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Craving of Prescription Opioids Among Veterans with Chronic Pain

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Introduction

The high prevalence of chronic pain, along with co-occurring Opioid Use Disorder (OUD) and overdose deaths, has led to a crisis in the United States and remains a national public health emergency. Among drug-related deaths, opioid overdose deaths constitute the highest number, reaching epidemic magnitudes. Particularly, prescription opioids constitute the primary source of opioid-related deaths (CDC, 2019). Over 17% of Americans filled at least one opioid prescription in the last year, with an average of 3.4 opioid prescriptions dispensed per patient (CDC, 2017). Additionally, as reported in 2017 by the Department of Veterans Affairs, 50–60% of Veterans have chronic pain and 16.1% receive opioid therapy [30].

A core symptom of addiction is craving [21; 45], as revealed by its recent addition to the diagnostic criteria for substance use disorders in the Diagnostic and Statistical Manual of Mental Disorders [5]. Craving is associated with continued drug use and can predict relapse [28]. Although, as noted in a public meeting by the US Food and Drug Administration (FDA) in 2018, while craving is considered a significant component of OUD and is one of the diagnostic criteria, the degree to which craving contributes to the continued consumption of prescription opioids among patients with chronic pain is unknown. Studies have examined whether craving at treatment entry predicts outcomes following treatment [7], with some supporting this association [4; 33], some finding no association [1; 11], and others finding associations only for particular craving types (e.g., stress-induced craving) [34]. Understanding whether we should consider craving and/or the reduction of craving in patients with chronic pain who are prescribed opioids is critical for developing effective treatment plans, including opioid tapering interventions.

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Craving, as a concept, is subjective with disputed definitions [38] and according to a recent viewpoint [20], is incompletely understood, especially in patients with chronic pain. The sparse available literature displays that craving for prescription opioids varies among patients with chronic pain. In some patients, craving reinforces opioid use and is related to symptoms of chronic pain [42]. In others, pain symptoms do not serve as the driver; rather, opioid consumption is influenced more by the patient's emotional state [40]. Importantly, craving is not synonymous with OUD, as some patients with chronic pain who are not diagnosed with OUD have reported craving, while others with OUD have not [42; 44]. Subsequently, there are gaps in understanding whether (1) craving is present among patients with chronic pain who are prescribed opioids, and (2) the degree to which craving reinforces prescription opioid use in patients with chronic pain. This study's goal was to examine craving in a large sample of Veterans with chronic pain who were prescribed opioids and evaluate whether craving relates to prescribed opioid doses, functional status, and/or co-morbid psychiatric diagnoses. Additionally, we explored the predictive relationship between clinical and demographic characteristics in Veterans with chronic pain and craving as an outcome, using a computer-based classification model. The goal of this exploratory analysis was to understand the main contributors to reported craving in our sample.

Methods

Study procedures were approved by the San Francisco Veterans Affairs Health Care System (SFVAHCS) and University of California San Francisco Institutional Review Boards. In this population-based cohort study, we utilized the VA Informatics and Computing Infrastructure (VINCI) to access the VA Corporate Data Warehouse (CDW) medical record information of 2152 adult Veteran patients who were screened at the SFVAHCS Pain Clinic. The SFVAHCS Pain Clinic provides specialty care in the management of chronic pain, including consideration for participation in an interdisciplinary pain rehabilitation program [3; 29], pain procedures (e.g., epidural steroid injections), spinal cord stimulator trials, and medication consultation. The clinic primarily cares for patients with chronic, non-cancer related pain conditions with functional impairments as a result of their pain. Referrals to the Pain Clinic are made by a primary care provider or other relevant specialty care provider (e.g., neurologist, neurosurgeon, rheumatologist, podiatrist, orthopedic surgeon) within the Veterans Integrated Service Network 21. All new patients to the clinic complete an assessment package of questionnaires (see below), which is the focus of the current work.

