The Impact of Military Sexual Trauma on Opioid Use Disorder and Related Outcomes in Men and Women Veterans

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Abstract

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This dissertation research included three primary aims related to military sexual trauma (MST) and opioid use disorder (OUD) among U.S. Veterans enrolled in Veterans Health Administration (VA) care. Specifically, aims were to (1) assess the relationship between MST and OUD, (2) assess the relationship between MST and treatment for OUD among Veterans who have an OUD diagnosis, and (3) evaluate the potential role of chronic pain as a mediator in the relationship between MST and OUD, as chronic pain is a common diagnosis in sexual trauma survivors and is a major cause of opioid use. Because gender plays a critical role in how a Veteran reacts to and copes with MST, the differential role of gender was assessed in all three aims. Data were derived from VA administrative data from fiscal years 2009-2017. Analyses included multivariable logistic regression in Aims 1 and 3, and multi-level logistic regression models to account for the facility-level factors that impact opioid prescribing and OUD treatment access in Aim 2. This research can be used to inform care planning and recommendations for Veterans who are survivors of MST that is sensitive to gender-related concerns, chronic pain diagnoses, and OUD risk. It also informs barriers to receipt of effective OUD treatment and care coordination at VA facilities for these high-risk patients.

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Chapter 1 – Introduction

1.1 Background

A substantial number of Veterans have experienced military sexual trauma (MST) – at least 1 in 4 women and 1 in 100 men who seek treatment from the Veterans Health Administration (VA). MST is defined by the VA as "a physical assault of a sexual nature, battery of a sexual nature, or sexual harassment which occurred while the Veteran was serving on active duty,"[1] Sexual assault or prolonged sexual harassment in the military can have devastating physical and mental health consequences, such as PTSD, in both the short and the long term,[1,2,3,4,5,6,] and can indicate a need for increased physical and mental health care.[7,8] While MST affects both men and women Veterans, the coping mechanisms, stigma, and consequences can differ.[7] For example, men with a history of MST and PTSD are more likely to develop substance use disorders (SUDs) such as alcohol use disorder than women with a history of MST and PTSD or than men without a history of MST and PTSD;[9] women with a history MST may be more likely than women without such a history to engage in problematic drug use or experience drug overdose.[10] Recent research has also shown that a positive MST screen is associated with a greater risk for some substance use disorders in women Veterans than in men Veterans, but whether or not this relationship extends to opioid prescription receipt and opioid use disorder (OUD) is unknown.[11]

One potential yet unexplored consequence of MST is the development of OUD (maladaptive opioid use that results in impaired health or function) or the receipt of high-risk prescriptions (long-term prescriptions or high morphine-equivalent doses).[12,13,14] Approximately 3 million people in the U.S. have a current or past OUD, and approximately 70,000 Veterans had been diagnosed with OUD as of 2017.[15,16] MST may increase risk for high-risk opioid prescriptions or OUD, as Veterans with MST histories commonly experience chronic pain, PTSD and alcohol and other substance use disorders (SUDs), all of which are also associated with increased risk of drug use.[12,17] High-risk opioid prescriptions and OUD are dangerous, often chronic conditions with substantial risk for overdose and death, including suicide, as

well as social and economic complications.[18-20,21,22]However, the majority of these consequences of OUD are preventable with appropriate prevention or treatment strategies.

The most effective treatment for OUD is referred to as medication-assisted treatment (MAT) or pharmacological treatment. There are three medications approved by the Federal Drug Administration (FDA) for use by patients diagnosed with OUD: buprenorphine, methadone, and naloxone.[23] Though evidence-based treatment for OUD is available, the majority of persons with OUD do not receive it.[24] Treatment for OUD is currently received by less than 40% of VA patients with OUD.[25] The VA has taken measures to address opioid overuse and pain management, such as changes in institutional treatment and prescription practices. However, the VA still faces challenges fully combating opioid misuse while providing the best access and care to all patients. Several studies in and outside of the VA have identified barriers to OUD treatment receipt, including female gender, mental health comorbidities, and stigma, which can result in patients being hesitant to seek treatment and/or providers being reluctant to offer treatment.[26,27] While no previous study has evaluated MST as a potential barrier to OUD treatment receipt, patients with a history of MST may be less likely than those without MST to receive OUD treatment due to the complexity of their trauma history and/or other conditions that providers may prioritize for treatment. Receipt of pharmacological treatment for OUD, as a stigmatized and difficult to access health service, can also be impacted by gender as women with sexual trauma histories could experience substance use treatment facilities differently than men, due to the higher prevalence of men in these facilities. A greater understanding of the relationship between MST and treatment for OUD, and how this relationship is moderated by gender, could inform treatment initiatives and practices among providers treating OUD as well as primary care providers referring patients to SUD specialty care.

It is also important to examine mechanisms which could explain the potential association between MST and OUD. Chronic pain may be one such mechanism because it is often comorbid with mental health conditions or trauma and is associated with increased receipt of high-risk opioid prescriptions, as opioids are typically prescribed in the presence of pain.[28,29] Chronic pain is more common among persons with a

history of MST than those without,[10,30] possibly because lower pain thresholds are associated with chronic pain, and the experience of sexual violence can lower physiologic pain thresholds,[28]. Although very little research to date has assessed the association between MST and chronic pain, women are more likely to be diagnosed with a pain condition and are also more likely to initiate opioid use through a prescription,[31] which could mean that if chronic pain is a mediator in the association between MST and OUD, and if that relationship is stronger for women, women with chronic pain and a history of MST could be targeted for alternative treatment plans and drug use counseling. Determining whether the presence of chronic pain influences the association between MST and high-risk opioid use and OUD could inform care for Veterans with MST and chronic pain by prioritizing use of non-opioid pharmaceuticals and non-pharmacological interventions in patients with MST and increasing chronic pain treatment education for providers who see many of these patients.

This dissertation capitalizes on the large, nationwide data available at the VA in order to assess a larger cohort than is typically available in sexual trauma and drug use research. While this cohort was developed for a funded R21 study (R21AA025973, PIs: Williams and Blosnich), it was also instrumental to this research on MST and OUD. The VA is the largest provider of substance use disorder specialty care in the country, providing a unique opportunity to assess risk factors for receipt of high-risk opioid prescriptions, OUD and OUD treatment at the individual level. Additionally, the VA's universal screening for MST provides the largest database of sexual trauma experiences, for both women and men, in the U.S. This has allowed researchers to assess many of the long-term effects of sexual trauma in a large, trauma-exposed population. This research used data from 2009 – 2017, which allowed for analysis of the association of MST and OUD in the context of the growing opioid epidemic and included more women Veterans than in previous cohorts using VA administrative data, as the number of women Veterans using VA healthcare is continually increasing.[13] The nature of this dataset and the selected analytic methods also allowed for adjustment by facility, which is important in the context of prescriptions and OUD treatment as these can vary substantially by facility and region.[27]

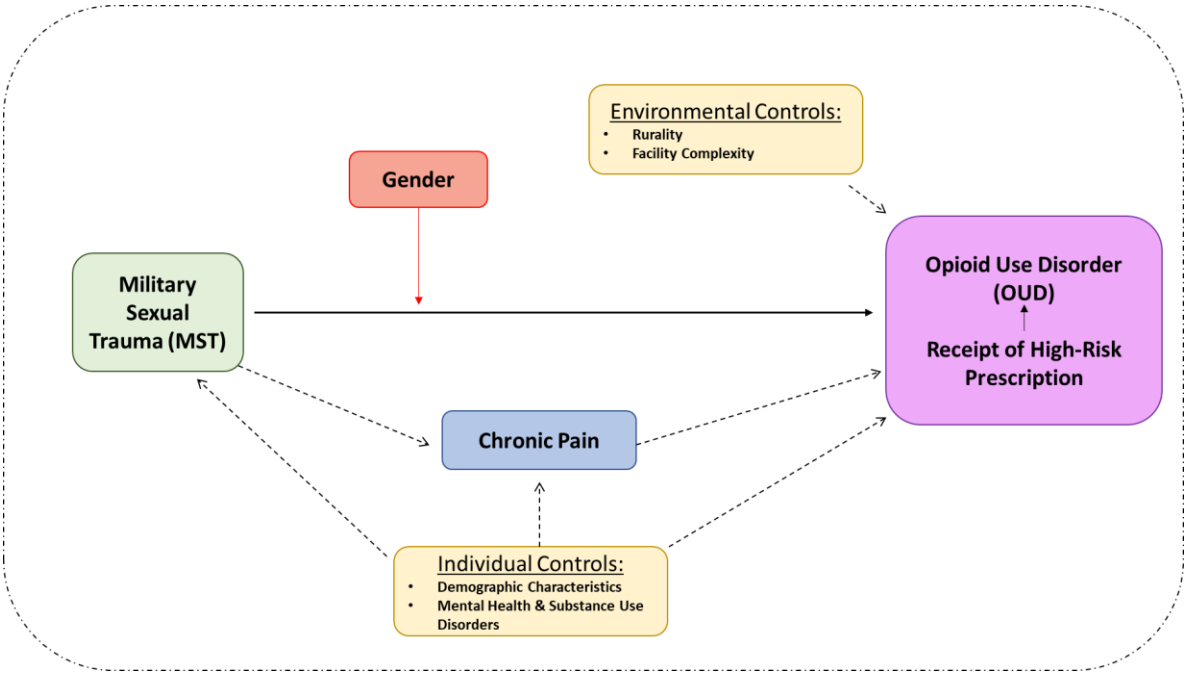
Specific aims of the dissertation were to (1) assess the relationship between MST and OUD, (2) assess the relationship between MST and treatment for OUD among Veterans who have an OUD diagnosis, and (3) evaluate the potential role of chronic pain as a mediator in the relationship between MST and OUD, as chronic pain is a common diagnosis in sexual trauma survivors and is a major cause of opioid use. This research expands the literature base in multiple fields, including MST, OUD, and gender disparities in Veteran health, all of which have implications for health services funding and delivery within the VA. MST research to date has focused mostly on women Veterans, without inclusion of male Veterans.[2,32] Additionally, women Veterans have been understudied in the drug use and drug use disorders literature.[33] It is important to study drug misuse in both women and men because they may utilize VA care in different ways and through different access points.[7,8] The OUD literature base is still small, and this research will provide important insights as to potential factors that can lead to OUD, associated mental and physical health conditions, as well as a deeper understanding of who is most at risk of development of OUD and of subsequently not receiving the treatment they need to recover from this condition.

1.2 Conceptual Framework

The conceptual framework (Figure1) which guided the research for Aims 1 and 3 posits that MST, a traumatic sexual event occurring during military service, is associated with OUD. MST is associated with significant mental and physical health conditions as well as increased risk of SUDs.[2,27,34] Rates of OUD in Veterans have been increasing, in spite of efforts to decrease opiate prescriptions throughout the VA system.[35,36] Lingering trauma from MST could explain part of this increase in diagnosed OUD cases. A proposed mechanism through which this association can occur is mediation by the presence of chronic pain.[37] Chronic pain is associated with sexual trauma, and long-term or high-dose opioid prescriptions opioids (often for chronic pain) are a leading cause of OUD and the opioid epidemic, indicating that chronic pain may account for many of the cases of OUD in the population of Veterans with MST.[10,38,39] In Veterans and civilians with OUD, the majority also have a chronic pain diagnosis,[40,41] and iatrogenic addiction could be present in up to 35% of chronic pain patients treated long-term with opioids.[42] The association between MST and OUD is hypothesized to be moderated by gender. Moderation should be

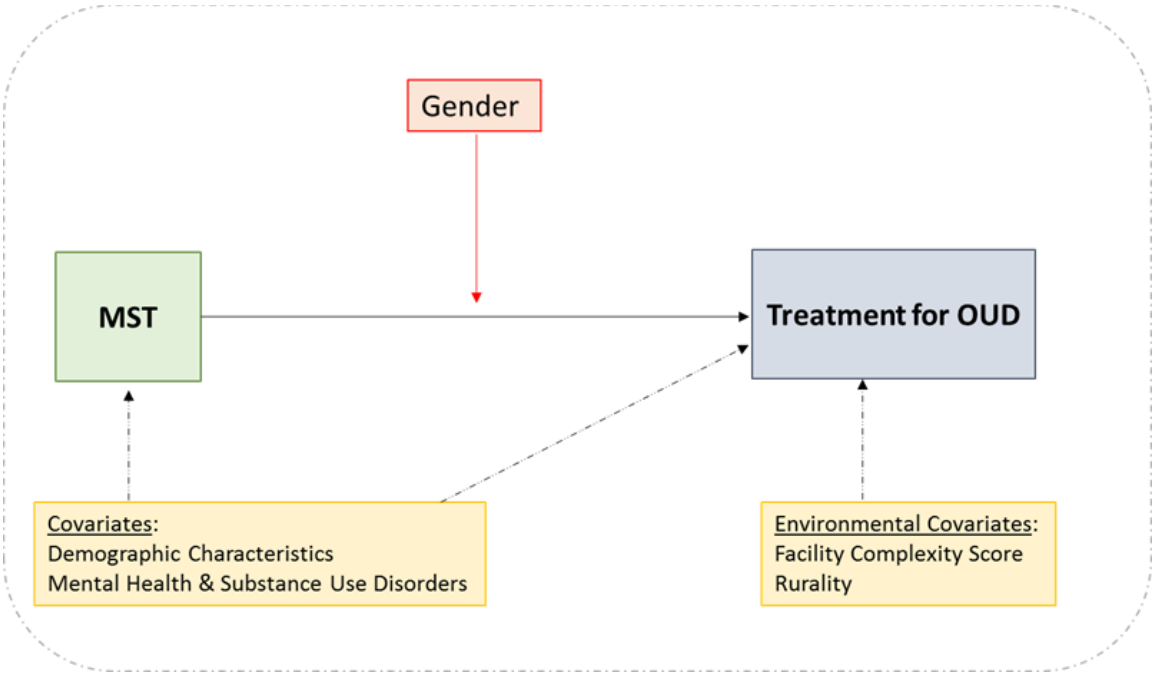
evaluated since men and women cope with MST in different ways[3,43,44], use opiates for different reasons,[14,45] and have different relationships with substance use.[33,46]

Fig. 1



The model for Aim 2 (Figure 2) shows that among Veterans with clinically diagnosed OUD, MST is associated with increased receipt of OUD treatment, and that this relationship is hypothesized to differ by gender. Evidence-based OUD treatment is often difficult to access, even in the VA despite the VA's status as the leading provider of specialty substance use treatment.[26,38] Evidence-based OUD treatment in the VA is less likely to be received by women, those with multiple mental health conditions, and those who are older than age 56;[27] in civilian populations, women have also been less likely to receive drug misuse treatment.[47] In both Veteran and civilian populations, this could be due to women substance users' higher rates of comorbid psychiatric conditions and concerns regarding stigma and safety in the treatment setting due to past trauma (such as MST).[33,48,49,50]

Fig. 2



In both of these models, demographic characteristics controlled for include age, race, and marital status. Both age and race are associated with MST and with OUD, chronic pain, high-risk prescriptions, and OUD treatment.[2,27,51,52] Marital status is included as a marker for social support and because women's SUDs are more likely than men's to have consequences for their personal life, resulting in separation or divorce.[53,54] Mental health and substance use disorders (such as depression, anxiety, alcohol use disorder, other drug use disorder, PTSD) are controlled for in both models, as they are associated with MST, OUD diagnosis, and non-receipt of OUD treatment.[2,4,5,21,27,51] These disorders are also associated with chronic pain.[17] Environmental characteristics being controlled for are rurality and facility complexity. Rurality is associated with OUD and OUD treatment, where those in rural areas are less likely to receive evidence-based treatment, yet drug abuse, opioid prescriptions and aberrant opioid use are more common in rural areas.[26,55] Less complex facilities are less likely to diagnose OUD (perhaps due to less SUD-specialty providers) and less likely to provide OUD treatment.[27,35]

Chapter 2: Associations Among Military Sexual Trauma, Opioid Use Disorder, and Gender

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2.1 Abstract

Introduction: Opioid use disorder (OUD) and high-risk opioid prescription (HRP) increase risks for overdose and death. In Veterans, military sexual trauma (MST) is associated with increased risk for assorted health conditions and may be related to risk of OUD and HRP receipt. This study evaluates the association of MST with OUD and HRP and potential moderation by gender.

Methods: In a national sample of Veterans Health Administration outpatients receiving care from October 1, 2009 to August 1, 2017, logistic regression models were fit to evaluate the associations between MST and OUD and HRP, adjusting for demographic and clinical covariates. A second set of models included a gender X MST interaction, followed by estimation of marginal means and post-estimation analyses of marginal effects. Analyses were conducted in 2020–2021.

