prescribed medications |
| 20 | Comparison of dose response pattern for e-cigarettes to the known literature on smoking/smokeless tobacco |
| **H. Harms** | |
| 21 | Harms of e-cigarette “dripping” |
| 22 | Investigate whether e-cigarette use leads to initiation or increased use of smoked or smokeless tobacco |
| 23 | Harms of ongoing exposure to e-cigarette vapors |
| 24 | Comparative health harms between e-cigarettes vs. smoke tobacco (including secondhand) |
| 25 | Effects of synthetic cathinones, synthetic cannabinoids, and NSOs on physical and psychological health |
| 26 | Impact of synthetic cathinones, synthetic cannabinoids, and NSOs on risky and/or violent behaviors |
| 27 | Impact of synthetic cathinones, synthetic cannabinoids, and NSOs on psychosocial and occupational functioning, such as family and operational military readiness |

# 10.0 Appendix D: Final Refined List of Potential Research Gaps

**Alcohol Use Disorder (n=11)**

- Effectiveness of novel drug candidates and the novel use of off-label drugs as pharmacotherapy for alcohol use disorder (AUD)
- Optimal sequencing of treatment delivery for AUD and comorbid psychological health disorders (i.e., sequential for each disorder, or combined, coordinated care for both)
- Effects of military culture issues (e.g., installation policies, drinking norms) on development of AUD and treatment outcomes
- Access to care, engagement in care, and treatment retention of women and minorities for AUD treatment
- Effects of military leadership behaviors, norms, and attitudes on unit drinking
- Effects of individual drinking on family or other social unit (e.g., peer) functioning
- Effects of alcohol on domestic violence and sexual assault
- Strategies to improve access to care, engagement, and continuity of care (e.g., care management) for AUD
- Impact of policies and procedures (e.g., confidentiality) on alcohol management and readiness
- Increased use of evidence-based interventions and improved pharmacotherapy uptake by providers and clinics for AUD
- Improved coordination of care for alcohol and comorbid psychological health conditions

**Prescription Opioids (n=11)**

- Effectiveness of screening measures, risk assessments (e.g., opioid risk tool, Stratification Tool for Opioid Risk Mitigation), and other strategies to predict opioid prescription drug misuse (PDM)
- Effectiveness of abuse deterrent formulations (e.g., naloxone) and brief interventions for patients at high risk for opioid use disorder (OUD) for preventing opioid PDM
- Effectiveness of current care recommendations, including current practice guidelines, written management plans, patient education, patient monitoring, and informed consent in preventing opioid PDM
- Effectiveness and long-term benefits of novel treatments for chronic pain (including treatments as an adjunct to long-term opioid therapy (LOT))
- Comparative effectiveness of other treatments of chronic pain (e.g., exercise and psychological therapies) vs. LOT
- Investigate timing, dosing, release schedule (extended-release/long-acting), and optimal conditions to decrease Morphine Equivalent Daily Dose
- Effectiveness of multidisciplinary pain interventions (e.g., combinations of behavioral health, pharmacological, physical therapy)
- Further research is needed on the efficacy of alternative treatments for pain and ways to mitigate risks of opioid-related adverse events, including in patients with substance use disorder and pain
- Comparative effectiveness of pharmacological agents for treatment of chronic pain, including administration, formulation, delivery, and different combinations (e.g., methadone vs. opioids, tramadol, nonsteroidal anti-inflammatory drugs, and buprenorphine)
- Effectiveness of prescription drug monitoring programs (ease of use, inter-operability, effect of system of care, treatment related outcomes: abuse, addiction, overdose, misuse) in reducing diversion and misuse
- Effective implementation of best practices (e.g., setting, care delivery) for the use of Medication-Assisted Treatment (MAT) and interventions to improve MAT prescribing practices, e.g., concordant with guidelines

