


A Research Agenda for Advancing Strategies to Improve Opioid Safety: Findings from a VHA State of the Art Conference



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US military Veterans have been disproportionately impacted by the US opioid overdose crisis. In the fall of 2019, the Veterans Health Administration (VHA) convened a state-of-the-art (SOTA) conference to develop research priorities for advancing the science and clinical practice of opioid safety, including both use of opioid analgesics and managing opioid use disorder. We present the methods and consensus recommendations from the SOTA. A core group of researchers and VA clinical stakeholders defined three areas of focus for the SOTA: managing opioid use disorder, long-term opioid therapy for pain including consideration for opioid tapering, and treatment of co-occurring pain and substance use disorders. The SOTA participants divided into three workgroups and identified key questions and seminal studies related to those three areas of focus. The strongest recommendations included testing implementation strategies in the VHA for expanding access to medication treatment for opioid use disorder, testing collaborative tapering programs for patients prescribed long-term opioids, and larger trials of behavioral and exercise/movement interventions for pain among patients with substance use disorders.

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INTRODUCTION

US military Veterans have been disproportionately impacted by the opioid overdose, morbidity, and mortality crisis, with a fatal overdose rate of 21.08 per 100,000 person years in 2016, a 65% increase from 2010.¹ Prescribed opioids, opioid misuse, and opioid use disorder (OUD) contribute to substantial risk

and negative impacts to individuals, including increased harms associated with other addictions, depression,² sexual dysfunction,³ infectious disease transmission,⁴ and a plethora of other physical and mental conditions.³ As such, improving opioid safety has emerged as a top priority in the Veterans Health Administration (VHA), spurring system-wide efforts to decrease risky opioid prescribing,⁵ improve access to the overdose reversal drug naloxone,⁶ and improve access to medications for OUD (MOUD).⁵ The VHA convened a state-of-the-art (SOTA) conference to develop research priorities for advancing the science and clinical practice of improving opioid safety. Herein, we present the methods and consensus recommendations for research priorities emanating from the SOTA.

METHODS

In the 6 months before the September 2019 SOTA, co-chairs recruited 14 investigators and key VHA clinical stakeholders, from within and outside VHA, who served as the SOTA planning committee. Through a series of teleconferences, the committee reached consensus on three areas of focus—managing OUD; long-term opioid therapy (LTOT) for pain, including consideration of tapering; and treatment of co-occurring pain and substance use disorders—and divided into three workgroups corresponding to the three focus areas.

Leaders of each workgroup convened teleconferences to further refine key questions, identify subject matter experts to participate in the SOTA, and select pre-conference readings. Participants were 56 subject matter experts from disciplines including general internal medicine, psychology, addiction medicine/psychiatry, nursing, pharmacy, pain medicine, neurology, clinical epidemiology, health services research, and health policy. Attending participants were assigned to one of the three workgroups and distributed pre-conference readings (a set of 3–5 recommended publications for each workgroup)

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along with key questions to help prepare for their workgroup's discussion at the conference.

On the first day of the SOTA conference, participants were briefed on conference objectives; then, workgroups met to discuss key questions and reach consensus on research, clinical, and policy priorities. On day 2, each workgroup presented a summary of their deliberations and consensus priorities to the full group, followed by open discussion. An expert panel responded to workgroup summaries. Below, and summarized in Table 1, we present the findings of each workgroup with respect to research gaps and priorities.

Managing Opioid Use Disorder

As opioid overdose mortality continues to increase among Veterans and illicit drug use shifts to highly potent synthetic opioids, there is an even more pressing need to deliver effective MOUD, including methadone, indicated buprenorphine formulations and naltrexone.^{1, 7, 8} As such, the OUD workgroup identified critical research gaps and priorities under two overarching themes of increasing access to MOUD and improving treatment quality and outcomes.

Increasing Treatment Access. In 2017, less than 36% of

patients in VHA diagnosed with OUD received MOUD. Access to treatment varies widely across the VHA.^{9, 10} Barriers to implementing MOUD include patient- and provider-level factors such as knowledge, attitudes, and stigma associated with MOUD and OUD. System-related factors include credentialing and privileging, training and staffing, and accessibility.⁹⁻¹⁴ To overcome these barriers, the workgroup emphasized several promising approaches requiring further research, including developing telemedicine models of MOUD treatment, lowering treatment thresholds, using peer support to improve navigation and engagement, and increasing access to MOUD prescribers.¹⁵⁻¹⁹