Results: Compared with those without MST (n=7,738,665), patients with MST (n=327,193) had 50% higher odds of OUD diagnosis (AOR=1.50, 95% CI=1.45, 1.54, p<0.001) and 5% higher odds of HRP (AOR=1.05, 95% CI=1.04, 1.07, p<0.001). In marginal effects analyses, gender modified only the MST–OUD association, with the effect of MST on OUD stronger in men than women (change in effect of MST: 0.005 vs 0.002, respectively, p<0.001). The predicted probability of OUD among men with MST (1.5%) was nearly double that of women with MST (0.8%).

Conclusions: MST was a significant risk factor for OUD and HRP, with the former association particularly strong in men. Clinical care for Veterans with MST should consider elevated risk of OUD and HRP.

2.2 Introduction

High-risk opioid prescribing (HRP) practices (long-term prescriptions or high morphine-equivalent doses) and opioid use disorder (OUD)[41,56] are persistent public health concerns associated with substantial risk for overdose and death.[38,57] Consequences of OUD are numerous and include medical, social, and economic complications, such as loss of employment and homelessness.[21,22] The Department of Veterans Affairs (VA) has made preventing and treating OUD a priority.[38]

Military sexual trauma (MST), defined as "a physical assault of a sexual nature, battery of a sexual nature, or sexual harassment which occurred while the Veteran was serving on active duty,"[1,12] is a focus area for the VA. MST is reported by approximately 1 in 4 women and 1 in 100 men enrolled in VA health care, although some estimates are even higher.[2,19,32,58] Recent research has shown that in men and women Veterans, history of MST is associated with a greater risk for some substance use disorders (SUDs)[11] in part because substances are often used to self-medicate in the presence of mental or physical distress.[59] History of MST may increase risk for receipt of HRP or OUD, as chronic pain, post-traumatic stress disorder (PTSD), and other SUDs are common in Veterans who have experienced MST, and these conditions are associated with increased opioid use.[2,12,19,51,60,61] A recent study of women Veterans found that history of MST was associated with more diagnosed pain conditions and more severe pain,[10] which could lead to receipt of HRP. Additionally, some chronic pain conditions associated with MST, such as chronic pelvic pain, are more often treated with HRP in Veterans with MST history, despite the fact that opioid therapy is not recommended for this type of pain.[62] No prior study has evaluated the association between MST and OUD or receipt of HRP. Should MST be independently associated with OUD or HRP, there may be important clinical implications such as targeted outreach or the development of OUD prevention programs among Veterans with histories of MST.

Previous research suggests that MST may impact men and women differently, in part because of the challenges it presents to understanding one's role in society.[43] For instance, women may fear reinforcing

negative beliefs about women in the military; men may face unique challenges with masculinity and attitudes surrounding gender roles post-MST.[3,43] There may be differential risk for the development of SUDs in men and women survivors of MST as a means of coping, although little research has been conducted directly comparing the coping mechanisms of men and women after MST.[12,63] One VA study demonstrated that a history of MST is a stronger risk factor for SUDs (not OUD specifically) in women than in men.[11] However, recent national survey results in the general population found a stronger association between experiencing sexual violence and self-reported opioid misuse (such as non-prescription/illicit use or improperly used prescriptions) in men than in women.[64] Because of inconsistencies observed in strengths of associations between experiencing sexual violence and SUDs in women and in men, and in the general population versus among Veterans, additional studies are needed.[21]

This study assesses associations between MST and OUD, MST and HRP, and whether gender moderates these relationships. This study hypothesizes that MST will be associated with greater risk of both OUD and HRP. Given mixed findings and limited research in this area, there are not specific hypotheses about whether and how gender will moderate those associations.

2.3 Methods

Study Sample

This observational, retrospective study reflects secondary analyses of data collected from VA's Corporate Data Warehouse for a National Institute of Alcohol Abuse and Alcoholism–funded study (R21AA025973) focused on alcohol use among Veterans and approved by the VA Puget Sound Healthcare IRB. Owing to the topic of the parent study, the data set included VA outpatients aged ≥18 years with a documented Alcohol Use Disorders Identification Test–Consumption alcohol screen between October 1, 2009 and August 1, 2017 within each VA facility. Because the Alcohol Use Disorders Identification Test–

Consumption is conducted among >90% of VA outpatients annually, the sample was largely representative of the full VA outpatient population.[65]

The date of each patient's most recently documented Alcohol Use Disorders Identification Test–Consumption served as the index date for all current analyses to reflect the most current VA prescribing practices and opioid-related safety policies. Study data included clinical diagnoses, patient demographics, and facility information (from administrative data). HRP was ascertained from pharmacy data, which represent filled prescriptions at VA pharmacies. The initial data set included 8,872,793 patients with a documented MST screen (positive or negative). Patients were excluded if they had an active cancer diagnosis as indicated by ICD-9-CM and ICD-10-CM codes (Appendix Table 1) (n=776,281), were transgender (as defined by ICD-9-CM and ICD-10-CM codes for likely transgender/gender dysphoria, n=8,174),[66] or were not Veterans (e.g., employees or beneficiaries, n=22,480). Patients with cancer were excluded owing to the use of opioids in many treatment plans; non-Veteran patients were excluded as MST only applies to Veterans. This study was limited to cisgender men and women because there is currently no self-reported gender identity field in the VA electronic medical record, and it is not possible to differentiate between trans men and trans women using ICD codes.[67] The total study population was 8,065,858 patients.

Measures

This study defined OUD by the presence of ≥1 ICD-9-CM or ICD-10-CM code for opioid abuse or dependence, not including in remission (Appendix Table 1) in the 12 months preceding the index date.[68] HRP includes prescriptions that are long-term (defined as prescription fills covering ≥90 days over the course of 1 year) or those filled with a mean daily dose of ≥50 morphine-equivalent daily dose milligrams over the course of a year, a definition that comes from VA/Department of Defense clinical practice guidelines and that is regularly used in VA research assessing HRP receipt.[69] Patients who filled ≥1 HRP in the 12 months before or after the index date were coded as receiving an HRP.

Presence of MST was identified using data generated from a provider-administered MST screen that queries Veterans about any experience of sexual harassment or assault during active military service.[70] A response of yes to either harassment or assault reflects MST; the administrative record does not differentiate between experience of harassment or assault (Appendix Table 2).

The electronic health record documents gender as man or woman. Transgender Veterans were removed from the study population.

Gender, age, race, and marital status were extracted from administrative data at the time of the index date. Race categories were condensed by prioritizing Black race (followed by American Indian then Asian/Pacific Islander) when multiple races were reported by the patient in order to reflect systems of social inequality.[71]

Other covariates were selected from a literature review to include variables known to be associated with HRP or OUD. Common clinical diagnoses and indicators of significant illness were included because they could influence types of prescriptions a patient receives or whether their OUD is documented/recognized. Facility complexity was included because a facility's prescription patterns, prevalence of OUD, and availability of specialty care services could influence HRP receipt or likelihood of OUD diagnosis. Mental health disorders (including depressive disorder, PTSD, anxiety disorders, other mood disorders, bipolar disorder, psychosis, and schizophrenia[2,3,10]) were identified via ICD-9-CM or ICD-10-CM codes in the 12 months prior to the index date. SUDs were determined based on having an ICD-9-CM or ICD-10-CM code for alcohol use disorder, cannabis use disorder, stimulant use disorder, hallucinogen use disorder, sedative use disorder, or other drug use disorder in the 12 months prior to the index date (Appendix Table 1 for both SUDs and mental health disorders).[72] Patient urban/rural status was linked to the patient's primary residential address at index date using a VA classification based on the U.S. government's rural–

urban commuting area code.[73] The Charlson Comorbidity Index was calculated from diagnoses in the medical record for the year prior to the index date.[74] Service connection, which represents degree of disability from military service and can also be considered a marker of SES, was presented as a categorical variable with the following categories: full VA service (50%–100% service connected), <50% service connected, not service connected, or missing.[75] Facility complexity is a VA classification of facility types based on patient care capabilities, patient volume, scope of research activities, and breadth of specialty care services. There are 5 complexity levels (1A–C, 2, 3) with 1A being the most complex and 3 the least. Patients were assigned to the facility where most of their care was received.[76]

Statistical Analysis

Descriptive statistics were computed for all study variables, stratified by history of MST and gender. Three logistic regression models, with MST as the independent variable, were fit for each outcome (OUD and receipt of HRP) to assess the main effect of MST on the outcome. For each outcome, the 3 models included an unadjusted model (including no covariates), a partially adjusted model (including gender, age, race, and marital status), and a fully adjusted model (adding all remaining covariates to the partially adjusted model. Next, an interaction term of MST X gender was added to each model to assess for moderation of the association by gender, evaluated using a Wald test. Because of challenges interpreting product terms and their significance (particularly in non-linear models), average predicted probabilities were calculated to estimate gender-specific associations.[77-79] The statistical significance of the difference between the average marginal effect was then calculated to quantify whether differences in adjusted probabilities by MST differed by gender. The difference in average marginal effect was considered the primary assessment of the interaction because of an interest in interpreting the scope of the probabilities of the outcomes. Given the large sample size, significance levels were set at $p<0.001$. All analyses were completed in 2020–2021 with Stata, version 16.

2.4 Results

Table 1 provides descriptive statistics for demographic, covariate, and outcome variables, stratified by history of MST and gender. The sample included 8,065,858 Veterans and reflected a typical VA population,[80] with 92% men. The mean age was approximately 60 years and 17% were Black. Women were considerably younger than men and more likely to be Black. The most common mental health diagnosis was PTSD (14% of Veterans). Overall prevalence of MST was 27.4% for women and 1.9% for men. Prevalence of both OUD and HRP was higher among men. Prevalence of OUD was 1% overall (n=80,707; 75,296 men [1.0%] and 5,411 women [0.8%]). Overall prevalence of HRP was 8% (n=641,257; 595,563 men [8.0%] and 47,694 women [7.0%]).

In main effects regression models, history of MST was associated with greater odds of OUD in all 3 iteratively adjusted models (Table 2). After adjusting for demographic, clinical, and facility characteristics, odds of OUD diagnosis were 50% higher (OR=1.5, 95% CI=1.5, 1.5) for Veterans with history of MST compared with those without.

In models assessing moderation by gender, the interaction term of MST and gender was not statistically significant at the indicated threshold in any model. However, in all models, the test comparing marginal effects between genders was statistically significant (all $p<0.001$), with the marginal effect of MST on OUD at least twice as high among men compared with women, reflecting moderation by gender (Table 3) (fully adjusted: 0.5% in men vs 0.2% in women). In the fully adjusted model, the predicted probability of OUD among men with history of MST was 1.5%, double the probability for women with a history of MST, where it was 0.8% (Figure 1).

In main effects models, history of MST was also significantly associated with receiving HRP at all levels of covariate adjustment (Table 2). After adjusting for all demographic and clinical covariates, the odds of HRP were 5% higher for Veterans with a history of MST (OR=1.05, 95% CI=1.04, 1.07, $p<0.001$) than those without. Although the interaction term was not statistically significant in any model, comparing the

marginal effect of MST on HRP between genders showed that the marginal effect of MST on HRP was significantly higher among men compared with women in the unadjusted model but not either of the adjusted models (Table 3) (unadjusted marginal effect of MST: 0.036 in men vs 0.031 in women, p<0.001). In the fully adjusted model, the probability of HRP was 8.5% and 7.6% for men and women with a history of MST, respectively (Figure 1).

2.5 Discussion

For patients and their families, OUD poses a significant challenge and is often fatal.[15,22] Understanding risk factors for OUD can increase identification of potential avenues for prevention.[81] The current study is the first to assess the associations between MST and OUD and with HRP. Consistent with previous research demonstrating that MST is associated with SUDs,[2,60] Veterans with a history of MST were significantly more likely to have a diagnosis of OUD and receive HRP than Veterans without history of MST. These findings contribute to the growing literature base showing the long-term adverse effects of MST on health.[2,11,19,60] Notably, MST history was independently associated with increased odds of OUD and HRP even after adjusting for demographic and clinical covariates such as PTSD and other SUDs.

The VA is prioritizing the prevention and treatment of OUD through several initiatives.[80,81] Preventive efforts are focused on reducing opioid use in treatment protocols and improving opioid safety initiatives. There are also several initiatives in the VA focused on increasing access to medications for treatment of OUD in non-SUD specialty care settings such as primary care, mental health, and specialty pain clinics.[82,83] This is particularly promising as Veterans may receive the majority of their care in these other settings. Findings from this study suggest that VA and other health systems may also consider expanding evidence-based interventions that treat mental health and SUDs simultaneously such as the Concurrent Treatment of PTSD and SUDs Using Prolonged Exposure (COPE).[84] This may be especially helpful given that PTSD is the most common comorbid mental health condition in Veterans with MST histories.

Providers who treat Veterans with history of MST may need to carefully screen for opioid misuse in addition to other SUDs.

Results indicated that MST history had a stronger marginal association with OUD in men than in women, but this did not hold true for HRP after adjustment for demographic and clinical covariates. This contradicts previous VA research showing a stronger association between MST and SUDs (both alcohol use disorder and drug use disorder, but not specifically OUD) in women than in men, [11] which may indicate a need to assess associations between MST history and specific SUDs by gender. This stronger association of MST history with OUD diagnosis in men than women could be a result of men Veterans with histories of MST being more likely than women to soothe feelings of loss of masculinity or conflicting feelings about their military service by using opioids.[3,43] When gender and societal roles are threatened, people may turn to substances as a means of coping.[85-87]By directly comparing the association of MST with opioid outcomes between men and women, this research adds to the sexual trauma literature by providing evidence that men are more likely to have OUD after MST; whether coping is the underlying mechanism for this association remains unclear. Receipt of opioids during episodes of pain after MST could potentially lead to stress or symptom relief.[88] Moreover, providers may be more likely to prescribe HRP to men than to women owing to bias in prescribing practices and pain treatment, with women less likely to receive chronic opioid therapy than men.[89] However, despite gender differences in the association of MST with OUD, it is unlikely this would lead to different approaches in clinical policy or interventions by gender, as the magnitude of the absolute difference is relatively small. From a clinical standpoint, results highlight that both men and women with histories of MST are at elevated risk of OUD and of receiving HRP. Thus, providers caring for Veterans should assess MST history, opioid use, and consider non-opioid therapy for pain.

Limitations

This study has several limitations. The sample only includes Veterans who receive VA care and were screened for alcohol use, and thus results may be less generalizable to Veterans not screened for unhealthy alcohol use (a minority) or enrolled in the VA. However, because VA has one of the most comprehensive substance use treatment programs in the country and a high percentage of younger Veterans receive care at the VA, it is likely that this data set captures most Veterans with OUD.[16] Additionally, it is possible that OUD is not always captured in the administrative record,[90] depending on types of care a Veteran receives and potential biases held by providers regarding SUDs. Systematic under-reporting by gender could influence the findings. MST may also be under-reported in this sample, as studies using non-administrative data often find higher prevalence rates.[32] Though MST by definition occurs during military service and could therefore be a causal mechanism for the development of OUD, this study is cross-sectional in nature, limiting causal inferences.[91] Future longitudinal studies would help to understand the temporal ordering of MST, initial receipt of HRP, and receipt of an OUD diagnosis, along with exploring additional possible mechanisms in the relationship between MST and OUD across gender. Finally, this study focuses on cisgender men and women Veterans, even though a history of MST is prevalent in transgender Veterans.[92] Future research should focus on this understudied population and their specific risk factors for OUD-related outcomes.

2.6 Conclusions

Despite these limitations, this study highlights an association between MST and opioid-related outcomes, which is particularly important given the current scope of the opioid epidemic and the increasing rates of MST.[56,93] Given the high prevalence of MST in Veterans, continued rise of reported MST among active-duty service members,[94] and national efforts to combat the epidemic of dangerous opioid use and OUD, this study provides further evidence to bolster programs and interventions for Veterans with a history of MST and to coordinate these efforts with other mental health and substance use treatment initiatives and to provide trauma-informed care when considering prescriptions and opioid-based treatment.