To create the study dataset, we combined medication records extracted from the CDW data, with the clinical data from the screening package provided by the Pain Clinic, for each patient. Additionally, we extracted psychological comorbidity diagnoses from the CDW data. In order to understand opioid craving, the medication information extracted included only VA outpatient opioid prescriptions. The Revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R, question #11) (see below) was used to evaluate a patient's opioid craving, as in other work [15].

The opioids reviewed in this study were the most commonly prescribed opioids among this Veteran sample. Specifically, we extracted pharmacy data for each patient for any dispenses of the following opioids: immediate release oxycodone (n=1074), sustained

release oxycodone (n=74), hydrocodone (n=845), immediate release morphine (n=76), sustained release morphine (n=326), hydromorphone (n=74), fentanyl patches (n=50), and tramadol (n=247).

In order to study the effects of opioids with an FDA approved indication for pain, we did not include medications indicated for the treatment of OUD, such as methadone, buprenorphine +/− naloxone sublingual film/tablet, or buprenorphine extended-release injection. Formulations of buprenorphine with an FDA approved indication for pain, such as buccal, intravenous, and transdermal preparations, were not commonly prescribed during the time period of the study, thus were excluded from this review [10; 32]. Medications indicated for the treatment of OUD were excluded from the study to narrow our focus to patients with chronic pain who were not prescribed Medication for Opioid Use Disorder (MOUD).

Outpatient doses of opioids were standardized to morphine equivalent daily dose (MEDD), calculated according to conversion factors obtained from the CDC [31]. Each medication dispense, per patient, was labeled with an ordinal timestamp in order to compare the medication dispensed before and after they completed the Pain Clinic questionnaires. In effort to better understand the relationship between craving and prescription opioid dose in patients with chronic pain in our sample, we filtered the medications to only include those medications that were dispensed within a +/− 6-month range of their initial questionnaire date – the date when the SOAPP-R craving rating was provided. Additionally, to understand this relationship between craving and MEDD, as these were acquired in a non-causal manner, these two data sources were aligned post-hoc, meaning we examined MEDD throughout the 12-month period to get the most robust available estimate of MEDD at the time of the craving evaluation.

As mentioned above, data for this study was retrospectively examined from the initial assessment completed in the Pain Clinic and combined with the CDW data. Please see the CONSORT diagram for the study flow (Figure 1). Of the 2152 patients that completed the initial assessment between May 21, 2010 and February 21, 2020, individuals were excluded from the data analysis if they were prescribed methadone or buprenorphine during the 12-month timeframe (n = 260). Two patients with a MEDD of 1200 and 755, respectively, were excluded under the rationale that their extreme outlier status could bias our findings. The final sample included 1890 participants.

Measures

Demographic and clinical data.—Patients self-reported clinical and demographic information included age, gender, race, years of education completed, duration of pain, and identified pain sites. Note that the records with multiple response options stated for demographic questions were combined to create a new response (e.g. What is your race? “Black, Asian” → “Multiple Races”).

Self-report Questionnaires

The Pain Disability Questionnaire (PDQ): The Pain Disability Questionnaire (PDQ) [2] is a 15-item measure of pain-related disability. Each item is rated from 0 to 10 with higher scores indicating greater pain-related disability. The measure is divided into two subscales: the functional status component and the psychosocial component. Scores on the PDQ are categorized in the following way: mild/moderate disability (0–70), severe disability (71–100), or extreme disability (101–150) [16].