The workgroup recognized that addiction treatment within the VHA is predominantly provided in specialty settings not available at every facility, especially those in rural areas and community-based outpatient clinics.²⁰ Primary care and other office-based settings are not often engaged in addiction care. The Stepped Care for Opioid Use Disorder Train the Trainer (SCOUTT) Initiative is a large national VHA initiative to enhance MOUD treatment within primary care, mental health, and pain clinics, patterned after ongoing research in the VHA to implement MOUD in low-performing VHA facilities; this presents an ideal opportunity to deploy implementation research to identify effective practices leading to greater MOUD uptake. To overcome system-level barriers to care, more national VHA directives and research on their implementation are needed, including offering incentives to provide MOUD care, removing barriers in prescribing MOUD (e.g., requiring additional credentialing and privileging), increasing use of telemedicine, and better integrating addiction care across care settings, including care of patients with polysubstance use.

Improving Quality of Care and Patient Outcomes.

Challenges and barriers to improving outcomes for patients with OUD include the absence of standards of high-quality MOUD care, especially related to the optimal frequency of drug monitoring and clinic visits. Developing interventions to improve treatment retention and avoid inappropriate discontinuation of MOUD by providers was identified as a priority. Research needs regarding psychosocial treatments were also considered, including the utility of mandating non-pharmacological treatment, the comparative effectiveness of the type and frequency of treatments, and determining which patients would benefit from psychosocial treatments. Improving retention in MOUD is a high priority because relapse and mortality increase when MOUD ceases. Discontinuation of treatment can occur for a variety of reasons related to patient (e.g., relapse), provider (e.g., quality of care), and system factors (e.g., arbitrary limits of duration of care).²¹⁻²⁶ Research priorities include understanding how to implement chronic disease management for MOUD, understanding factors leading to MOUD discontinuation, and re-engaging patients who discontinue care.²⁷ Finally, studying interventions to link patients who have a non-fatal overdose to MOUD treatment was deemed a high priority.^{6, 28, 29}

Table 1 Research Priorities Identified at the State of the Art Conference to Advance Strategies to Improve Opioid Safety

Management of opioid use disorder (OUD)	Implementation strategies and use of telemedicine to address barriers (e.g., patient/provider knowledge deficits, stigma) and promote facilitators (e.g., provider incentives) to increase medication treatment for OUD Impact of various OUD treatment adherence monitoring strategies Individual vs. group psychosocial treatment comparisons including to address polysubstance use Effectiveness of community supports/peer support/family support Implementing chronic disease management model in OUD care
Long-term opioid therapy for pain, including tapering	Benefits and harms of opioid dose reduction and discontinuation Strategies for safe, effective opioid tapering Role for initiating or continuing low-dose/intermittent opioid dosing among older Veterans with chronic pain compared to non-opioid medications Characteristics of patients for whom the benefits of low-dose, intermittent opioid regimens outweigh risks
Co-occurring pain and substance use disorders	Behavioral and exercise/movement interventions for chronic pain among patients with SUDs Role of buprenorphine for chronic pain compared to placebo or other analgesics Buprenorphine/naloxone rotation vs. traditional taper when reduction in long-term opioid therapy is indicated Managing acute pain among patients on medications for OUD Potential SUD-related harms of cannabis, ketamine, and gabapentin for pain

Long-term Opioid Therapy for Pain, Including Tapering

Workgroup members agreed that LTOT, typically defined as receiving ≥ 90 consecutive days of prescribed opioid analgesics, has been overused, and that many patients receiving LTOT could benefit from dose reduction or discontinuation. LTOT commonly results in physiological adaptations that make opioid discontinuation difficult while potentially contributing to the persistence or worsening of pain.³⁰ Workgroup members agreed with the Centers for Disease Control and Prevention³¹ and Department of Veterans Affairs/Department of Defense³² recommendations that prescribers should, whenever possible, use a collaborative approach and individualize the rate of tapering when LTOT benefits no longer outweigh harms. Members were concerned about policies and practices that may encourage patient abandonment or abrupt opioid reduction, potentially harming patients.^{33, 34} The workgroup focused on three priority areas for additional research: (1) benefits and harms of opioid dose reduction and discontinuation (2); opioid tapering strategies; and (3) the role of continuation or initiation of LTOT.

Updated background information on benefits and harms of dose reduction came from a rapid evidence review by the VA Evidence Synthesis Program.³⁵ Consistent with a prior review,³⁶ authors found low-quality evidence that pain severity and function may improve with intensive voluntary programs that incorporate opioid tapering and may not change with less intensive interventions. The workgroup agreed that additional research was needed to understand outcomes of dose reduction and discontinuation, including benefits (pain intensity and interference, quality of life, physical function, social/emotional function, satisfaction), harms (protracted withdrawal symptoms, mental health symptoms, suicide, overdose, transition to illicit opioid use), and health services outcomes such as retention in VHA care.