Table 2.1 Characteristics of Men and Women U.S. Veterans With Military Sexual Trauma (MST) Screen

	Men (N=7,388,439)		Women (N=677,419)		Total
Variables	**Negative MST screen N=7,246,564 (98.1%)**	**Positive MST screen N=141,875 (1.9%)**	**Negative MST screen N=492,101 (72.6%)**	**Positive MST screen N=185,318 (27.4%)**	**N=8,065,858**
	No. (%) or M (SD)	**No. (%) or M (SD)**	**No. (%) or M (SD)**	**No. (%) or M (SD)**	**No. (%) or M (SD)**
Individual characteristics					
Race, n (%)					
White	5,595,371 (77.2)	105,547 (74.4)	298,141 (60.6)	116,793 (63.0)	6,115,852 (75.8)
Black	1,145,687 (15.8)	25,886 (18.3)	151,196 (30.7)	51,323 (27.7)	1,374,092 (17.0)
Asian/Native Hawaiian/ Pacific Islander	153,314 (2.1)	2,759 (1.9)	14,987 (3.1)	4,888 (2.6)	175,948 (2.2)
American Indian/ Alaska Native	72,381 (1)	1,988 (1.4)	6,421 (1.3)	3,722 (2)	84,512 (1.1)
Unknown/missing	279,811 (3.9)	5,695 (4.0)	21,356 (4.3)	8,592 (4.6)	315,454 (3.9)
Age, mean (SD)	61.5 (17.5)	58.2 (15.5)	47.0 (16.2)	46.4 (13.2)	60.1 (17.8)
18–34, years, n (%)	804,856 (11.1)	14,703 (10.4)	138,239 (28.1)	44,976 (24.3)	1,002,774 (12.4)
35–49, years, n (%)	950,824 (13.1)	22,099 (15.6)	144,622 (29.4)	58,445 (31.5)	1,175,990 (14.6)
50–64, years, n (%)	1,844,185 (25.5)	51,946 (36.6)	145,604 (29.6)	68,300 (36.9)	2,110,035 (26.2)
≥65, years, n (%)	3,646,699 (50.3)	53,127 (37.5)	63,636 (12.9)	13,597 (7.3)	3,777,059 (46.8)
Marital status, n (%)					
Married	3,947,683 (54.5)	62,288 (43.9)	172,239 (35.0)	60,695 (32.6)	4,242,905 (53)
Divorced	1,820,915 (25.1)	47,168 (33.3)	170,801 (34.7)	77,186 (41.7)	2,116,070 (26)
Widowed	474,342 (6.6)	6,384 (4.5)	26,146 (5.3)	5,847 (3.2)	512,719 (6)
Single	963,260 (13.3)	25,551 (18.0)	118,713 (24.1)	40,380 (21.8)	1,147,904 (14)
Unknown	40,364 (0.6)	484 (0.3)	4,202 (0.9)	1,210 (0.7)	46,260 (1)
Mental health diagnosis, n (%)					
Any mental health diagnosis	2,056,076 (28.4)	76,347 (53.8)	182,148 (37.0)	122,945 (66.3)	2,437,516 (30.2)
PTSD	928,293 (12.8)	46,406 (32.7)	48,077 (9.8)	76,595 (41.3)	1,099,371 (13.6)
Major depressive disorder	682,763 (9.4)	29,089 (20.5)	80,053 (16.3)	55,345 (29.9)	847,250 (10.5)
Schizophrenia	54,191 (0.8)	3,254 (2.3)	2,655 (0.5)	1,697 (0.9)	61,797 (0.8)
Bipolar	152,204 (2.1)	9,972 (7.0)	19,020 (3.9)	16,610 (9.0)	197,806 (2.5)
Anxiety disorders	456,297 (6.3)	16,288 (11.5)	58,944 (12)	33,812 (18.3)	565,341 (7.0)
Psychoses	58,630 (0.8)	3,120 (2.2)	2,851 (0.6)	2,220 (1.2)	66,821 (0.8)
Other mood disorders	241,598 (3.3)	9,035 (6.4)	22,411 (4.6)	12,361 (6.7)	285,405 (3.5)
Substance use diagnosis, n (%)					
Any substance use diagnosis (non-OUD)	1,158,917 (16.0)	37,113 (26.2)	52,111 (10.6)	30,717 (16.6)	1,278,858 (15.9)
Past-year alcohol use disorder	458,069 (6.3)	17,572 (12.4)	13,289 (2.7)	11,297 (6.1)	500,227 (6.2)
Cannabis use disorder	110,706 (1.5)	6,448 (4.5)	4,387 (0.9)	4,309 (2.3)	125,850 (1.6)
Tobacco use disorder	802,624 (11.1)	23,537 (16.6)	39,882 (8.1)	20,412 (11.0)	886,455 (11.0)

Amphetamine/ Stimulant use disorder	22,502 (0.3)	1,680 (1.2)	985 (0.2)	996 (0.5)	26,163 (0.3)
Cocaine use disorder	78,506 (1.1)	5,655 (4.0)	1,990 (0.4)	2,490 (1.4)	88,641 (1.1)
Hallucinogen use disorder	1,143 (0.02)	80 (0.06)	34 (0.01)	42 (0.02)	1,299 (0.02)
Sedative use disorder	12,535 (0.2)	784 (0.6)	643 (0.1)	708 (0.4)	14,670 (0.2)
Other drug use disorder	120,426 (1.7)	7,012 (4.9)	4,902 (1.0)	4,879 (2.6)	137,219 (1.7)
Charlson Comorbidity Score, mean (SD)	0.86 (1.39)	0.92 (1.56)	0.36 (0.85)	0.39 (0.88)	0.82 (1.37)
Service connection, n (%)					
Full VA coverage	1,800,229 (24.8)	52,220 (36.8)	143,987 (29.3)	92,595 (50.0)	2,089,031 (25.9)
<50% service connected	1,580,934 (21.8)	27,399 (19.3)	121,964 (24.8)	34,245 (18.5)	1,764,542 (21.9)
Non-service connected	3,326,463 (45.9)	51,754 (36.5)	187,456 (38.1)	45,549 (25.6)	3,611,222 (44.8)
Missing	538,938 (7.4)	10,502 (7.4)	38,694 (7.9)	12,929 (7.0)	601,063 (7.5)
Patient rurality, n (%)					
Urban	4,570,679 (63.9)	92,036 (65.5)	352,018 (72.8)	132,829 (72.6)	5,147,562 (64.7)
Rural	2,477,799 (34.7)	46,642 (33.2)	126,741 (26.2)	48,359 (26.4)	2,699,541 (33.9)
Highly rural	99,236 (1.4)	1,724 (1.2)	4,082 (0.8)	1,656 (0.9)	106,698 (1.3)
Insular island	3,322 (0.1)	52 (0.04)	440 (0.1)	71 (0.04)	3,885 (0.1)
Outcomes					
OUD diagnosis, n (%)	71,415 (1)	3,881 (2.7)	2,770 (0.6)	2,641 (1.4)	80,707 (1)
High risk prescriptions, n (%)					
Any high-risk opioid prescription	577,193 (8.0)	16,370 (11.5)	30,491 (6.2)	17,203 (9.3)	641,257 (8.0)
MEDD over 50	190,124 (2.6)	5,803 (4.1)	9,430 (1.9)	5,462 (3.0)	210,819 (2.7)
Days' supply over 90/year	503,125 (6.9)	14,497 (10.2)	25,843 (5.3)	14,857 (8.0)	558,322 (6.9)
Facility characteristics, n (%)					
Complexity[a]					
1a	3,072,736 (42.6)	52,062 (36.9)	231,498 (47.3)	87,787 (47.5)	3,444,083 (42.9)
1b	1,538,239 (21.3)	26,083 (18.5)	97,533 (19.9)	36,398 (19.7)	1,698,253 (21.2)
1c	1,302,015 (18.1)	19,725 (14.0)	89,108 (18.2)	31,391 (17.0)	1,442,239 (18.0)
2	567,840 (7.9)	8,415 (6.0)	35,152 (7.2)	12,643 (6.8)	624,050 (7.8)
3	729,841 (10.1)	34,914 (24.7)	36,641 (7.5)	16,548 (9.0)	817,944 (10.2)

[a]Facility complexity is a VA categorization based on size of facility, research/teaching conducted, and services offered, with 1a being the most complex and 3 representing the least complex.

Table 2.2 Multivariate Logistic Regression Models Predicting Opioid Use Disorder and High-Risk Prescriptions

Variables	Unadjusted OR (95% CI)	*p*-value	Partially adjusted[a] OR (95% CI)	*p*-value	Fully adjusted[b] OR (95% CI)	*p*-value
Opioid use disorder						
Main effect						
Military sexual trauma	2.10 (2.05, 2.16)	**<0.001**	2.28 (2.22, 2.35)	**<0.001**	1.50 (1.45, 1.54)	**<0.001**
Interaction effect						
Military sexual trauma x gender (ratio of ORs)	0.90 (0.85, 0.96)	**0.002**	1.05 (0.99, 1.12)	0.125	0.99 (0.93, 1.06)	0.836
High-risk prescriptions						
Main effect						
Military sexual trauma	1.34 (1.33, 1.36)	**<0.001**	1.40 (1.38, 1.41)	**<0.001**	1.05 (1.04, 1.07)	**<0.001**
Interaction effect						
Military sexual trauma x gender	1.03 (1.00, 1.06)	**0.035**	1.02 (0.99, 1.05)	0.169	0.99 (0.97, 1.02)	0.527

Notes: Boldface indicates statistical significance ($p<0.05$).

[a]Adjusted for gender, race, age, and marital status.

[b]Adjusted for the above in addition to mental health diagnoses, substance use disorder diagnoses, Charlson score, rurality, facility of most care, facility complexity, and service connection.

Table 2.3 Marginal Means of OUD and of High-Risk Prescriptions Associated With Military Sexual Trauma, Gender, and Their Interaction in Unadjusted, Partially Adjusted and Fully Adjusted Models

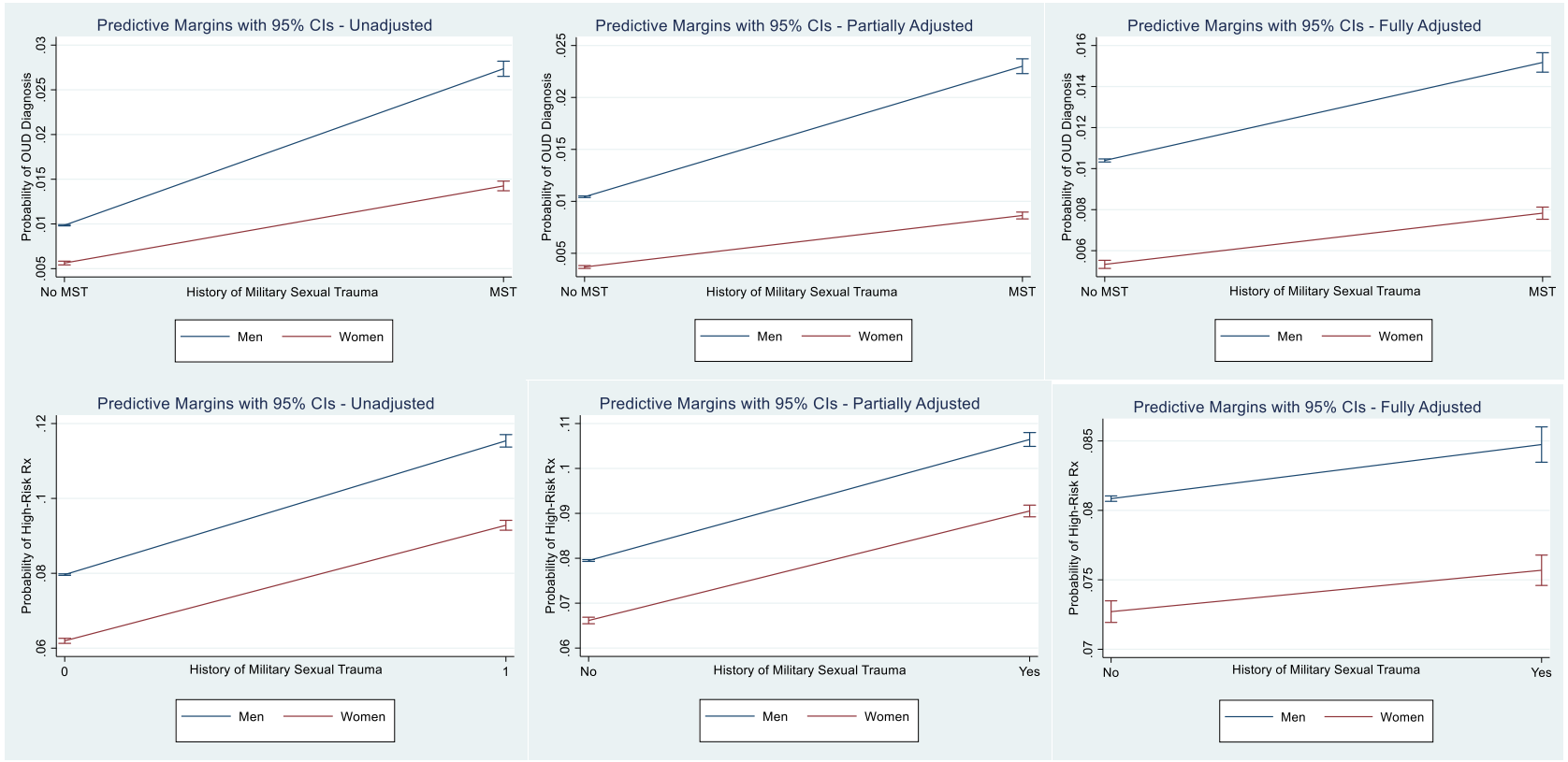
Variables	Predicted probability (95% CI)	*p*-value	Partially adjusted[a] predicted probability (95% CI)	*p*-value	Fully adjusted[b] predicted probability (95% CI)	*p*-value
Opioid use disorder (OUD)						
Military sexual trauma (MST) x gender						
MST= no x men	0.010 (0.010, 0.010)	**<0.001**	0.010 (0.010, 0.011)	**<0.001**	0.010 (0.010, 0.010)	**<0.001**
MST = yes x men	0.027 (0.027, 0.028)	**<0.001**	0.023 (0.022, 0.024)	**<0.001**	0.015 (0.015, 0.016)	**<0.001**
MST= no x women	0.006 (0.005, 0.006)	**<0.001**	0.004 (0.004, 0.004)	**<0.001**	0.005 (0.005, 0.006)	**<0.001**
MST= yes x women	0.014 (0.014, 0.015)	**<0.001**	0.009 (0.008, 0.009)	**<0.001**	0.008 (0.008, 0.008)	**<0.001**
Marginal effects: Difference in mean OUD prevalence between no MST and yes MST when:						
Gender = Men	0.018 (0.017, 0.018)		0.013 (0.012, 0.013)		0.005 (0.004, 0.005)	
Gender = Women	0.009 (0.008, 0.009)		0.005 (0.004, 0.005)		0.002 (0.002, 0.003)	
Test of marginal effects, chi2	285.5	**<0.001**	348.7	**<0.001**	56.7	**<0.001**
High-risk prescriptions (HRP)						
MST x gender						
MST= no x men	0.080 (0.079, 0.080)	**<0.001**	0.079 (0.079, 0.080)	**<0.001**	0.081 (0.081, 0.081)	**<0.001**
MST = yes x men	0.115 (0.114, 0.117)	**<0.001**	0.106 (0.105, 0.108)	**<0.001**	0.085 (0.083, 0.086)	**<0.001**
MST= no x women	0.062 (0.061, 0.063)	**<0.001**	0.066 (0.065, 0.067)	**<0.001**	0.073 (0.072, 0.073)	**<0.001**
MST= yes x women	0.093 (0.092, 0.094)	**<0.001**	0.091 (0.089, 0.092)	**<0.001**	0.076 (0.075, 0.077)	**<0.001**
Marginal effects: Difference in mean HRP between no MST and yes MST when:						
Gender = Men	0.036 (0.034, 0.037)		0.027 (0.025, 0.029)		0.004 (0.003, 0.005)	
Gender = Women	0.031 (0.029, 0.032)		0.024 (0.023, 0.026)		0.003 (0.002, 0.004)	
Test of marginal effects, chi2	18.2	**<0.001**	5.55	**0.0185**	0.95	0.3287

Notes: Boldface indicates statistical significance ($p<0.05$).

[a]Adjusted for gender, race, age, and marital status.

[b]Adjusted for the above in addition to mental health diagnoses, substance use disorder diagnoses, Charlson score, rurality, facility of most care, facility complexity, and service connection.