The Oswestry Disability Index (ODI): The Oswestry Disability Index (ODI) (also known as the Oswestry Low Back Pain Disability Questionnaire) is a 10-item questionnaire that uses a 6-point Likert scale to indicate the degree to which pain affects one's ability to manage in everyday life. The 10 section items are: Pain intensity, Personal care (washing, dressing etc.), Lifting, Walking, Sitting, Standing, Sleeping, Sex life (if applicable), Social life, and Traveling. The total score is calculated as a percentage, and interpretation of scores is as follows: 0–20% "minimal disability", 21–40% "moderate disability", 41–60% "severe disability", 61–80% "crippling back pain", and 81–100% patients are either "bed-bound or exaggerating their symptoms". The ODI is considered the 'gold standard' of low back functional outcome tools [12]

The Patient Health Questionnaire (PHQ-9): The Patient Health Questionnaire (PHQ-9) [22] is a nine-item self-report measure of depressive symptoms. Questions correspond to diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Each item is rated from 0–3 on a Likert scale (ranging from 0 = not at all, to 3 = nearly every day). Total scores are interpreted in the following way: minimal depression (0–4); mild depression (5–9); moderate depression (10–14); moderately severe depression (15–19); and severe depression (20–27). The questionnaire has been shown to be reliable, with good sensitivity and specificity [27].

Revised Screener and Opioid Assessment for Patients with Pain-2 [8] (SOAPP-R).: The SOAPP-R is a 24-item, self-administered screening instrument used to assess risk potential for future opioid misuse. Items are rated on a 5-point Likert scale (ranging from 0 = never to 4 = very often). The SOAPP-R has been shown to have good predictive validity, with an area under the curve ratio of 0.88 (95% confidence interval [CI], .81–.95). A cutoff score of 18 shows adequate sensitivity (.86) and specificity (.73) for predicting prescription opioid misuse. Item #11 of the SOAPP-R, specifically addresses craving, i.e., "How often have you felt a craving for medication?"

Data Analysis—All statistical analyses were performed using the statistical program R version 4.0.2, RStudio, & STATA version 16.1. The missing values in the self-report measures were imputed using multivariate imputation by chained equations (MICE) consisting of 5 multiple imputations with 3 iterations, in R using the MICE package version 3.12.0. For the self-report measures, imputation was used for patients that had < 20% of a questionnaire missing. No patients had >20% of the questionnaire missing, and thus no patients had to be removed from the dataset for a lack of sufficient data. In order to understand the effects of craving, and considering that there is a tendency to under-report

desire for opioid medication [46], patients were categorized into 2 groups -- 'no craving' (N-CRV) and 'craving' (CRV) -- based on their response to SOAPP-R Question 11, "How often have you felt a craving for medication?" (Never [0], Seldom [1], Sometimes [2], Often [3], Very Often [4]). The N-CRV group consisted of subjects that answered "Never [0]", while the CRV group consisted of subjects that answered either "Seldom [1]", "Sometimes [2]", "Often [3]", or "Very Often [4]". Demographic data and questionnaire data such as psychological measures, pain levels, and average MEDD were compared between groups using parametric T-tests and nonparametric Mann-Whitney U tests, depending on whether the variable was normally distributed or not, respectively. All tests were controlled for age, sex, and the year of assessment as covariate variables, using ANCOVA tests. The statistics included in this paper are covariate-adjusted. The data that support the findings of this study are available upon request from the authors.

Training and Evaluation of the Random Forest Classifier—The main goal of this analysis was to rank the predictors in order of their contribution to predicting craving group in our study. Using the significantly different variables identified from the bivariate analyses as predictor variables, the data was split into training and test sets. Note that only overall pain-related disability (PDQ) was used, rather than all significant predictors related to disability, to avoid redundancy due to high correlations. The training set was used to train the classifier, and the test set was held out for validation, after the model had been trained [37]. We held out 30% of the sample for validation, training on 75% of the remainder and testing on 25% of the remainder. We performed repeated cross validation (n=10 and 5 repeats). As the percentage of no craving to craving is 66% to 34%, respectively, it creates a class imbalance problem, which makes the classification problem challenging [37]. We used Synthetic Minority Oversampling Technique (SMOTe) [9] in which, instead of putting in exact data (as in upsampling), synthetic data is imputed to reduce reliance on the specific subject. The balanced training set was used to train the random forest classifier. The classifier was then used to predict the outcomes (craving/no craving) for the observations in the holdover, or test data set. The process was repeated 25 times and the average performance measures were computed. The analysis was conducted using *caret* [23], *randomForest* [24], & *DMwR* [39] packages in the R programming language. The performance of the classifier was evaluated using sensitivity and specificity. Sensitivity, or recall, is the ability of the classifier to correctly identify those with craving (true positive rate), while specificity reveals the ability of the classifier to correctly identify those without craving (true negative rate). A classifier such as this, with a high sensitivity, usually has low specificity; therefore, the model is successful in finding actual cases of craving, but it also has a relatively high rate of false positives.