Strategies for opioid tapering should be studied in conjunction with patient-reported benefits and harms because dose reduction alone may not improve outcomes. The workgroup discussed inherent difficulties in studying tapering strategies, such as patients' unwillingness to enroll and accept randomization to alternative treatment strategies.³⁶ Because clinical trials are voluntary, results of tapering trials will be most relevant to patients who wish to taper. Challenges of observational research include the importance of patient-reported outcomes and detailed clinical data often unavailable in large administrative data sets.

Despite these challenges, the workgroup agreed that additional research was needed to evaluate the effectiveness and safety of opioid tapering strategies, including collaborative care models, non-pharmacologic approaches, medication protocols, clinician training, patient education, interventions to enhance patient or family engagement, and technology-based interventions. Discussion focused on buprenorphine as a promising medication to assist with opioid risk reduction and

opioid dose reduction/discontinuation. Issues of confusing terminology and evolving clinical diagnostic strategies related to addiction, OUD, dependence, and related concepts were considered to be a barrier to research in this area. Members called for a Delphi study as a first step toward developing a diagnostic approach to patients who have difficulties reducing prescribed opioids despite harms outweighing benefits.

Finally, as research has demonstrated dose-dependent harms of LTOT, the workgroup discussed whether low-dose, intermittent opioids may have benefits that outweigh harms for some patients. Harms such as tolerance, dependence, and hyperalgesia may be less likely with lower dose or intermittent opioids. The workgroup identified a need for research to evaluate benefits and harms of the following comparisons: (1) continuing versus discontinuing low-dose, intermittent opioids among patients on LTOT and (2) initiating low-dose, intermittent opioid medications versus non-opioid medications for older adults with chronic pain.³⁷

Co-occurring Pain and Substance Use Disorders

Acknowledging that pain and substance use disorders (SUDs) very commonly co-occur and that persons with SUDs too often receive low-quality pain care, this workgroup focused on the following topics: (1) behavioral interventions for treating chronic pain among patients with SUDs, (2) use of buprenorphine for pain, and (3) managing acute pain among patients on MOUD.

Several studies have found benefits of modified evidence-based behavioral interventions for chronic pain such as cognitive-behavioral therapy for chronic pain to be delivered to patients with SUDs, usually in SUD settings.³⁸⁻⁴⁰ These treatments varied the degree to which they focused on pain versus SUD content. Future research should consider how to implement behavioral treatments targeting chronic pain and SUD in other settings (e.g., primary care) and how to optimize their use within existing VHA care models; how to combine treatment modalities (e.g., behavioral treatment and medication); and how to improve veteran engagement in non-pharmacological treatments for pain. Furthermore, improving access to non-opioid therapies via telemedicine platforms was deemed particularly important for patients who may have difficulty accessing in-person treatments. At least one feasibility study examined yoga among patients with co-occurring chronic pain and OUD with favorable results,⁴¹ suggesting the need for larger-scale studies of exercise/movement interventions for this population.

The workgroup examined the evidence of effectiveness of buprenorphine in various formulations for pain-related outcomes in patients with SUD. A recent systematic review found that transdermal buprenorphine is an effective analgesic in patients with chronic pain and that buccal buprenorphine is also promising, but these studies did not focus on patients with chronic pain and co-morbid SUD. Future research should

examine buprenorphine specifically in patients with pain and non-ODU SUD and consider potential benefits of using buprenorphine/naloxone vs. traditional taper among patients for whom a taper from LTOT is indicated.

The workgroup also discussed managing acute pain among patients receiving MOUD, reviewing an evidence brief conducted by the VA Evidence Synthesis Program.⁴² The review identified 8 studies on acute pain management for patients with OUD. Though noting limitations in methodology for all studies, the authors concluded that continuing MOUD after surgery may reduce the need for additional opioids, that patients receiving MOUD may need higher doses of opioids for acute pain control, and that ineffective management of acute pain may lead to disengagement from care. Workgroup members identified a need for randomized trials or well-designed observational studies to understand optimal peri-operative approaches for patients on MOUD.

CONCLUSION

Based on the findings of a 2-day VHA SOTA conference, we have outlined a research agenda related to managing OUD; LTOT for pain; and treatment of co-occurring pain and SUDs. Highest priority topics were implementation studies for expanding access to MOUD, research on tapering programs for patients prescribed LTOT, and larger trials of behavioral and exercise/movement interventions for pain among patients with SUD.

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