Figure 2.1 Marginal Means of OUD and High-Risk Prescriptions, for MST x Gender at Three Adjustment Levels



Chapter 3: The Impact of Military Sexual Trauma and Gender on Receipt of Evidence-based Medication Treatment among Veterans with Opioid Use Disorder

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3.1 Abstract

Introduction: Opioid use disorder (OUD), a chronic illness associated with substantial morbidity and mortality, is common in Veterans. Despite several national Department of Veteran Affairs (VA) initiatives over the last 15 years to increase access to medications to treat OUD (MOUD), including 2013's Opioid Safety Initiative (OSI), MOUD remain underutilized. Known factors associated with lower MOUD receipt include having comorbidities and being a woman. The present study evaluated associations between military sexual trauma (MST), one common comorbidity among Veterans, and receipt of MOUD among VA outpatients. We also evaluated whether gender moderated the MST-MOUD association and whether the association differed prior to vs. after the OSI.

Methods: In a cross-sectional study using a national sample of 80,845 Veterans with OUD who sought care at VA facilities from 2009–2017, we fit mixed-effects logistic regression models to assess the association between MST and MOUD, adjusting for demographic and clinical characteristics, and with facility modeled as a random effect. Secondary analyses added an interaction term of MST x gender to evaluate whether the MST and MOUD association varied by gender and stratified the original models by time period (2009-2013 vs. 2014-2017, pre- and post-OSI). A p-value threshold of .001 was used to determine significance due to multiple comparisons and large sample size.

Results: Overall, 35% of Veterans with OUD received MOUD. MST (8.1% overall; 5.2% of men, 48.8% of women) was not significantly associated with receipt of MOUD in a fully adjusted model (OR= 1.08; 99% CI 1.00, 1.17). There was no significant MST x gender interaction (p=0.377) nor a notable difference in the MST and MOUD association between time periods.

Conclusions: Both men and women Veterans with and without a history of MST appear to be receiving MOUD treatment at similar rates. However, there is still considerable room for improvement in MOUD receipt?? and future research should continue to assess barriers to MOUD receipt.

3.2 Introduction

Opioid use disorder (OUD) is often a chronic condition[15] and is associated with substantial risk for overdose and death, including suicide.[18,19,20] Approximately 80,000 Veterans in the Department of Veteran Affairs (VA) Healthcare System have diagnosed OUD. To help these Veterans, the VA has led several initiatives to increase access to evidence-based treatments for OUD.[38]

Evidence-based medications for treatment of OUD (MOUD) include buprenorphine, methadone, or extended-release naltrexone.[13,15] Of these, opioid agonists—buprenorphine or methadone—are most effective; methadone must be delivered in certified opioid treatment programs whereas buprenorphine can be offered in outpatient settings.[15] These medications are associated with reductions in non-prescribed opioid use, overdose, mortality, and other OUD-associated sequelae.[95] Despite these benefits, these medications are underutilized.[96]

In 2013, the VA introduced the Opioid Safety Initiative (OSI), an effort to reduce morbidity and mortality from OUD by transforming opioid prescribing across its healthcare system, increasing awareness of OUD, and improving access to MOUD.[38] The OSI built on other past initiatives, such as the 2007 Buprenorphine in the VA (BIV) Initiative and the 2010 “Academic Detailing” program,[16] aimed at providing education and consultation services to VA providers so that MOUD could be available at every VA facility in the country.[83] Despite these initiatives, as of 2017 about 35% of Veterans in the VA with OUD were receiving MOUD.[16] An additional Academic Detailing program specifically designed to encourage providers to prescribe MOUD was launched in 2017,[16] alongside other recent initiatives such as the Stepped Care for Opioid Use Disorder Train the Trainer initiative (SCOUTT), which is specifically focused on increasing access to MOUD in non-substance use disorder (SUD) specialty care settings.[83]

Because of the consequences of underutilization of MOUD, several studies in and outside of the VA have focused on identifying barriers to receipt of MOUD. Known barriers include female gender, mental health

comorbidities, and stigma. In Fiscal Year 2017, women Veterans were 13% less likely than their men counterparts to have received MOUD.[97] The reasons for this gender disparity are unclear, but women may be more likely to present with mental health comorbidities such as depression, which are also a known treatment barrier.[27] Women also receive much of their VA care at women-specific primary care clinics,[98,99] and the initiatives to increase MOUD access may impact MOUD prescribing in these clinics differently or have less impact than in general primary care clinics. In addition to gender, mental health comorbidities are also associated with decreased receipt of MOUD.[27] Patients with mental health conditions may be less likely to receive MOUD because providers may be more focused on treatment for the mental health conditions than OUD. Finally, stigma has also been identified as a barrier for MOUD, as it can result in patients being hesitant to seek treatment and/or providers being reluctant to offer treatment.[26,27,100] Internalized stigma, a process in which individuals apply negative messages and/or stereotypes about their mental health to themselves, is a particularly relevant barrier to care for Veterans with a history of military sexual trauma (MST).[101,102]

MST, which includes the experience of sexual harassment or sexual assault during military service, has not been previously evaluated as a potential barrier to MOUD. History of MST is common in Veterans (3.9% of men and 38.4% of women)[32] and has been found to be independently associated with OUD diagnosis using VA administrative records.[92] Moreover, history of MST is associated with both female gender and with increased risk of mental health diagnoses (such as PTSD), both of which are associated with lower receipt of MOUD.[2,5,32] It is possible that patients with a history of MST may be less likely than those without access MOUD, possibly because their trauma history poses treatment challenges, feelings of institutional betrayal,[103,104] or discomfort in substance use clinics that serve predominantly men Veterans. For women specifically, those with a history of MST often receive care at specialized women-only clinics due to feelings of discomfort in clinics that treat men, which could limit their access to MOUD.[105,106]

The present study evaluated associations between history of MST and receipt of MOUD among VA outpatients from 2009-2017. We hypothesized that Veterans with MST histories would be less likely than those without to receive MOUD. Because gender is an important correlate of MOUD and may modify the association between MST and MOUD receipt, we also considered gender as an effect modifier. Moreover, because treatment rates for OUD may have changed over time as VA treatment priorities have evolved, we conducted secondary analyses assessing these associations in the years 2009 – 2013 and 2014 – 2017. Taken together, this research will provide novel and up-to-date information about MST and MOUD in the VA.

3.3 Material and Methods

Data and Sample

This observational, retrospective study involves secondary analyses of administrative data collected from VA's Corporate Data Warehouse (CDW) for a National Institute of Alcohol Abuse and Alcoholism-funded R21 (1R21AA025973) focused on alcohol use among transgender Veterans and approved by the VA Puget Sound Healthcare IRB.[107] The dataset for this manuscript included administrative, encounter, and pharmacy data for all cisgender VA patients aged 18 or older with documented alcohol screening between October 1, 2009, and August 1, 2017, a documented MST screen, and a documented OUD diagnosis (N= 80,845). OUD diagnoses were determined by the presence of at least one International Classification of Diseases version 9 or 10 (ICD-9 or ICD-10) code for opioid abuse or dependence, not including in remission (see Appendix A for codes) in the 12 months prior to the alcohol screen.[68] Each patient's most recent alcohol screening was used as their index date. Although gender occurs on a spectrum, for the purposes of this study, gender was defined as cisgender man and woman (based on documented gender in the electronic health record) in order to focus on covariates and gender differences that apply to these two most common genders.

Measures

Outcome Variable

MOUD receipt was measured using both pharmacy and visit data documented in the 12 months before and after the index date (most recent alcohol screen) coupled with ICD codes for OUD in the 12 months prior to receipt. The time frame for MOUD receipt was selected in order to allow treatment delays after an OUD diagnosis, as OUD is a chronic condition and treatment does not always follow an acute-care pattern. Pharmacy data were used to measure fills for buprenorphine (excluding IV medications and patches because those formulations are used for non-OUD indications) and extended-release naltrexone.[23] Documented visits to a certified VA Opioid Treatment Program were used to measure receipt of methadone treatment. Although some patients received multiple instances or types of MOUD, only one was required to be considered "treated".

Predictor Variables

Presence of MST was measured using health factors generated from a clinical reminder used nationally to prompt and document MST screening. The VA's universal MST screen is asked of all Veterans seen in VA facilities and queries them regarding whether they experienced sexual harassment or assault during active military service; any 'yes' response indicates MST.

Covariates

Covariates were selected according to a literature review that identified individual demographic, clinical, and healthcare system-level variables which were likely to confound the association between MST and receipt of mental health and/or substance use-related care.[2,34,97]

The electronic health record (EHR) records gender as man or woman. Diagnostic codes for gender dysphoria were used to identify transgender Veterans and as noted above, they were removed from the study population. Gender was also used in secondary analyses for effect modification. Age, race and

marital status were extracted in the year of the index date. Race categories were condensed by prioritizing Black race (followed by American Indian then Asian/Pacific Islander) when multiple races were reported by the patient in order to reflect systems of social inequality; if only one race was reported then a patient was categorized as that race.[71] The patient's primary address at index date was used to determine patient urban/rural status. This analysis used a broader categorization of rural-urban commuting area (RUCA) codes for urban, rural, and highly rural. RUCA codes are assigned by the US government, where census tracts are classified using measures of population density, urbanization, and daily commuting. Census tracts are then applied to the zip codes where they are located to get a RUCA code for the patient's zip code.

Service connection, which represents degree of disability resulting from military service, was categorized as follows: full VA service (50-100% service connected), less than 50% service connected, not service connected, or missing.[75] Mental health and substance use disorders (SUDs) were identified via ICD-9 or ICD-10 codes in the 365 days prior to the index date. Mental health conditions (depressive disorder, other anxiety disorders, other mood disorders, bipolar disorder, psychosis, and schizophrenia) and SUDs (alcohol use disorder, cannabis use disorder, stimulant use disorder, hallucinogen use disorder, sedative use disorder, or other drug use disorder) were condensed into two variables such that a single diagnosis in that category would be marked as positive for mental health or SUD.[22,60,72] The validated Charlson Comorbidity Index (CCI) was calculated from ICD-9 and ICD-10 diagnoses in the year prior to the index date.[74]

Facility complexity is a VA classification of facility type based on patient care capabilities, patient volume, scope of research and teaching that occur within the facility, and breadth of specialty care services. There are 5 complexity levels (1a-c, 2, 3) with 1a being the most complex and 3 the least. Patients were assigned to the facility where most of their care was received.

Data Analysis

Descriptive statistics were computed for all study variables, stratified by gender and history of MST (e.g., men with and without history of MST, women with and without history of MST). Three multi-level logistic regression models were fit: an unadjusted model (MST only), a partially adjusted model (adding gender, age, race, and marital status), and a fully adjusted model (adding all covariates to the partially adjusted model). All three models included the facility where the patient received the most care as a random effect to account for intra-cluster correlation.

Secondary analyses included an interaction term of MST x gender to assess for moderation of the association between MST and MOUD receipt by gender in all three logistic models, evaluated using the Wald test. We calculated the average predicted probabilities to estimate gender-specific associations.[77,78] We then calculated the statistical significance of the difference in the average marginal effect for the MST-gender subgroups to determine whether differences in adjusted probabilities by MST differed by gender.[79,109]

Finally, because the OSI in the VA was launched in 2013, we separated the data into two time periods using the index date (2009-2013 and 2014-2017) to assess the association between MST and MOUD for each time period separately using the three multi-level logistic regression models described above. Each model included the facility where the Veteran received the most care as a random effect. The variance of the random effect was assessed to determine the extent of influence facility had on the association between MST and MOUD in each time period. Due to the large sample size and multiple comparisons, significance levels were set at $p<.001$. All analyses were completed in 2021 with Stata v.16.

3.4 Results

Descriptive Results and Sample Characteristics

The overall sample of Veterans with OUD diagnoses from 2009-2017 was predominantly white (76%), aged 50-64 (42%), divorced or single (69%), and male (93%) (Table 3.1). Women veterans were on average younger and less likely to be Black than men veterans in the sample. Most of the sample (58%) came from index dates in 2016-2017, as a result of using the most recent alcohol screen (i.e., index date) for each patient. Across the sample, 35% received at least one documented MOUD treatment, with 24% receiving Buprenorphine, 18% receiving Methadone and 2% receiving extended-release Naltrexone, including some patients who received more than one type of MOUD treatment. The majority of the sample also had a comorbid substance use (66%) or mental health diagnosis (72%) (Table 3.1). Compared to those without a history of MST, those who had experienced MST were more frequently over 50 years of age, had a higher prevalence of mental health disorders, and had higher prevalence of past-year alcohol use disorder and other SUDs.

Primary Analysis

MST was significantly associated with greater receipt of MOUD in the partially adjusted model, where odds of MOUD receipt were 11% higher for Veterans with a history of MST than for those without (OR= 1.11; 99% CI 1.02, 1.21, p=.001), but not in the unadjusted or fully adjusted models (Table 3.2). After fully adjusting the model, MST was no longer significantly associated with receipt of MOUD (OR= 1.08; 99% CI 1.00, 1.17, p=.012) at the a priori level of significance.

Secondary Analyses

The association between MST and MOUD did not differ by gender in either the regression models (Supplemental Table 3) or in the predicted probabilities and test of marginal effects (Supplemental Table 4).

When stratifying results by time period, there were no notable differences in odds ratios between the two time periods for the overall effect of MST on MOUD (Table 3.3). The cluster variance of the random effect for facility of most care decreased by about 30% from the early time period to the later period (from 1.10 to 0.77, where the farther away from zero the variance lies, the greater the impact of that random effect on the outcome), indicating that over time, where a Veteran received care became less critical to whether or not they received MOUD for their OUD (Table 3.3).

3.5 Discussion

This manuscript fills an important gap in the understanding of MOUD access within the VA by assessing whether MST history is associated with MOUD receipt in Veterans with OUD. Contrary to our hypothesis, a history of MST was not significantly associated with receipt of MOUD in VA facilities. Indeed, the partially adjusted model suggested that history of MST was associated with greater odds of treatment receipt, rather than less – a finding that was no longer significant in the adjusted model with our high significance threshold. We also found no indication that the association between MST and MOUD was modified by gender, suggesting that MST does not confer greater risk to differential treatment receipt for women.

In this national sample of Veterans with OUD receiving care in VA facilities, prevalence of MOUD receipt was 35% (35.3% for men, 33.8% for women), indicating that the majority of veterans with OUD do not receive evidence-based treatment. While this finding indicates room for improvement, it also highlights that the VA is a leader in the administration of MOUD across the nation. Recent research from 2016 shows that approximately 20% of persons with OUD in the United States receive MOUD[110] and that only 18% of admissions to SUD residential treatment facilities in Medicaid-expansion states received MOUD (only 1.9% of admissions to these facilities in states without Medicaid-expansion received MOUD).[111] Despite the VA's leadership in this field, a 2019 synthesis of barriers and facilitators to MOUD in VA found no VA papers published between 2014-2019 on the topic.[82] The authors of that synthesis identified

patient-level barriers through relevant non-VA research, such as stigma, mental health comorbidities, treatment experiences, and logistics. Even though non-VA-based studies found that mental health disorders, which are highly correlated with MST in Veterans, and other comorbidities were strong barriers to receiving MOUD, no prior studies have assessed whether MST is associated with MOUD receipt in Veterans.

MST was not significantly associated with MOUD receipt under the conservative threshold used. However, in the partially adjusted model (which only adjusted for demographic characteristics and did not include mental health and substance use comorbidities), Veterans with MST histories were 11% more likely to receive MOUD than those who had not experienced MST. Patients with MST histories often have complex treatment needs; our findings that OUD patients with a history of MST were not less likely to receive MOUD is promising. This could reflect effective care coordination within the VA, the fact that many patients in VA have complex treatment needs and these patients are often prioritized for care, and/or a lack of providers' bias towards complex patients in need of MOUD care. Additionally, VA population-based initiatives and policies that have strived to expand MOUD access may have assisted with reducing differences in treatment across patient characteristics, including MST. As MOUD access should be improved for all Veterans with OUD, further expansion of some types of MOUD (buprenorphine and naltrexone) into non-SUD specialty care clinics may be especially important for patients who have complex trauma histories (such as those with a history of MST) who may not be comfortable in specialty care treatment environments or with unfamiliar providers.

Although the association between MST and MOUD was similar in men and women, clinic setting should still be considered for those Veterans with OUD who are not yet receiving MOUD and may have additional care needs or barriers to care due to experiences they had in military service. A 2018 qualitative study about SUD treatment preferences for women Veterans noted that women desired both women's only treatment groups and women's only spaces (such as waiting areas); this desire for an environment safe and free from harassment was particularly salient for those women who had

experienced MST.[48] As approximately 15% of women Veterans received methadone to treat OUD, which is only delivered in SUD specialty clinics, future planning for MOUD delivery in these settings especially should consider adapting the physical spaces of SUD clinics to accommodate Veterans with a history of MST more comfortably.