Results

In order to understand the effects of craving, patients were categorized into 2 groups – No-Craving (N-CRV) and Craving (CRV). The N-CRV group represented the majority of our sample with N = 1255 or 66.4% of the sample. The CRV group had N = 635 or 33.6% of the sample, which include craving ratings of "Seldom" (N = 354), "Sometimes" (N = 186), "Often" (N = 66), and "Very Often" (N = 29).

Demographics

The two groups did not differ significantly in age ($p = 0.352$) (see Table 1). The proportion of women in each group was relatively small, as expected from the Veteran population, yet the percentage of women in the N-CRV group was nearly three times that in the CRV group ($p < 0.001$). The craving groups did not differ significantly on race, claims, employment status, or marital status (p's > 0.05).

Morphine Equivalent Daily Dose

As the prescribed opioid doses were of primary interest in this work, MEDD were compared between the two craving groups. The average MEDD during the 12-month timeframe ranging from 6 months prior to their assessment date to the 6 months following their assessment date were significantly different between groups (N-CRV: $M = 25.2$; CRV: $M = 33.6$; p's < 0.001). The mean MEDD in the CRV group (Pre: $M = 33.9$; Post: $M = 33.4$) was significantly higher than that in the N-CRV group (Pre: $M = 25.7$; Post: $M = 24.6$). However, there was no within group differences in the average MEDD before and after rating the degree of craving of opioids. In other words, both groups showed stable MEDD in the examined time frame. To further examine whether the presence/absence of craving was influencing MEDD in our sample, we only examined a subsample of patients who had changes in their MEDD over 12 months – a trend that overall was not seen in the entire sample, nor within each group. 502 subjects had a decrease of at least 10 MEDD when comparing their mean MEDD before and after the screening battery completion date, while 421 subjects displayed an increase of at least 10 MEDD. In addition, 268 subjects showed a decrease of at least 20 MEDD, while 219 subjects showed an increase of at least 20 MEDD. Among all four of these identifiable groups, we found no significant relationship with craving (p's > 0.05).

Clinical and Psychological Characteristics

Clinical and psychological self-reported measures for each group are graphically represented by the Radar Charts in Figure 2 (A and B). As seen in Figure 2A all groups had overlapping distribution of the primary pain sites (p's > 0.05). Conversely, as can be seen in Figure 2B, clinical and psychological measures showed some variation across the pain levels, psychological measures, and MEDD values.

The means of typical pain among the two groups were significantly different ($p < 0.001$). Subjects in the CRV group ($M = 7.06$) reported significantly higher typical pain rating compared to the N-CRV group ($M = 6.76$).

Figure 3 shows patient reported outcomes among the two groups. As determined by the Mann-Whitney U test, the means of the SOAPP-R were significantly different ($p < 0.001$) (Figure 3A). Subjects in the N-CRV group ($M = 16.4$) reported significantly lower SOAPP-R scores compared to the CRV group ($M = 28.7$). Results were identical when the craving question was removed ($p < 0.001$; N-CRV $M = 16.4$; CRV $M = 27.1$). Notably, 50% of the subjects that had positive SOAPP-R (≥18 total score), indicating potential for future opioid misuse, did not report any craving, while 12.9% of the subjects reported craving without misuse, i.e., had negative SOAPP-R indication of misuse (<18 total score).