**Novel Synthetic Drugs (n=10)**

- Investigate normative perceptions and their impact on synthetic cathinone, synthetic cannabinoid, and novel synthetic opioids (NSOs) use among active-duty Service members (ADSMs)
- Rates and demographics of synthetic cathinone, synthetic cannabinoid, and NSO use in ADSMs
- Social network/geographic factors associated with synthetic cathinone, synthetic cannabinoid, and NSO use
- Effect of public health and education campaigns and of interventions (e.g., Primed for Life) on prevention of synthetic cathinone, synthetic cannabinoid, and NSO use
- Develop, improve, and validate effective screening methods for synthetic cathinone, synthetic cannabinoid, and NSO use
- Develop and/or evaluate interventions to improve provider knowledge and practices regarding screening, diagnosing and management of patients using synthetic cathinones, synthetic cannabinoids, and NSOs
- Determine clinical presentation associated with synthetic cathinone, synthetic cannabinoid, and NSO use and addiction
- Investigate whether e-cigarette use leads to initiation or increased use of smoked or smokeless tobacco
- Effects of synthetic cathinones, synthetic cannabinoids, and NSOs on physical and psychological health
- Impact of synthetic cathinones, synthetic cannabinoids, and NSOs on psychosocial and occupational functioning, such as family and operational military readiness

# 11.0 Appendix E: PHCoE's Rationale Regarding Retaining, Revising, or Removing Potential Gaps (After Reviewing Published Literature)

**Table E1. Rationale Regarding Retaining, Revising, or Removing Potential Gaps**

| | Potential Gaps | Decision and Rationale (Retained, Revised, or Removed) | Final Gaps |
|---|---|---|---|
| | **Alcohol Use Disorder** | | |
| 1 | Optimal sequencing of treatment delivery for alcohol use disorder (AUD) and comorbid psychological health disorders (i.e., sequential for each disorder, or combined, coordinated care for both). | **Retained and Revised.** Individual interventions are well researched, but research is needed on coordinated health systems models in the military health system (MHS). | Examine the optimal integrative treatment approach for patients with AUD plus comorbid psychiatric conditions in the MHS (within and across settings). |
| 2 | Effectiveness of novel drug candidates and the novel use of off-label drugs as pharmacotherapy for AUD. | **Removed.** A multitude of published and in-progress research addresses this topic outside of the MHS and may be used to inform military health. Research recommendations, such as systematically reporting on quality of life outcomes, are included under General Recommendations (pg. 24). | |
| 3 | Effects of military culture issues (e.g., installation policies, drinking norms) on development of AUD and treatment outcomes. | **Retained and Revised.** The literature review led to more specific language to clarify the intended target of public health interventions. The literature is well established to identify specific elements of military culture that are associated with increases in problem drinking. | Develop effective public health interventions that address specific elements of military culture identified as being associated with increases in problem-drinking. |
| 4 | Access to care, engagement in care, and treatment retention of women and minorities for AUD treatment. | **Retained and Revised.** Numerous studies, mostly cross-sectional, examine the relationship between specific social identity characteristics and specific outcomes related to alcohol use. Overall, the findings are mixed, and few studies holistically examine how different factors together affect AUD treatment-seeking, engagement, and retention. | Examine the effects of social identity characteristics (e.g., age, gender, race/ethnicity, sexual orientation) on AUD treatment-seeking, engagement, and retention. (Findings may inform military programs to improve treatment in minorities.) |
| 5 | Effects of military leadership behaviors, norms, and attitudes on unit drinking. | **Retained and Revised.** The research gap was broadened to include other elements of group membership (e.g., strength of identification with military group, such as unit or branch of service) that might interact with Service members' perceptions of leaders' attitudes. | Examine the effects of leadership attitudes, group characteristics, and group identification factors on drinking in the military. |
| 6 | Effects of individual drinking on family or other social unit (e.g., peer) functioning. | **Retained and Revised.** Numerous studies document adverse effects of individual drinking on family functioning. The gap was revised to address effects of drinking on military unit functioning. | Examine the effects of hazardous alcohol use/AUD on Service member readiness and unit functioning. |
| 7 | Effects of alcohol on domestic violence and sexual assault. | **Retained and Revised.** The literature identifies alcohol as a risk factor for alcohol-involved sexual assault perpetration and victimization. The gap was revised to target prevention efforts specific to Service members. | Investigate the effectiveness of interventions for prevention of alcohol-related sexual assault/domestic violence in the military (both for victims and perpetrators). |