As hypothesized due to new and ongoing initiatives, secondary analyses showed that the trending positive association between MST and MOUD receipt was stronger in the later time period (2014–2017 vs. 2007-2013). Nationally, according to both survey and hospital data, high-risk and long-term opioid prescriptions have dropped, but rates of OUD have remained relatively consistent, indicating a need to improve treatment access for OUD along with continuing to reduce non-recommended opioid prescribing practices (National Academies of Sciences, Engineering, and Medicine, 2017). Some newer initiatives, such as the VA's STEPPED Care model,[83] are seeking to further integrate MOUD into primary care as recommended by researchers and providers who have noticed that many at-risk patients are getting much of their healthcare in non-specialty care settings such as primary care, general mental health, and pain clinics. This is particularly important for increasing access in rural areas, where SUD specialty clinics are less common, and methadone in particular (available only in opioid treatment programs) is nearly impossible to access[112] as well as for women Veterans who may be uncomfortable in mostly male SUD clinics. The VA's initiatives to date appear to be effective at increasing receipt of MOUD across the Veteran population, and particularly among complex patients who may have comorbidities that were previously barriers to treatment, but there is still room for improvement. Future research should continue to assess mechanisms underlying potential disparities in MOUD receipt in order to craft solutions that will be effective at increasing MOUD uptake and reducing disparities in evidence-based care.

Limitations

This study has several limitations. This study only includes Veterans who receive care at the VA and is not generalizable to Veterans receiving care in the community or the general US population. However, its

focus on Veterans is noteworthy because VA has one of the most comprehensive substance use treatment programs in the country, and it is likely that it includes the overwhelming majority of Veterans with OUD. Despite a comprehensive SUD treatment program, it is difficult to track methadone visits in VA data, so it is possible that there are Veterans in the dataset unknowingly receiving Methadone although there is no reason to believe this misclassification would differ by MST status or by gender. It is also possible that there are Veterans who receive care at the VA who receive their MOUD at other facilities and are thus misclassified; nonetheless, since the VA offers more SUD treatment than any other health system and MOUD can be difficult to access outside the VA, it is unlikely that this would have a large impact on our results. Additionally, this study is cross-sectional in nature, limiting causal inferences.[91] Finally, this study focuses on cisgender men and women Veterans, despite the fact that transgender Veterans have a high prevalence of MST[92] and for those with OUD they may also have challenges accessing MOUD. Because the risks and barriers for transgender patients with OUD are likely to overlap with but be specific to this population, we considered such an analysis beyond the scope of the present study. However, future research should focus on this understudied population and their ability to access MOUD when needed.

3.6 Conclusions

Despite limitations, this study contributes important findings to the MOUD literature. MST was not significantly associated with MOUD treatment receipt using a conservative significance threshold, but there was a trend towards Veterans with a history of MST having greater odds of MOUD receipt, particularly after initiatives like the OSI, indicating that providers for Veterans with OUD who have MST histories may be attending to these potentially complex treatment needs. Additionally, the importance of the facility where treatment was received was less salient in the period 2014-2017 than in 2009-2013, suggesting that the location where a Veteran seeks treatment for OUD has become a less important indicator of MOUD receipt. While these results are promising, they also highlight that nearly two thirds of patients with OUD throughout the VA are not receiving MOUD and that more needs to be done to identify and address treatment barriers.

Table 3.1 Demographic and Health Characteristics of Men and Women Veterans with Opioid Use Disorder in the Veterans Health Administration- 2009 – 2017.

	Men (N = 75,417 – 93.3%)		Women (N = 5,428 – 6.7%)		TOTAL N=80,845
	Negative MST N = 71,531 (94.9%)	Positive MST N = 3,886 (5.2%)	Negative MST N = 2,778 (51.2%)	Positive MST N = 2,650 (48.8%)	Total MST = 6,536 (8.1%)
Individual Characteristics	**No. (%) or M (SD)**	**No. (%) or M (SD)**	**No. (%) or M (SD)**	**No. (%) or M (SD)**	**No. (%) or M (SD)**
Race					
White	54,165 (75.7%)	2,700 (69.5%)	2,205 (79.4%)	2,056 (77.6%)	61,126 (75.6%)
Black	13,445 (18.8%)	983 (25.3%)	389 (14%)	394 (14.9%)	15,211 (18.8%)
Asian/Native Hawaiian/ Pacific Islander	800 (1.1%)	46 (1.2%)	44 (1.6%)	44 (1.7%)	934 (1.2%)
American Indian/ Alaska Native	735 (1.0%)	45 (1.2%)	49 (1.8%)	49 (1.9%)	878 (1.1%)
Unknown/missing	2,386 (3.3%)	112 (2.9%)	91 (3.3%)	107 (4%)	2,696 (3.3%)
Age					
18-34	16,835 (23.5%)	489 (12.6%)	866 (31.2%)	673 (25.4%)	18,863 (23.3%)
35-49	14,057 (19.7%)	758 (19.5%)	915 (32.9%)	849 (32%)	16,579 (20.5%)
50-64	29,554 (41.3%)	2,160 (55.6%)	859 (30.9%)	1,042 (39.3%)	33,615 (41.6%)
65+	11,085 (15.5%)	479 (12.3%)	138 (5%)	86 (3.3%)	11,788 (14.6%)
Married	20,054 (28%)	869 (22.4%)	723 (26%)	532 (20.1%)	22,178 (27.4%)
Divorced	30,786 (43%)	1,903 (49%)	1,252 (45.1%)	1,381 (52.1%)	35,322 (43.7%)
Widowed	2,407 (3.4%)	163 (4.2%)	131 (4.7%)	109 (4.1%)	2,810 (3.5%)
Single	18,121 (25.3%)	948 (24.4%)	660 (23.8%)	624 (23.6%)	20,353 (25.2%)
Unknown	163 (0.2%)	3 (0.1%)	12 (0.4%)	4 (0.2%)	182 (0.2%)
Rurality					
Urban	51,746 (72.8%)	2,970 (76.8%)	1,997 (72.9%)	1,939 (74.0%)	58,652 (73.1%)
Rural	18,709 (26.3%)	870 (22.5%)	717 (26.2%)	663 (25.3%)	20,959 (26.1%)
Highly rural	582 (0.8%)	28 (0.7%)	25 (0.9%)	19 (0.7%)	654 (0.8%)
Mental Health diagnosis					
Any mental health dx	50,597 (70.7%)	3,344 (86.1%)	2,213 (79.7%)	2,381 (89.9%)	58,535 (72.4%)
PTSD	24,407 (34.1%)	2,290 (58.9%)	823 (29.6%)	1,780 (67.2%)	29,300 (36.2%)
Major Depressive disorder	20,801 (29.1%)	1,471 (37.9%)	1,075 (38.7%)	1,178 (44.5%)	24,525 (30.3%)
Schizophrenia	1,122 (1.6%)	128 (3.3%)	33 (1.2%)	42 (1.6%)	1,325 (1.6%)
Bipolar	7,477 (10.5%)	721 (18.6%)	484 (17.4%)	623 (23.5%)	9,305 (11.5%)
Anxiety disorders	13,231 (18.5%)	808 (20.8%)	806 (29%)	724 (27.3%)	15,569 (19.3%)
Psychoses	2,524 (3.5%)	218 (5.6%)	67 (2.4%)	104 (3.9%)	2,913 (3.6%)
Other mood disorders	8,846 (12.4%)	635 (16.3%)	387 (13.9%)	384 (14.5%)	10,252 (12.7%)
Serious mental illness	10,126 (14.2%)	954 (24.6%)	553 (19.9%)	703 (26.5%)	12,336 (15.3%)
Non-OUD Substance Use Diagnosis					
Any non-OUD dx	47,183 (66%)	2,908 (74.8%)	1,616 (58.2%)	1,765 (66.6%)	53,472 (66.1%)
Past-year Alcohol Use Disorder	25,458 (35.6%)	1,821 (46.9%)	654 (23.5%)	867 (32.7%)	28,800 (35.6%)
Cannabis Use Disorder	13,100 (18.3%)	895 (23%)	381 (13.7%)	484 (18.3%)	14,860 (18.4%)
	28,617 (40.0%)	1,770 (45.6%)	995 (35.8%)	1,031 (38.9%)	32,413 (40.1%)

Tobacco use disorder	5,333 (7.5%)	375 (9.7%)	231 (8.3%)	280 (10.6%)	6,219 (7.7%)
Amphetamine/ Stimulant use disorder	14,579 (20.4%)	1,213 (31.2%)	411 (14.8%)	539 (20.3%)	16,742 (20.7%)
Cocaine use disorder	351 (0.5%)	29 (0.8%)	14 (0.5%)	9 (0.3%)	403 (0.5%)
Hallucinogen use disorder	6,636 (9.3%)	454 (11.7%)	290 (10.4%)	353 (13.3%)	7,733 (9.6%)
Sedative use disorder	17,985 (25.1%)	1,212 (31.2%)	596 (21.5%)	746 (28.2%)	20,539 (25.4%)
Other drug use disorder					
Charlson Comorbidity Score	0.812 (1.56)	0.945 (1.66)	0.453 (1.03)	0.532 (1.15)	0.797 (1.54)
Year of AUDIT-C					
2009	0	0	0	0	0
2010	3,350 (4.7%)	159 (4.1%)	112 (4.0%)	93 (3.5%)	3,714 (4.6%)
2011	3,513 (4.9%)	139 (3.6%)	128 (4.6%)	117 (4.4%)	3,897 (4.8%)
2012	4,245 (5.9%)	192 (5.0%)	155 (5.6%)	134 (5.1%)	4,726 (5.9%)
2013	5,069 (7.1%)	220 (5.7%)	187 (6.8%)	152 (5.8%)	5,628 (7.0%)
2014	6,048 (8.5%)	336 (8.7%)	217 (7.8%)	209 (7.9%)	6,810 (8.4%)
2015	8,403 (11.8%)	459 (11.8%)	302 (10.9%)	244 (9.2%)	9,408 (11.7%)
2016	16,289 (22.8%)	957 (24.7%)	639 (23.1%)	687 (26.0%)	18,572 (23.0%)
2017	24,498 (34.3%)	1,419 (36.6%)	1,030 (37.2%)	1,005 (38.1%)	27,952 (34.6%)
Outcomes					
OUD treatment received	25,214 (35.3%)	1,393 (35.9%)	931 (33.6%)	901 (34.1%)	28,439 (35.2%)
Treatment type					
Subutex	6 (0.01%)	0	0	0	6 (0.01%)
Buprenorphine	16,978 (23.7%)	931 (24.0%)	722 (26%)	674 (25.4%)	19,305 (23.9%)
Methadone	12,996 (18.2%)	720 (18.5%)	409 (14.7%)	397 (15.0%)	14,522 (18.0%)
Naltrexone	1,168 (1.6%)	71 (1.8%)	44 (1.6%)	59 (2.2%)	1,243 (1.7%)
Facility-level Characteristics					
Complexity[*]					
1a	29,233 (40.9%)	1,529 (39.4%)	1,160 (41.8%)	1,156 (43.6%)	33,078 (40.9%)
1b	16,893 (23.6%)	808 (20.8%)	631 (22.7%)	573 (21.6%)	18,905 (23.4%)
1c	13,021 (18.2%)	669 (17.2%)	455 (16.4%)	438 (16.5%)	14,583 (18.1%)
2	4,090 (5.7%)	170 (4.4%)	195 (7.0%)	164 (6.2%)	4,619 (5.7%)
3	8,256 (11.6%)	707 (18.2%)	337 (12.1%)	318 (12.0%)	9,618 (11.9%)

*Facility complexity reflects type of medical center or clinic with 1a offering the most services/medical student training/most patients/ICU capacity, and 3 have the fewest patients, little to no teaching/research, and the fewest types of specialists available.

Table 3.2 Mixed Effects Logistic Regression of the Association of MST on MOUD at Various Levels of Adjustment

	Unadjusted OR (99% CI)	*p*-value	Partially Adjusted OR (99% CI)[1]	*p*-value	Fully Adjusted OR (99% CI)[2]	*p*-value
Military Sexual Trauma	1.03 (.95, 1.10)	0.371	1.11 (1.02, 1.21)	**0.001**	1.08 (1.00, 1.17)	**0.012**
Cluster Variance: Facility of Most Care	0.88 (.62, 1.26)	-	0.92 (.64, 1.31)	-	0.80 (.56, 1.34)	-

1 Adjusted for gender, age, race, and marital status

2Adjusted for gender, age, race, marital status, mental health and substance use diagnoses, Charlson Comorbidity Score, service connection, rurality, year of alcohol screen, and facility complexity

Table 3.3 Mixed Effects Logistic Regression of MST on MOUD Stratified by Fiscal Years, 2009-2013 and 2014-2017

FY 2009 – 2013, *N*=17,945						
	Unadjusted OR (99% CI)	*p*-value	Partially Adjusted OR (99% CI)[1]	*p*-value	Fully Adjusted OR (99% CI)[2]	*p*-value
Military Sexual Trauma	0.92 (.76, 1.11)	.251	1.06 (.86, 1.31)	.477	1.07 (.86, 1.32)	.417
Cluster Variance: Facility of Most Care	1.20 (.79, 1.84)	-	1.26 (.83, 1.92)	-	1.10 (.72, 1.68)	-
FY 2014-2017, *N*=62,721						
Military Sexual Trauma	1.02 (.94, 1.07)	.499	1.09 (1.00, 1.20)	.010	1.09 (1.00, 1.20)	.010
Cluster Variance: Facility of Most Care	0.84 (.59, 1.20)	-	0.88 (.62, 1.26)	-	0.77 (.54, 1.10)	-

1 Adjusted for gender, age, race, and marital status

2Adjusted for gender, age, race, marital status, mental health and substance use diagnoses, Charlson Comorbidity Score, service connection, rurality, and facility complexity

Chapter 4: Military Sexual Trauma, Chronic Pain, and Opioid Use Disorder

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4.1 Abstract

Introduction: Opioid use disorder (OUD) is a chronic condition with severe and potentially fatal outcomes. Military sexual trauma (MST) has been associated with OUD among both men and women Veterans. Both MST and OUD are also associated with non-cancer chronic pain. Because chronic pain is often treated with opioid therapy, we hypothesized that chronic pain may mediate the association between MST and OUD.

Methods: We assessed mediation among 8,065,858 Veterans Health Administration (VA) patients with outpatient appointments from 2009-2017. We conducted a nonparametric, counterfactual-based mediation analysis, stratified by gender, which provided estimates of the natural direct effect (NDE), natural indirect effect (NIE), and the marginal total effect (MTE) of chronic pain measured by ICD diagnoses for men and women.

Results: Chronic pain was highly prevalent (37%) , and 4% had a history of MST and 1% were diagnosed with OUD. The relationship between MST and OUD was mediated by chronic pain among men (NDE estimate: 1.42, 95% CI: 1.38, 1.47; NIE estimate: 1.01, 95% CI: 1.00, 1.01; MTE estimate: 1.43, 95% CI: 1.38, 1.48), but there was no mediation among women in primary analyses. In sensitivity analyses, MST mediated the OUD-chronic pain association (2-20%) for both men and women with: 1) an alternative definition of pain, 2) only demographic adjustment, and 3) in a subsample of the population that had no mental health or substance use comorbidities.

Conclusion: Contrary to hypotheses, chronic pain may play only a minor, if any, role in mediating the relationship between MST and OUD in women and men Veterans. Future research should explore other possible mechanisms explaining the relationship between MST and OUD, such as psychosocial needs or mental health and substance use comorbidities.

4.2 Introduction

One of the most common treatment methods for both acute and chronic pain is opioid therapy. Relative to the rest of medicine, pain treatment and pain research are relatively new. When opioids became widely available, they quickly became the dominant treatment strategy due to an assortment of regulatory, health system, and provider factors.[113] Although it was initially thought that prescription opioids could be used safely for treatment of chronic pain without increasing the risk of opioid use disorder (OUD), the risk of iatrogenic addiction is increasingly recognized.[40,114] OUD is a chronic condition associated with a high prevalence of overdose and mortality and is a persistent public health concern in Veteran and civilian populations.[38] The non-fatal consequences of OUD are numerous and varied, including medical and social complications.[21,22] For example, one recent survey found that up to 35% of persons using opioids long-term met diagnostic criteria for OUD,[42] while another recent study, the Prescription Opioid Addiction Treatment Study,[115] found that, among patients who had chronic pain and were physically dependent on prescription opioids, 83% initially used opioids to manage that pain.[116,117] Thus, treatment of chronic pain with prescription opioids has likely contributed to the rise in OUD.[118]

Although chronic pain affects the veteran and civilian populations, the prevalence of chronic pain is greater among veterans than non-veterans. Approximately 66% of Veterans experience chronic pain, compared to 11-40% among adults in the general population[119] Veterans may experience greater burden of chronic pain because chronic pain is more likely among persons with a history of trauma or traumatic stress. For example, a recent study of women Veterans found that a history of military sexual trauma (MST) was associated with more diagnosed pain conditions and greater severity of pain.[10]

A history of MST is associated with increased risk of significant mental and physical health sequelae such as PTSD, depression and anxiety disorders, unhealthy alcohol and other substance use, and opioid use disorder.[2,120] Because opioids are often used to alleviate pain, whether through a prescription or illicit use,

and sustained use of opioids can be motivated by a desire to reduce unwanted physical or physiological symptoms (self-medication),[121] pain may be an important mechanism mediating the association between MST and OUD. Furthermore, a 2018 literature review of comorbid chronic pain and OUD identified several risk factors for development of OUD in chronic pain patients, including history of trauma, psychiatric disorders, and significant psychosocial stressors, all of which are associated with MST[122] Thus, it is plausible that pain would account for at least some of the association between MST and OUD.

Chronic pain is more frequently reported by women than men, and most population-based studies have found a higher prevalence of pain in women than in men.[123] While exact reasons for this gender difference are unclear, some hypothesized mechanisms include greater risk of depression and anxiety in women and the increasingly physical nature of women's military service, which can take a toll on the body.[124] Notably, women have also been shown to be more likely than men to use opioids to cope with distress, negative affect, and pain – despite no differences in reported pain severity between men and women.[14] These gender differences suggest that chronic pain may play a stronger or differential role in the association of MST and OUD among women.

Taken together, the extant literature suggests that chronic pain may mediate the association between MST and OUD. Additionally, because chronic pain presents more frequently in women, and women are more likely to initiate prescription opioids,[14] the potential mediation of the relationship between MST and OUD could be stronger for women (i.e., the indirect effect of pain in the association between MST and OUD would be larger than it is for men).[125] The goal of this study was thus to assess chronic pain as a possible mediator explaining the association between MST and OUD, and to examine these associations in men and women Veterans using data from the nationwide Veterans Health Administration (VA).

4.3 Methods

Dataset:

This observational, retrospective study reflects secondary analyses of data collected in 2019 from VA's Corporate Data Warehouse for a National Institute of Alcohol Abuse and Alcoholism-funded study (R21AA025973) focused on alcohol use among Veterans and approved by the VA Puget Sound Healthcare Institutional Review Board.[107,126] Due to the focus of the parent study, the dataset included VA outpatients aged 18 or older with a documented Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) alcohol screen between October 1, 2009, and August 1, 2017 within each VA facility. Because the AUDIT-C is conducted among over 90% of VA outpatients annually, the sample is largely representative of the full VA outpatient population.[65]

Sample:

The total sample population was 8,065,858 patients and represented all patients whose MST history was known, who were not identified as transgender, and who did not have an active cancer diagnosis. Full sampling procedure can be found in previously published manuscripts using this dataset.[120] For the purposes of variable definition, the date of the alcohol screen represents the index date in this study.

Measures:

Outcome: OUD was defined by the presence of at least one International Classification of Diseases (ICD 9th and 10th edition) code for opioid abuse or dependence, not including in remission (Supplemental Table 3) in the 12 months preceding the index date.[68]

Exposure: Presence of MST was identified using data generated from a combination of a provider-administered MST screen and ICD codes which indicated MST. The MST screen queries Veterans about any experience of sexual harassment or assault during active military service.[70] A response of "yes" to either harassment or assault reflects MST; the administrative record does not differentiate between the experience of harassment and/or assault (Supplemental Table 4).

Mediator: Chronic pain is commonly defined by providers and medical associations as the experience of moderate to severe, non-cancer pain beyond normal healing time or for at least 3-6 months.[127] The pain can be in any place on the body and can result in varied diagnoses depending on the source of the pain. In research, this definition is often operationalized in one of two different ways: using ICD codes or a series of NRS pain screenings. For the purposes of this study, the primary definition of chronic pain was an ICD-9 or ICD-10 diagnosis of one of several chronic pain conditions (musculoskeletal pain, back pain, rheumatism, arthritis, osteoarthritis, chronic joint pain, pelvic pain, and pain not elsewhere classified) over the 12 months prior to the index date (see Appendix 1 for codes). ICD-9 codes were taken from published chronic pain research,[114] and corresponding ICD-10 diagnoses were determined via manual review of results from an online code translator (see appendix 1 for codes and link). The use of ICD9 and ICD10 diagnoses as a primary indicator of pain for research purposes is consistent with previous research on chronic pain both in and outside of the VA.[40,68,115] We also measured an alternative definition of chronic pain for sensitivity analyses. In this measure chronic pain was defined using the Numeric Rating Score (NRS), a scale from 0-10 that is administered in clinical encounters. Chronic pain was considered present if there were 3 or more NRS ≥4 in the 12 months prior to the index date.[128]

Covariates: Gender, age, race and marital status were extracted from administrative data at the index date. Race categories were condensed by prioritizing Black race (followed by American Indian then Asian/Pacific Islander) when multiple races were reported by the patient in order to reflect systems of social inequity.[71]

Other covariates were selected from a literature review and included variables known to be associated with MST, chronic pain and/or OUD. Mental health disorders, including anxiety disorders, depression, PTSD, and forms of serious mental illness were identified via ICD-9-CM or ICD-10-CM codes in the 12 months prior to the index date.[2] Substance use disorders (SUDs) were determined based on having a ICD-9-CM or ICD-10-CM code for a non-OUD SUD in the 12 months prior to the index date (see Supplemental Table 1 for both SUDs and mental health disorders).[72] Mental health conditions and SUDs

were included because they are both strongly associated with both MST and OUD. The Charlson Comorbidity Index (CCI), a continuous variable, was calculated from diagnoses in the medical record for the year prior to the index date.[74] These clinical diagnoses and indicators of significant illness were included because they could influence pain conditions or whether a patient's OUD is documented/recognized due to other treatment needs possibly becoming a priority. Patient urban/rural status was linked to the patient's primary residential address at index date using a VA classification based on the US government's rural-urban commuting area (RUCA) code, and was included to account for potential differences in care access and healthcare utilization.[73] Service connection, which along with being associated with SUDs,[129] represents degree of disability from military service and can also be considered a marker of socioeconomic status, was used as a categorical variable with the following categories: full VA service (50-100% service connected), less than 50% service connected, not service connected, or missing.[75]

Analysis:

Descriptive analyses of all covariates along with the exposure, outcome, and mediator were conducted across gender and MST status.

Two primary mediation analyses were conducted: one for men and one for women, due to gender differences in pain prevalence, treatment, and opioid use.[120] In both analyses, MST status was the primary exposure, chronic pain diagnosis was the mediator, and OUD diagnosis was the outcome – all dichotomous variables. Covariates for primary analyses included age, marital status, race, any substance use diagnosis (yes/no), any mental health diagnosis (yes/no), Charlson score, patient rurality (categorical), and service connection (categorical).

As a secondary measure for the chronic pain diagnosis, we assessed whether those with chronic pain diagnoses were also categorized as having chronic pain defined using NRS pain scores.[130] Additionally,

we conducted several sensitivity analyses for the mediation models. The first sensitivity analysis used NRS pain scores rather than ICD diagnoses for pain, controlling for the same set of covariates. The final two sensitivity analyses were conducted post-hoc to explore the potential confounding role of mental health conditions and non-OUD SUDs which are frequently comorbid with MST, chronic pain, and OUD as well as having a potential causal relationship with chronic pain. The first of these analyses used ICD pain diagnoses as the mediator (as in the primary models) but limited the covariates to demographic variables only (race, age, and marital status). The second of these kept the ICD diagnoses as a mediator and controlled for demographic variables, but only in a subsample that removed all Veterans with mental health and SUD diagnoses (2,746,029 men and 332,258 women).

Mediation was conducted using the PARAMED module for Stata, which is appropriate for binary outcomes and mediators and allows the user to indicate preferred regression types for the direct and indirect effects. Both the direct and indirect effect regressions were logistic regressions in this analysis. Using PARAMED, two models were estimated: one assessing the mediator conditional on exposure, and one for the outcome conditional on exposure. PARAMED extends the Baron and Kenny mediation procedure to allow for potential exposure-mediator interaction and uses counterfactual definitions of the direct and indirect effects.[131,132] The analysis produced three estimates: the natural direct effect (NDE), the natural indirect effect (NIE), and the marginal total effect (MTE). The NDE measures the expected increase in the odds of the outcome when changing the exposure (i.e., from no history of MST to a history of MST) and keeping the mediator at the value it would have had if the exposure was not changed. The NIE measures the expected increase in the odds of the outcome when the mediator changes (i.e., from no chronic pain to the presence of chronic pain) and keeping the exposure constant. The NIE can also be interpreted as the effect of MST on OUD that could be prevented when the effect of MST on chronic pain is removed; a significant NIE indicates the presence of mediation. The MTE is the sum of NIE and NDE and measures the change in the outcome (OUD) when there is a change in the exposure (MST history) while accounting for the effect of the mediator (chronic pain) and controlling for the average level of the covariates. No interaction terms were included, and 95% confidence intervals were calculated using the

delta method were used. The proportion of the association between the exposure and outcome accounted for by the mediator was calculated using the equation (NDE * (NIE-1))/ (NDE * NIE -1). This mediation method did require several assumptions, including that no unmeasured confounding was present and that there is a causal relationship among MST, chronic pain, and OUD. All analyses were conducted in 2021 using Stata v.16 (Statacorp, College Station, Texas).

4.4 Results

Table 4.1 provides descriptive statistics for demographic, covariate and outcome variables, stratified by history of MST and gender. The sample included 8,065,858 Veterans, was 92% men, and had a mean age of 60 for men and 46 for women, and was approximately 17% Black. Prevalence of MST was 27% for women and 2% for men. Women were more likely to be Black. Mental health conditions were present in 30% of the sample and were more common among Veterans with a history of MST (54% of men and 66% of women). Based on diagnosis codes, chronic pain was present in 45% of women in the sample and 36% of men, as well as in 47% of Veterans with MST (50% of women with a history of MST, and 43% of men with a history of MST). Using NRS pain scores rather than diagnoses, chronic pain was present in 15% of women and 11% of men in the sample, as well as in 20% of Veterans with MST (22% of women with a history of MST and 18% of men with a history of MST). Prevalence of OUD was 1% overall (n = 80,707; 75,296 men (1.0%) and 5,411 women (0.8%)).

In the primary analysis, the relationship between MST and OUD was mediated by chronic pain among men (NIE estimate: 1.01, 95% CI: 1.00, 1.01). The percentage of the effect mediated by chronic pain was 2.03%. In women, the indirect effect was not significant (Table 4.2).

Among Veterans with chronic pain ICD diagnoses, 24% also had chronic pain based on the NRS pain score definitions (Table 4.1). In all three sets of mediation sensitivity analyses, chronic pain significantly mediated the association between MST and OUD for both women and men (Table 4.2). Using NRS

scores instead of ICD diagnoses, chronic pain mediated 7% of the MST-OUD association in women (NDE estimate: 1.41, 95% CI: 1.33, 1.49; NIE estimate: 1.02, 95% CI: 1.02, 1.02; MTE estimate: 1.44, 95% CI: 1.36, 1.52) and 5% of the association in men (NDE estimate: 1.39, 95% CI: 1.35, 1.44; NIE estimate: 1.02, 95% CI: 1.01, 1.02; MTE estimate: 1.42, 95% CI: 1.37, 1.47). When using ICD diagnoses for the pain mediator but only controlling for demographic covariates, chronic pain mediated 6% of the MST-OUD association for women (NDE estimate: 2.24, 95% CI: 2.13, 2.37; NIE estimate: 1.03, 95% CI: 1.03, 1.04; MTE estimate: 2.32, 95% CI: 2.20, 2.45) and 7% for men (NDE estimate: 2.18, 95% CI: 2.11, 2.25; NIE estimate: 1.04, 95% CI: 1.04, 1.04; MTE estimate: 2.27, 95% CI: 2.19, 2.34). When using the subsample of Veterans with no MH or SUD diagnoses, chronic pain mediated 20% of the MST-OUD association for women (NDE estimate: 2.07, 95% CI: 1.71, 2.50; NIE estimate: 1.01, 95% CI: 1.00, 1.02; MTE estimate: 2.08, 95% CI: 1.72, 2.52) and 2% for men (NDE estimate: 1.79, 95% CI: 1.58, 2.03; NIE estimate: 1.01, 95% CI: 1.00, 1.01; MTE estimate: 1.80, 95% CI: 1.59, 2.05).

4.5 Discussion:

We aimed to assess the role of chronic pain as a mediator in the relationship between MST and OUD at a population level among men and women Veterans. While MST is associated with both chronic pain and OUD diagnosis, chronic pain did not mediate the MST-OUD association in women as hypothesized in the primary analysis but did mediate 6-20% of the association in women in sensitivity analyses. Although chronic pain did mediate some of the MST-OUD association in men, it was only 2% of the total effect in the primary analysis, suggesting that chronic pain is likely not an important driver of the association. The variation in mediation by chronic pain among women was surprising given that both chronic pain and MST are more prevalent in women Veterans than men Veterans. Despite these inconsistent findings, this is the first study to evaluate mechanisms explaining the MST-OUD association and is thus important as it can guide future research in this area.

Interestingly, the sensitivity analyses showed a different pattern of results than the primary analysis. There was evidence that chronic pain, as determined by NRS pain score, mediated the association between MST and OUD for both women and men. For the NRS definition to capture chronic pain, a patient has to visit a provider three times throughout the year, whereas the ICD diagnosis requires only one visit. Therefore, the NRS score is capturing a narrower subpopulation of Veterans with pain. Research has shown that women Veterans with chronic pain utilize healthcare more regularly than their men counterparts, even when adjusting for mental health comorbidities.[133] This measure could be more sensitive for women, thus explaining why chronic pain mediated more of the MST-OUD association for women when using this chronic pain definition as opposed to ICD diagnoses. Future research should evaluate the sensitivity and specificity of these pain measures across genders.

The mediation analyses that explored the confounding role of MH and SUDs (whether as a covariate or in the subsample without Veterans who had diagnosed MH conditions and SUDs) also showed increased mediation percentages, although the two analyses showed different patterns. When conducting mediation in the full sample without controlling for MH and SUDs, the results showed a similar pattern to the NRS pain score mediation. This indicates that selection of potential confounders should be carefully considered when assessing pain-related outcomes. It also indicates that MH and SUDs likely make up some part of the MST-OUD pathway while either mediating or pre-dating the association between MST and OUD. However, when conducting the mediation analysis in only the subsample with no MH or SUD conditions, chronic pain accounted for 20% of the MST-OUD association in women and only 2% in men. This may be thought of as a distinct population of Veterans with OUD, who did not have other mental health or SUD comorbidities. The findings suggest that among women with OUD who do not have these other comorbidities, pain may mediate the relationship between MST and OUD. This may be because women Veterans with a history of MST experience pain that is not adequately treated or recognized and then turn to opioids to self-medicate. Clinicians often under-estimate women's pain compared with men's pain and are more likely to prescribe psychotherapy to women in pain and pharmacotherapy to men in pain.[134] Thus, consistent with original hypotheses, these findings indicate that mechanisms for women

and men may indeed differ and deserve additional attention. There are both individual patient and systemic level factors influencing opioid use and OUD, thus these results also highlight the importance of examining subgroups of Veterans.

These findings also suggest that mental health and SUD sequelae could play a role in the MST-OUD relationship, as various traumas, mental health conditions such as PTSD, and substance use disorders can increase risk of OUD and are also associated with chronic pain.[135,136] Mental health conditions and SUDs are common sequelae of trauma, and in particular of sexual trauma, which is much less likely to be disclosed by the victim than other types of trauma due to stigma.[137] Therefore, the victim may try to cope alone and/or without professional help.[138] When these sequelae are not being treated, they can manifest or evolve into pain, which is a psychological as well as physiological condition.[139] The need or desire to self-medicate or cope with this pain can result in dangerous use of opioids and, ultimately, in OUD. Despite this evidence for mediation in the sensitivity analyses, chronic pain only accounted for 20% or less of the association between MST and OUD, indicating that despite a significant indirect effect, factors other than chronic pain are important.