**Table E1. Continued**

| | | | |
|---|---|---|---|
| 8 | Strategies to improve access to care, engagement, and continuity of care (e.g., care management) for AUD. | **Retained and Revised.** The literature indicates several strategies have proven effective in improving access to care, engagement, and continuity of care for AUD. The gap was revised to address the need for research to improve the implementation and sustainment of these proven approaches into standard care. | Identify factors that improve effective implementation of evidence- and population-based approaches for the treatment and management of alcohol misuse/AUD in the MHS. |
| 9 | Impact of policies and procedures (e.g., confidentiality) on alcohol management and readiness. | **Retained and Revised.** After reviewing the current literature, the text was expanded to explicate types of policies and procedures that need to be examined and to provide some examples of promising areas to examine. | Examine the impact of relevant Department of Defense- (DoD) and Service-specific policies and procedures on Service member problem-drinking and Service member readiness (e.g., confidentiality, type of treatment services available, disciplinary consequences for infringement, and the cost of alcohol on base). |
| 10 | Increased use of evidence-based interventions and improved pharmacotherapy uptake by providers and clinics for AUD. | **Retained and Revised.** Multi-faceted strategies (i.e., professional and/or organizational and/or patient-orientated) demonstrate the strongest effects on AUD outcomes compared with professional-orientated strategies alone. The gap was revised to address a significant gap in determining the comparative effectiveness of different multifaceted strategies. | Develop and comparatively test multi-faceted (i.e., professional, organizational, and patient-oriented) strategies to increase use of evidence based practices for the treatment of AUD in the MHS. |
| 11 | Improved coordination of care for alcohol and comorbid psychological health conditions. | **Removed.** Not considered a unique gap as it is redundant with Gap #1. | |
| | **Prescription Opioids** | | |
| 12 | Effectiveness of screening measures, risk assessments (e.g., opioid risk tool, Stratification Tool for Opioid Risk Mitigation), and other strategies to predict opioid prescription drug misuse (PDM). | **Retained and Revised.** Substantial research exists on individual screeners, with varied strength of evidence. Valid screeners exist, but there is limited evidence on integration of screeners into a larger health systems approach to opioid misuse mitigation. Research is needed but is not ongoing in MHS on comprehensive (health services) screening approaches to identifying and mitigating risk. | Investigate the effectiveness of opioid prescription drug misuse screening approaches within the context of existing MHS opioid misuse mitigation strategies (e.g., comprehensive screening approaches like the Stratification Tool for Opioid Risk Mitigation). |
| 13 | Effectiveness of abuse deterrent formulations (ADFs) (e.g., naloxone) and brief interventions for patients at high risk for opioid use disorder (OUD) for preventing opioid PDM. | **Retained and Revised.** No studies were found on brief interventions without some kind of medication. This potential gap was made into two questions, with effectiveness of brief interventions folded into #18. We revised the remaining element and added "military-relevant outcomes." DoD seeks to prevent opioid abuse/misuse by Service members, as many chronic pain patients are prescribed opioids that may impair functioning or lead to them being medically discharged. No directly relevant ongoing research was found. | Investigate the effectiveness of ADFs for preventing/minimizing opioid abuse and misuse, with a focus on military-relevant outcomes (e.g., fitness for duty, medboard). |