Despite chronic pain not being a consistently prominent mechanism explaining much of the association between MST and OUD, it is still highly prevalent in both men and women Veterans with a history of MST, which has important implications for clinical care. Chronic pain was present in 37% of the sample (defined by ICD codes) and was higher in patients with MST histories and women Veterans, using both pain definitions. It is important for both primary care and specialty care providers to screen for pain in Veterans who have a history of MST. Many Veterans with history of MST also have complex comorbidities requiring care in mental health and SUD clinics, where pain may not be the primary concern of providers. The VA is engaged in many different initiatives to improve access to appropriate pain care such as stepped care models, which are highly flexible and accommodate a patient's changing needs over time.[122] These models have been successful for a number of health conditions, including OUD.[83] The VA is also undergoing a transformation to provide care using a Whole Health approach that promotes non-

pharmacologic treatments for pain. In this approach, the Veteran's chief complaint is addressed with consideration of the full context of the Veteran's life and goals.[140] This is extremely promising for concerns such as pain and OUD, where trauma history, gender, and other life experiences can influence ability to seek treatment, find acceptable care, and adhere to treatment plans. In a Whole Health model, all these components can be considered when evaluating and treating a patient.

Limitations:

These data are cross-sectional, which makes interpretation of the temporal ordering of diagnoses for the mediator and outcome impossible. However, pain typically precedes OUD development, and this is likely true for the majority of the sample, although this relationship can also happen in the reverse. Future research using prospective data is warranted to assess this relationship. Use of causal mediation analysis requires that certain assumptions (that there are no unmeasured confounders present in the regression relationships) be met. This analysis controlled for suspected confounders, but there is the possibility that there were unknown and unmeasured confounders of these relationships which would bias the results. Moreover, pain can be difficult to measure, and various methods can be used; the ICD diagnoses are dependent on provider prescribing practices and potential provider and institutional bias regarding who gets diagnosed with chronic pain. While NRS scores are also frequently used to define chronic pain, they were not the primary definition in this study because it requires multiple visits to care providers and therefore may miss individuals who are less engaged in care. Additionally, MST may also be underreported in this sample, as studies using non-administrative data often find higher prevalence rates of MST.[32] Recent research has also found that higher rates of self-stigma increase likelihood of non-disclosure during MST screening in female Veterans, indicating that there are likely to be many Veterans with a history of MST who are not disclosing their experiences. However, whether or not these Veterans who don't disclose their MST history are more or less likely to experience OUD or chronic pain is unknown.[139]

4.6 Conclusion

In contrast to hypotheses, chronic pain did not significantly mediate the relationship between MST and OUD in women Veterans and mediated only 2% of this relationship in men Veterans in the primary analysis. Sensitivity analyses, particularly among women with a history of OUD and no mental health or SUD comorbidities, aligned more closely with hypotheses. And, although we selected an a priori measure of pain and a model of its role in the MST-OUD relationship, the findings suggest that appropriate definitions and the role of pain vary widely depending on the specific subpopulation of concern. Future clinical practice should consider prioritizing trauma exposure in the assessment and treatment of pain conditions such as with a whole health approach. Future research should explore other potential mechanisms for the MST-OUD association, such as psychosocial needs and/or mental health or SUD comorbidities. Clinicians who treat patients with history of MST should be mindful of chronic pain and the role it plays in their overall health in the development of treatment plans.

Table 4.1 Characteristics of Men and Women Veterans, 2009-2017

	Men (N = 7,388,439)		Women (N = 677,419)		TOTAL
	Negative MST N = 7,246,564	Positive MST N = 141,875 (2%)	Negative MST N = 492,101	Positive MST N = 185,318 (27.4%)	8,065,858
Individual Characteristics	**No. (%) or M (SD)**	**No. (%) or M (SD)**	**No. (%) or M (SD)**	**No. (%) or M (SD)**	**No. (%) or M (SD)**
Race					
White	5,595,371 (77.2%)	105,547 (74.4%)	298,141 (60.6%)	116,793 (63.0%)	6,115,852 (75.8%)
Black	1,145,687 (15.8%)	25,886 (18.3%)	151,196 (30.7%)	51,323 (27.7%)	1,374,092 (17.0%)
Asian/Native Hawaiian/ Pacific Islander	153,314 (2.1%)	2,759 (1.9%)	14,987 (3.1%)	4,888 (2.6%)	175,948 (2.2%)
American Indian/ Alaska Native	72,381 (1%)	1,988 (1.4%)	6,421 (1.3%)	3,722 (2%)	84,512 (1.1%)
Unknown	279,811 (3.9%)	5,695 (4.0%)	21,356 (4.3%)	8,592 (4.6%)	315,454 (3.9%)
Age					
18-34	804,856 (11.1%)	14,703 (10.4%)	138,239 (28.1%)	44,976 (24.3%)	1,002,774 (12.4%)
35-49	950,824 (13.1%)	22,099 (15.6%)	144,622 (29.4%)	58,445 (31.5%)	1,175,990 (14.6%)
50-64	1,844,185 (25.5%)	51,946 (36.6%)	145,604 (29.6%)	68,300 (36.9%)	2,110,035 (26.2%)
65+	3,646,699 (50.3%)	53,127 (37.5%)	63,636 (12.9%)	13,597 (7.3%)	3,777,059 (46.8%)
Marital Status					
Married	3,947,683 (54.5%)	62,288 (43.9%)	172,239 (35.0%)	60,695 (32.6%)	4,242,905 (52.6%)
Divorced	1,820,915 (25.1%)	47,168 (33.3%)	170,801 (34.7%)	77,186 (41.7%)	2,116,070 (26.2%)
Widowed	474,342 (6.6%)	6,384 (4.5%)	26,146 (5.3%)	5,847 (3.2%)	512,719 (6.4%)
Single	963,260 (13.3%)	25,551 (18.0%)	118,713 (24.1%)	40,380 (21.8%)	1,147,904 (14.2%)
Unknown	40,364 (0.6%)	484 (0.3%)	4,202 (0.9%)	1,210 (0.7%)	46,260 (0.6%)
Any mental health diagnosis	2,056,076 (28.4%)	76,347 (53.8%)	182,148 (37.0%)	122,945 (66.3%)	2,437,516 (30.2%)
Any Substance Use Diagnosis (non-OUD)	1,158,917 (16.0%)	37,113 (26.2%)	52,111 (10.6%)	30,717 (16.6%)	1,278,858 (15.9%)
Charlson Comorbidity Score *[M (SD)]*	0.86 (1.39)	0.92 (1.56)	0.36 (0.85)	0.39 (0.88)	0.82 (1.37)
Service Connection %					
Full VA Coverage (50-100%)	1,800,229 (24.8%)	52,220 (36.8%)	143,987 (29.3%)	92,595 (50.0%)	2,089,031 (25.9%)
<50% service connected	1,580,934 (21.8%)	27,399 (19.3%)	121,964 (24.8%)	34,245 (18.5%)	1,764,542 (21.9%)
Non-service connected	3,326,463 (45.9%)	51,754 (36.5%)	187,456 (38.1%)	45,549 (25.6%)	3,611,222 (44.8%)
Missing	538,938 (7.4%)	10,502 (7.4%)	38,694 (7.9%)	12,929 (7.0%)	601,063 (7.5%)
Rurality					
Urban	4,570,679 (63.9%)	92,036 (65.5%)	352,018 (72.8%)	132,829 (72.6%)	5,147,562 (64.7%)
Rural	2,477,799 (34.7%)	46,642 (33.2%)	126,741 (26.2%)	48,359 (26.4%)	2,699,541 (33.9%)
Highly rural	99,236 (1.4%)	1,724 (1.2%)	4,082 (0.8%)	1,656 (0.9%)	106,698 (1.3%)
Insular Island	3,322 (0.1%)	52 (0.04%)	440 (0.1%)	71 (0.04%)	3,885 (0.1%)
Outcome					

OUD diagnosis	71,415 (1.0%)	3,881 (2.7%)	2,770 (0.6%)	2,641 (1.4%)	80,707 (1.0%)
Mediator					
Chronic Pain					
Based on ICD Diagnosis	2,583,888 (35.6%)	61,140 (43.1%)	213,323 (43.0%)	93,211 (50.1%)	2,951,962 (36.5%)
Based on NRS	769,560 (10.6%)	25,797 (18.2%)	63,453 (12.8%)	40,088 (21.6%)	898,898 (11.1%)
Either definition	2,744,322 (37.9%)	66,094 (46.6%)	222,727 (45.3%)	99,037 (53.4%)	3,132,180 (38.8%)

OUD= Opioid Use Disorder; NRS = Numeric Rating Scale; ICD = International Classification of Diseases

Table 4.2 Measures of Direct, Indirect, and Total Effects among Men and Women Veterans in the Veterans Health Administration, 2009-2017.

	Natural Direct Effect		Natural Indirect Effect		Marginal Total Effect		% of MST-OUD Association Mediated
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	
Primary analysis: ICD pain definition[a]							
Men	1.42***	1.38, 1.47	1.01**	1.00, 1.01	1.43***	1.38, 1.48	2%
Women	1.45***	1.37, 1.54	1.00	.99, 1.01	1.45***	1.37, 1.54	0
Sensitivity analysis: NRS pain definition[a]							
Men	1.39***	1.35, 1.44	1.02***	1.01, 1.02	1.42***	1.37, 1.47	5%
Women	1.41***	1.33, 1.49	1.02***	1.02, 1.02	1.44***	1.36, 1.52	7%
Sensitivity analysis: minimally adjusted ICD pain definition[b]							
Men	2.18***	2.11, 2.25	1.04***	1.04, 1.04	2.27***	2.19, 2.34	7%
Women	2.24***	2.13, 2.37	1.03***	1.03, 1.04	2.32***	2.20, 2.45	6%
Sensitivity analysis: ICD pain definition, subsample[c]							
Men	1.79***	1.58, 2.03	1.01**	1.00, 1.01	1.80***	1.59, 2.05	2%
Women	2.07***	1.71, 2.50	1.01*	1.00, 1.02	2.08***	1.72, 2.52	20%

* p<.05, ** p<.01, ***p<.001
a. adjusted for race, age, marital status, mental health conditions, substance use disorders, rurality, Charlson score, and service connection
b. adjusted for race, age, marital status
c. patients with mental health and substance use diagnoses removed; adjusted for race, age, marital status

Chapter 5: Conclusion, Implications and Limitations

5.1 Importance

MST is an unfortunately common occurrence in the military, where rates of this trauma are increasing every year.[141] This dissertation has contributed to the literature on both MST and OUD—both persistent health threats—by providing epidemiological evidence on the relationship between MST and OUD. While the MST literature base is broad and includes research on a host of mental and physical health sequelae of MST, before now it did not include research on the association with OUD, receipt of high-risk prescriptions, or receipt of evidence-based treatments for OUD. Also, despite the importance chronic pain has on quality of life and its association with both MST and OUD, chronic pain had not been considered as a potential mediator in the relationship between MST and OUD. This epidemiological evidence contributes to a greater understanding of both the risk factors for OUD and the long-term consequences of MST. This evidence can be used to improve public health interventions related to sexual trauma, chronic pain, and OUD, in addition to health services for Veterans.

5.2 Public Health Implications & Clinical Significance

There are several public health implications of this research. First, because OUD is such a dangerous and deadly condition, exploring potential risk factors and causal mechanisms is an important step for prevention and identification of OUD. Although OUD, like all SUDs, is a chronic disease, it is also one with alarmingly high mortality (estimated at a pooled standard mortality ratio (SMR) of 14.7, with overdose as the leading cause of death).[40] Second, although this research was conducted specifically among Veterans, sexual trauma (more broadly than MST) is common in civilian populations as well. Indeed, most of the potential health consequences of MST hold true for civilian sexual trauma and severe sexual harassment as well.[142-144] And, although the VA treats MST-related conditions free of charge, there are still many Veterans who have experienced MST who have never received care in the VA. Therefore, this research may be noteworthy not only for VA providers but for mental health and primary care providers more broadly who treat individuals with sexual trauma histories. For example, providers may need to be

mindful to take thorough substance use screenings and assessments, given risk for OUD. Third, as the VA makes changes in its prescribing guidelines, screening practices, and system-wide initiatives to treat OUD, these practices are regularly studied and then adapted by other health systems. For example, the Substance Use Stepped Care for Opioid Use Disorder Train the Trainer (SCOUTT) initiative, which was started in 2018, aims to increase access to MOUD by training providers in non-SUD specialty settings (such as primary care, mental health, and pain clinics) to prescribe MOUD.[83] It is likely at least partly through initiatives like this that VA has achieved the success it has with MOUD access. The success of initiatives like this could be the reason we are not seeing a disparity in MOUD access by MST history. This also suggests that adapting similar initiatives in other health systems could help sexual trauma survivors with OUD access MOUD.

Treatment efforts within the VA for MST are focused on detection and access to care, as well as ensuring that care is patient-centered.[145] Implementing universal screening for detection has been successful, and access to care has improved due to several factors such as the establishment of MST coordinators in all VA hospitals and making care associated with the MST free of charge regardless of whether that Veteran qualifies for other VA care.[70] However, access to care is defined by more than putting care in place and reducing cost. Other potential barriers to accessing care include geographic availability, lack of time, childcare, feeling uncomfortable with providers, and feeling uncomfortable in the care environment. Research shows that rates of accessing care are high for women with a history MST, and that satisfaction is also fairly high.[8] However, that same research also indicates that women with a history MST are not getting all the care they need,[8] some of which may involve pain care and substance use treatment.[133] Men with a history of MST also do not access care for their MST-related concerns as frequently as women, and continued research into mechanisms explaining these gender-related differences in MST-related care is warranted.[146,147]

The VA is the largest provider of SUD treatment in the US. And yet, by 2017 only 35% of patients diagnosed with OUD were receiving medication to treat that disorder.[16] At this time, there is wide facility-

level variation, with rates of prescribing for OUD treatment ranging from 1- 68%, and a number of patient-level characteristics that decrease likelihood of receiving treatment, including female gender, older age, being Black/African American, homeless status, rural residence, and disability due to military service.[16] Many of these patient-level characteristics are also associated with a history of MST, but this dissertation research did not find that MST was a barrier to receiving potentially life-saving medication for OUD. Treatment receipt for patients with OUD at the VA appears to be received at the same rate among those who have a history of MST and among those who do not. This is significant because Veterans who have experienced MST also frequently have comorbid conditions, such as PTSD, depression, or other chronic physical ailments, that can complicate care. This lack of a disparity in treatment may indicate that MST coordinators or other care coordination efforts between mental health and substance use treatment providers are working. Additionally, the results from Aim 2 showed that the facility where a Veteran received care was less likely to be a determinant of receipt of medications for OUD (MOUD) in the years 2013-2017 than in the early years of the study (2009-2012). This is another positive sign that MOUD is becoming more widespread across the VA system rather than only in select facilities.

Other initiatives spreading throughout the VA healthcare system include the push toward a Whole Health approach in clinical interactions, which is particularly relevant for pain care.[140] Pain care has evolved significantly over the past twenty years, and a multi-faceted approach involving medication in addition to complementary therapies such as massage or cognitive behavioral therapy is now recognized as necessary for treatment of persistent pain. The research from this dissertation supports a multi-faceted approach as it shows that chronic pain is highly prevalent in Veterans and is particularly high among Veterans with a history of MST. Taking a whole health approach is an important way for clinicians to consider trauma exposure in the assessment and treatment of pain conditions and to limit use of pharmacologic interventions that pose further risk of harm.

Many of the successes that the VA has achieved in caring for patients with sexual trauma and/or patients with OUD is a result of top-down initiatives to prioritize care for these vulnerable populations based on

research conducted within the institution. Smaller health systems and individual care centers do not regularly have the same capacity to conduct research or set priorities for system-wide changes. Some of the barriers to opioid-related care are likely to remain the same, but it is also likely that there are additional barriers in a less centralized healthcare system. This can lead to patients with complex care needs not receiving care for all their conditions at once – particularly in a care environment where the emergent issue is the only one a provider has time to attend to in their short visit with a patient. However, taking significant findings from the VA and adapting them to civilian settings can help prioritize research agendas when resources are limited.

5.3 Future Research

Because the research base on OUD and OUD treatment is still relatively small, there are many gaps that need to be filled in our understanding of this disorder. This research fills several gaps while also providing evidence for expanded research. Aims 1 and 3 showed that while MST is associated with both OUD and HRP, and in the case of OUD that association is stronger in men than women, chronic pain did not explain much of this association. Future research should explore other potential mechanisms for this association such as PTSD, depression, and possibly social factors such as feelings of institutional betrayal, where a Veteran resides, or economic opportunity. Aim 2 showed no disparity in treatment receipt by history of MST, but unsurprisingly showed low overall treatment uptake. Research should continue to explore mechanisms explaining why approximately 60% of Veterans who receive care at the VA and who have OUD are not receiving MOUD.

While this research does use an innovative approach by directly comparing both men and women, which is rare in MST research, it also exposes how little research there is comparing the long-term consequences and clinical implications of MST in men and women. This dissertation tested the possibility of chronic pain as a mechanism explaining the association between MST and OUD. While that analysis was inconclusive due to the variability in results when using different definitions of chronic pain, it did

reveal the possibility that mental health conditions or the presence of non-OUD SUDs may explain some of the MST-OUD association. Future research should explore this possibility as well as other potential mechanisms. Overall, there is a considerable body of research exploring associations between MST and mental and physical health conditions, but very little that evaluates mechanisms explaining potential associations. Research that searches for mechanisms is possible in large datasets such as those available at the VA and can uncover important nuance in exposure-outcome relationships that can lead to significant clinical care improvements.

Qualitative research with Veterans who have experienced MST and also have an OUD diagnosis will also be an important complement to this work. Qualitative research could identify potential mechanisms for the MST-OUD association aside from chronic pain or mental health conditions. It could also help elucidate some of the reasons why men with MST histories are more likely than women with MST histories to be diagnosed with OUD. Additionally, survey research that achieves more detail regarding the MST (whether it was assault or harassment, what year it occurred, if the perpetrator was known to the survivor) could do a better job of exploring the reasons behind the association between MST and OUD, by connecting this association to other important aspects of sexual assault recovery, such as assault characteristics or psychological functioning at the time of the trauma.

Another prominent direction for future work in this field is the inclusion of transgender Veterans as well conducting this research in non-Veteran or non-VA populations. Transgender Veterans with MST histories are at greater risk of drug use when compared to transgender Veterans without MST, and the transgender Veteran population comes into the military with complex trauma histories, complicating their recovery from traumas experienced during military service.[55] Because of the marginalization experienced by this population, determining if transgender Veterans with MST are at greater of OUD or decreased risk of receiving OUD treatment is important for outreach programs and care coordination with this population.

While MST and civilian sexual trauma share many characteristics, MST is also unique in several ways (e.g., survivors often having to live and work alongside perpetrator, feelings of institutional betrayal). Thus, replicating the current research among civilians and evaluating the association between sexual trauma more broadly and OUD and MOUD will be important to ensure generalizability.

5.4 Limitations

This dissertation has several limitations, primarily falling under the domains of measurement and study design/dataset. Several of the primary variables have potential measurement concerns. Patient under-report of opioid use due to stigma could bias the results. Another potential reporting issue is with respect to chronic pain. In order to get prescribed opioids, the patient typically needs to be in pain. It is possible that some percentage of the Veterans with chronic pain diagnoses do not actually suffer from chronic pain conditions, and are instead engaging in drug-seeking behavior.[148] However, research indicates that drug-seeking behavior for pain relief is a greater problem in the emergency room; using chronic pain diagnoses, which are often not given until the patient has been seen more than once with the same complaints, may limit the sample of "false" chronic pain patients in the sample.[149] Data from all retail opioid prescriptions in 2008 show that approximately 0.7% of patients were engaged in "doctor-shopping" in order to obtain opioids;[150] since this time, most states have implemented prescription monitoring programs to further reduce this phenomenon. An additional issue with chronic pain rates is that the diagnosis of chronic pain is dependent on provider preference, accurate interpretation of patient complaints and inherent biases the provider may hold.[88,151] The MST screen is generally considered to be applied universally, however some Veterans do refuse to answer the screen, so those Veterans are left out of the sample, which could bias the results. However, previous research has indicated this is only about 1% of Veterans.[70]

The study design is cross-sectional and used the most recent alcohol screen as the index date. A cross-sectional design limits the ability to determine causation and requires the assumption that certain events

happened prior to outcomes. MST, by definition occurring during active-duty service, would have occurred prior to care received at the VA. However, it's possible that some diagnoses (physical or mental health and SUDs) were present prior to the experience of MST. The cross-sectional design also doesn't allow for determining whether a chronic pain diagnosis came before or after the development and/or diagnosis of OUD. However, there is evidence that most OUD patients had existing chronic pain prior to developing OUD. In the Prescription Opioid Addiction Treatment Study, 83% of patients with chronic pain and prescription opioid dependence initially used opioids in order to manage that pain,[116,117] indicating that the vast majority of patients with both chronic pain and OUD developed the OUD after initial treatment for chronic pain relief. Limiting the dataset to the most recent alcohol screen as an index date means that some patients may have been classified as not having OUD if it was not recorded in the administrative record in the past year. Also, individuals with OUD who had not yet been diagnosed would not have been classified as having OUD in this sample.

Beyond the study design concerns, the administrative dataset presents several limitations. The MST screen asks about both harassment and assault, but the database combines the two into one screen category because both are considered a "duty-related hazard, similar to combat exposure".[70] The dataset also does not have additional information about other duty-related hazards experienced such as combat trauma, the presence of which could compound or complicate sequelae of MST, or about stigma coming from providers or the military which could influence disclosure or care-seeking behavior. Additionally, there is evidence that many people who experience MST have experienced previous instances of sexual trauma and abuse, particularly in childhood. The administrative database does not allow for exploration of trauma history, which would provide additional context about who is most at risk of OUD after MST. Characteristics of the sexual trauma including severity, age and maturity at the time of trauma, relationship with the perpetrator, and larger cultural factors such as racial power dynamics or stigma can all influence the mindset of the survivor and their ability to move on from and process the event(s).[37,,152,153] There is evidence that a more violent/severe assault or prolonged severe harassment can have stronger

negative impacts on the mental health of the survivor, and there are many people who experience harassment who experience no long-term consequences.[37,152,154-156]

5.5 Conclusion

Both the experience of MST and a diagnosis of OUD are urgent, prominent epidemics facing our country's Veterans. This dissertation found that Veterans who have experienced MST are more likely to be diagnosed with OUD, and that the odds of OUD diagnosis with a history of MST is higher for men than women. The association between MST and OUD remained significant even when accounting for a host of demographic characteristics and comorbidities. Additionally, chronic pain is likely not a clinically significant mediator of the MST-OUD association, although this is somewhat dependent on how chronic pain is measured; there are likely other factors explaining the MST-OUD relationship. Finally, among Veterans with an OUD diagnosis, those with a history of MST were not less likely to receive MOUD than Veterans with no MST history, a promising and optimistic finding. Taken together, these findings add to the evidence base of adverse conditions associated with MST, the importance of considering and disaggregating results by gender, as well as highlight the importance of future research focused on mechanisms and factors associated with evidence-based care. Such work can help inform practice and policy in the service of Veterans with histories of MST and/or OUD.

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Supplemental Table 1. ICD 9 and ICD 10 Codes for Diagnoses Used

Condition	ICD 9 Codes	ICD 10 codes
Opioid Use Disorder (OUD)	304.0-304.02; 305.5-305.52	F11.20, F11.10, F11.122, F11.222, F11.120, F11.129, F11.229, F11.23, F11.99, F11.14, F11.188, F11.159, F11.150, F11.181, F11.182, F11.19, F11.922, F11.929
Major depressive disorder	296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36	F32.0, F32.1, F32.2, F32.3, F32.4, F32.5, F32.9, F33.0, F33.1, F33.2, F33.3, F33.40, F33.41, F33.42, F33.9
PTSD	309.81	F43.10, F43.11, F43.12
Anxiety Disorders	300.0, 300.01, 300.02, 300.09, 300.20, 300.21, 300.23, 300.29, 300.3	F06.4, F40.00, F40.01, F40.02, F40.10, F40.11, F40.210, F40.218, F40.220, F40.228, F40.230, F40.231, F40.232, F40.233, F40.240, F40.241, F40.242, F40.243, F40.248, F40.290, F40.291, F40.298, F40.8, F40.9, F41.0, F41.1, F41.3, F41.8, F41.9, F42, F42.2, F42.3, F42.4, F42.8, F42.9, F45.20, F45.21, F45.29, F93.0
Bipolar	296.0-296.1x; 296.4-296.8x	F30.10, F30.11, F30.12, F30.13, F30.2, F30.3, F30.4, F30.8, F30.9, F31.0, F31.10, F31.11, F31.12, F31.13, F31.2, F31.30, F31.31, F31.32, F31.4, F31.5, F31.60, F31.61, F31.62, F31.63, F31.64, F31.70, F31.71, F31.72, F31.73, F31.74, F31.75, F31.76, F31.77, F31.78, F31.81, F31.89, F31.9, F34.0
Psychoses	297.0-297.3x; 297.8-297.9x; 298.0-298.4x; 298.8-298.9x	F06.0, F06.2, F22x, F23x, F24, F28, F29
Schizophrenia	295.0-295.4x; 295.6-295.9x	F20.0, F20.1, F20.2, F20.3, F20.5, F20.81, F20.89, F20.9, F21, F25.0, F25.1, F25.8, F25.9
Alcohol Use Disorder	303.90, 303.91, 303.92, 305.00, 305.01, 305.02	F10.10, F10.120, F10.121, F10.129, F10.14, F10.150, F10.151, F10.159, F10.180, F10.181, F10.182, F10.188, F10.19, F10.20, F10.220, F10.221, F10.229, F10.230, F10.231, F10.232, F10.239, F10.24, F10.250, F10.251, F10.259, F10.26, F10.27, F10.280, F10.281, F10.282, F10.288, F10.29
Tobacco Use Disorder	305.1	F17.200, F17.201, F17.203, F17.208, F17.209, F17.210, F17.211, F17.213, F17.218, F17.219, F17.220, F17.221, F17.223, F17.228, F17.229, F17.290, F17.291, F17.293, F17.298, F17.299
Amphetamine Use Disorder	304.4-304.42; 305.7-305.72	F15.10, F15.120, F15.121, F15.122, F15.129, F15.14, F15.150, F15.151, F15.159, F15.180, F15.181, F15.182, F15.188, F15.19, F15.20, F15.220, F15.221, F15.222, F15.229, F15.23, F15.24, F15.250, F15.251, F15.259, F15.280, F15.281, F15.282, F15.288, F15.29
Cocaine Use Disorder	304.2-304.22; 305.6-305.62	F14.10, F14.120, F14.121, F14.122, F14.129, F14.14, F14.150, F14.151, F14.159, F14.180, F14.181, F14.182, F14.188, F14.19, F14.20, F14.220, F14.221, F14.222, F14.229, F14.23, F14.24, F14.250, F14.251, F14.259, F14.280, F14.281, F14.282, F14.288, F14.29

Stimulant Use Disorder	304.2-304.22; 305.6-305.62; 304.4-304.42; 305.7-305.72	F14.10, F14.120, F14.121, F14.122, F14.129, F14.14, F14.150, F14.151, F14.159, F14.180, F14.181, F14.182, F14.188, F14.19, F14.20, F14.220, F14.221, F14.222, F14.229, F14.23, F14.24, F14.250, F14.251, F14.259, F14.280, F14.281, F14.282, F14.288, F14.29, F15.10, F15.120, F15.121, F15.122, F15.129, F15.14, F15.150, F15.151, F15.159, F15.180, F15.181, F15.182, F15.188, F15.19, F15.20, F15.220, F15.221, F15.222, F15.229, F15.23, F15.24, F15.250, F15.251, F15.259, F15.280, F15.281, F15.282, F15.288, F15.29
Cannabis Use	304.3-304.32; 305.2-305.22	F12.10, F12.120, F12.121, F12.122, F12.129, F12.150, F12.151, F12.159, F12.180, F12.188, F12.19, F12.20, F12.220, F12.221, F12.222, F12.229, F12.250, F12.251, F12.259, F12.280, F12.288, F12.29
Hallucinogen Disorder	304.5-304.52; 305.3-305.32	F16.10, F16.120, F16.121, F16.122, F16.129, F16.14, F16.150, F16.151, F16.159, F16.180, F16.183, F16.188, F16.19, F16.20, F16.220, F16.221, F16.229, F16.24, F16.250, F16.251, F16.259, F16.280, F16.283, F16.288, F16.29
Sedative Use Disorder	304.1-304.12; 305.4-305.42	F13.10, F13.120, F13.121, F13.129, F13.14, F13.150, F13.151, F13.159, F13.180, F13.181, F13.182, F13.188, F13.19, F13.20, F13.220, F13.221, F13.229, F13.230, F13.231, F13.232, F13.239, F13.24, F13.250, F13.251, F13.259, F13.26, F13.27, F13.280, F13.281, F13.282, F13.288, F13.29
Other drug use disorder (non-OUD)	304.3-304.32; 305.2-305.22; 304.1-304.12; 304.5-304.52; 305.3-305.32; 305.4-305.42	F12.10, F12.120, F12.121, F12.122, F12.129, F12.150, F12.151, F12.159, F12.180, F12.188, F12.19, F12.20, F12.220, F12.221, F12.222, F12.229, F12.250, F12.251, F12.259, F12.280, F12.288, F12.29, F16.10, F16.120, F16.121, F16.122, F16.129, F16.14, F16.150, F16.151, F16.159, F16.180, F16.183, F16.188, F16.19, F16.20, F16.220, F16.221, F16.229, F16.24, F16.250, F16.251, F16.259, F16.280, F16.283, F16.288, F16.29, F13.10, F13.120, F13.121, F13.129, F13.14, F13.150, F13.151, F13.159, F13.180, F13.181, F13.182, F13.188, F13.19, F13.20, F13.220, F13.221, F13.229, F13.230, F13.231, F13.232, F13.239, F13.24, F13.250, F13.251, F13.259, F13.26, F13.27, F13.280, F13.281, F13.282, F13.288, F13.29
Cancer	140.0 - 208.9	C00 - C26, C30 - C58, C60 - C80, C7A, C7B, C81 - C96

Supplemental Table 2. MST Screen Questions and Definition

Type of MST	Typical Screening Question Language	Response Options
Harassment	While you were in the military . . . Did you receive uninvited and unwanted sexual attention, such as touching, cornering, pressure for sexual favors, or verbal remarks?	Yes to either question: MST history = yes No/decline to respond to both questions: MST history = no
Assault	While you were in the military . . . Did someone ever use force or threat of force to have sexual contact with you against your will?"	

Supplemental Table 3. Mixed Effect Associations Between MST and MOUD at Various Adjustment Levels with Assessment for Effect Modification by Gender

	Unadjusted OR (99% CI)	***p*-value**	**Partially Adjusted OR (99% CI)**	***p*-value**	**Fully Adjusted OR (95% CI)**	***p*-value**
Military Sexual Trauma	1.06 (.99, 1.14)	0.114	1.14 (1.04, 1.25)	<.001	1.10 (1.00, 1.21)	0.010
Gender						
Men	*REF*		*REF*		*REF*	
Women	0.97 (.89, 1.05)	0.555	0.85 (.76, .95)	<.001	0.83 (.74, .93)	<.001
MST x Gender	0.95 (.79, 1.13)	0.428	0.91 (.76, 1.10)	0.192	0.94 (.78, 1.13)	0.377

*analyses are clustered by facility of most care

Supplemental Table 4. Marginal Means of MOUD Associated with Military Sexual Trauma, Gender, and their Interaction in Unadjusted, Partially Adjusted and Fully Adjusted Models

	MOUD					
	Predicted Probability (99% CI)	***p*-value**	**Partially Adjusted[a] Predicted Probability (99% CI)**	***p*-value**	**Fully Adjusted[b] Predicted Probability (99% CI)**	***p*-value**
MST x Gender						
MST= no x men	.347 (.308, .383)	<.001	.345 (.308, .382)	<.001	.349 (.312, .385)	<.001
MST = yes x men	.357 (.315, .399)	<.001	.372 (.330, .414)	<.001	.364 (.324, .405)	<.001
MST= no x women	.340 (.297, .382)	<.001	.312 (.271, .352)	<.001	.311 (.272, .351)	<.001
MST= yes x women	.350 (.307, .393)	<.001	.328 (.287, .370)	<.001	.324 (.283, .364)	<.001
Marginal Effects: Difference in Mean MOUD Prevalence between No MST and Yes MST When:						
Gender = Men	.012 (-.007, .030)	0.107	.026 (.007, .045)	<.001	.016 (-.003, .034)	0.027
Gender = Women	.010 (-.020, .040)	0.395	.017 (-.012, .045)	0.135	.013 (-.016, .041)	0.254
Test of Marginal Effects, chi2	0.01	0.907	0.55	0.460	0.06	0.813

[a]Adjusted for gender, race, age, and marital status

[b]Adjusted for the above in addition to mental health diagnoses, substance use disorder diagnoses, Charlson score, rurality, facility of most care, facility complexity, and service connection.