**Table E1. Continued**

| | | | |
|---|---|---|---|
| 14 | Effectiveness of current care recommendations, including current practice guidelines, written management plans, patient education, patient monitoring, and informed consent in preventing opioid PDM. | **Retained and Revised.** Current care recommendations are typically evidence-based or evidence-informed. However, providers often do not adhere to these recommendations. Several multi-faceted approaches demonstrate promising results in improving provider uptake of care recommendations for prescription opioids. Further research is needed to evaluate the implementation of these strategies in the MHS. | Apply and evaluate structured strategies that aim to increase uptake of current opioid clinical practice guideline (CPG) recommendations to prevent abuse/ misuse. |
| 15 | Effectiveness and long-term benefits of novel treatments for chronic pain (including treatments as an adjunct to long term opioid treatment (LOT)). | **Retained and Revised.** Incorporated elements from multiple gaps (#15, 16, 20). Many relevant studies are being conducted but are often methodologically weak so that strong conclusions cannot be made. Little published research exists on adjunctive therapies. While there is a good amount of active research, none addresses the measurement of this risk. The gap is very broad, (combines 3 gaps) not considered to be closed. | Investigate treatments for chronic pain other than conventional opioids that reduce risk for prescription opioid use, abuse, and misuse. |
| 16 | Comparative effectiveness of other treatments of chronic pain (e.g., exercise and psychological therapies) vs. LOT). | **Removed.** Elements combined with #15. Few studies directly compare LOT to alternative treatments. Alternative treatments are usually compared to "treatment as usual" that does not necessarily include opioids. It is rare to replace opioid therapy entirely with alternative approaches. High-quality research on this question may not be ethically feasible. | |
| 17 | Investigate timing, dosing, release schedule (extended-release/long-acting), and optimal conditions to decrease Morphine Equivalent Daily Dose. | **Removed.** CPGs related to chronic pain answer parts of this gap. There is no clear agreement in the literature on how well CPGs/recommendations translate into practice (depending on future findings, e.g., Cochrane review in progress, gap may be closed). | |
| 18 | Effectiveness of multidisciplinary pain interventions (e.g., combinations of behavioral health, pharmacological, physical therapy). | **Removed.** Multidisciplinary interventions are not consistent, so it is hard to make fair comparisons. It is not viable to look at so many types of interventions comparatively. Outcomes are more related to pain, not SUD. Research can be done in civilian population and generalized to military. | |
| 19 | Further research is needed on the efficacy of alternative treatments for pain and ways to mitigate risks of opioid-related adverse events, including in patients with substance use disorder and pain. | **Removed.** There is an extensive research literature addressing non-opioid treatments for pain. Research recommendations, such as tracking outcomes for at least one year, are included under General Recommendations (pg. 24). | |

**Table E1. Continued**

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| 20 | Comparative effectiveness of pharmacological agents for treatment of chronic pain, including administration, formulation, delivery, and different combinations (e.g., methadone vs. opioids, tramadol, nonsteroidal anti-inflammatory drugs, and buprenorphine). | **Removed.** Elements are combined with #15. There is a lot of research on this topic. Efficacy is established and the treatment-related outcomes, like comparative effect, long-term effects, how well tolerated, safety, and cost are known. This is research that can be done in the civilian world (there is an industry that supports this kind of research on its own). This is not a military-specific gap. | |
| 21 | Effectiveness of prescription drug monitoring programs (PDMPs), including ease of use, inter-operability, effect of system of care, treatment related outcomes (e.g., abuse, addiction, overdose, misuse) in reducing diversion and misuse. | **Removed.** The state of the literature is fairly poor with regard to reducing diversion and misuse. PDMP's impact on high prescribers is known to be effective, but these programs have not yet been able to show an impact on opioid diversion and misuse. | |
| 22 | Effective implementation of best practices (e.g., setting, care delivery) for the use of Medication-Assisted Treatment (MAT) and interventions to improve MAT prescribing practices, e.g., concordant with guidelines. | **Removed.** MAT element incorporated into #14 but subsequently removed after review of in-progress literature. There is good research on the first part of the question; the remaining gap relates to how to increase uptake of MAT, which is an implementation science gap. Evaluations suggest MATs are severely underused in military. | |
| | **Novel Synthetic Drugs** | | |
| 23 | Investigate normative perceptions and their impact on synthetic cathinone, synthetic cannabinoid, and novel synthetic opioid (NSO) use among active-duty Service members (ADSMs). | **Removed.** Key elements are covered in #25 without limiting to military. The topic was deemed too limited in scope to stand on its own. | |
| 24 | Rates and demographics of synthetic cathinone, synthetic cannabinoid, and NSO use in ADSMs. | **Retained and Revised.** The gap was expanded to include differences across Services. | Examine prevalence and demographics of synthetic cathinone, synthetic cannabinoid, and NSO use in ADSMs across services, including among the general active-duty population. |
| 25 | Social network/geographic factors associated with synthetic cathinone, synthetic cannabinoid, and NSO use. | **Retained and Revised.** Elements were inserted from #23, social factors were expanded and explicated, and some geographic factors were moved to #24. | Examine the effects of social factors (e.g., social networks, social media, interpersonal relationships, military community) on awareness, initiation, cessation, and prevention of the use of synthetic cathinones, synthetic cannabinoids, and NSOs. |
| 26 | Effect of public health and education campaigns and of interventions (e.g., Primed for Life) on prevention of synthetic cathinone, synthetic cannabinoid, and NSO use. | **Retained and Revised.** There is little or no published evidence to document, evaluate, or test preventative public health and educational activities for synthetic cathinone, synthetic cannabinoid, and NSO use. The gap was refined to be more specific to the military community. | Investigate public health and educational activities to prevent synthetic cathinone, synthetic cannabinoid, and NSO use in the military community. |
| 27 | Develop, improve, and validate effective screening methods for synthetic cathinone, synthetic cannabinoid, and NSO use. | **Removed.** There is a large body of research with many ongoing studies. Numerous valid screening measures exist. Although the changing landscape of synthetic compounds requires continued research, civilian research is well funded and should translate adequately to military populations. | |

**Table E1. Continued**

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| 28 | Develop and/or evaluate interventions to improve provider knowledge and practices regarding screening, diagnosing, and management of patients using synthetic cathinones, synthetic cannabinoids, and NSOs. | **Retained.** The research on this topic is nascent. Data are needed to determine the extent to which clinicians receive training on the properties, screening, diagnosing and treatment of synthetic drug use and toxicity. This gap applies to the civilian and military sectors. | Develop and/or evaluate interventions to improve provider knowledge and practices regarding screening, diagnosing, and management of patients using synthetic cathinones, synthetic cannabinoids, and NSOs. |
| 29 | Determine clinical presentation associated with synthetic cathinone, synthetic cannabinoid, and NSO use and addiction. | **Removed.** There is a nascent civilian literature on signs and symptoms, with a paucity of single drug-type research. Most studies included polydrug users, which is not perceived as feasible in military populations. Education of providers was considered a more pressing issue and is addressed in #28. | |
| 30 | Investigate whether e-cigarette use leads to initiation or increased use of smoked or smokeless tobacco. | **Removed.** An adequate literature exists. The topic was deemed more appropriate for civilian research efforts. | |
| 31 | Effects of synthetic cathinones, synthetic cannabinoids, and NSOs on physical and psychological health. | **Retained and Revised.** Many recent studies examine the pharmacology of these drugs as well as symptoms associated with their use, but very little has been done to explore lasting effects. This research may not be relevant in a military setting. The topic was expanded to include psychosocial and occupational functioning and targeted specifically to military readiness. | Investigate the effects of synthetic cathinone, synthetic cannabinoid, NSO use on functioning (e.g., psychosocial, occupational, readiness) in ADSMs. |
| 32 | Impact of synthetic cathinones, synthetic cannabinoids, and NSOs on psychosocial and occupational functioning, such as family and operational military readiness. | **Removed.** Key elements of psychosocial and occupational functioning were incorporated into #31. The impact of synthetic drugs on psychosocial and occupational functioning represents a significant research gap. There has been a steep rise in emergency department visits related to synthetic drug related problems among young adults but not a proportionate rise in the literature on the social impacts. | |