Likewise, the means of the PHQ-9 were significantly different ($p < 0.001$) between the two groups, with subjects in the N-CRV group having a lower PHQ-9 mean ($M = 10.8$) than the CRV group ($M = 14.1$). (Figure 3B). As depicted in Figure 3B, on average both the N-CRV and CRV groups reported moderate depression symptoms. Between-group differences were observed in the PDQ ($p < 0.001$), indicating that subjects in the N-CRV group ($M = 86.9$) reported significantly lower PDQ scores compared to the CRV group ($M = 98.6$). As depicted in Figure 3C, on average, both the N-CRV and CRV groups reported results that correspond with severe disability. Comparisons of the ODI scores indicated that subjects in the N-CRV group ($M = 46.2\%$) reported ODI scores that differed significantly compared to those in the CRV group ($M = 51.0\%$, $p < 0.001$). As depicted in Figure 3D, using ODI scores, both groups correspond with severe disability.

Comorbid Diagnoses:

Opioid Use Disorder: The overall prevalence of a lifetime diagnosis of OUD in the entire sample was 6.82%. The means of the number of subjects with this diagnosis were significantly different among the N-CRV and CRV groups ($p < 0.001$), with the prevalence of OUD at 5.10% in the N-CRV group and 10.27% in the CRV group.

Lifetime Depression Diagnosis: The overall prevalence of a lifetime diagnosis of depression or a depressive disorder in the entire sample was 57.35%. The means of the number of subjects with such a disorder were significantly different between the N-CRV and CRV groups ($p < 0.001$), with the prevalence of a lifetime depression diagnosis at 52.99% in the N-CRV group and 65.98% in the CRV group.

Lifetime Psychotic/Mood Disorder: The overall prevalence of a lifetime diagnosis of psychosis or a psychotic disorder in the entire sample was 18.13%. The means of the number of subjects with such a disorder were significantly different between the N-CRV and CRV groups ($p = 0.001$), with the prevalence of a lifetime diagnosis of a psychotic disorder at 16.10% in the N-CRV group and 22.20% in the CRV group.

Lifetime Post-Traumatic Stress Disorder: The overall prevalence of a lifetime diagnosis of post-traumatic stress disorder (PTSD) in the entire sample was 32.72%. The means of the number of subjects with this disorder were not significantly different among the craving groups ($p = 0.465$), with the prevalence of a lifetime diagnosis of PTSD at 32.75% in the N-CRV group and 32.60% in the CRV group.

Alcohol Use Disorder: The overall prevalence of a lifetime diagnosis of Alcohol Use Disorder (AUD) in the entire sample was 21.09%. The means of the number of subjects with this disorder were significantly different among the groups ($p = 0.006$), with the prevalence of a lifetime diagnosis of AUD at 25.20% in the N-CRV group and 32.60% in the CRV group.

Random Forest Classifier

The random forest classifier ranked the predictors in order of their contribution to predicting craving class. We selected the significant variables identified from the bivariate analyses as

predictors for this model, which included sex, age, PHQ, PDQ, MEDD before and after the reporting of craving, and typical pain. Relative importance (%) is reported in Figure 4. The highest contribution to reporting craving is the severity of depressive symptoms (PHQ-9) and pain-related disability (PDQ). The average performance measures for the Random Forest classifier were (Sensitivity = 0.71±0.03; Specificity = 0.46±0.05, $\chi 2$ = 14.36, $p < 0.001$). The classifier shows higher sensitivity over specificity. That means, it correctly identifies most with craving, but flags some incorrectly. If specificity were higher than sensitivity, the classifiers would miss a higher percentage of those reporting craving.

Discussion

This study's goal was to assess prescription opioid craving in a large sample of Veterans with chronic non-cancer pain, prescribed opioids for pain management, and evaluate craving's relationship to opioid prescription, functional status, and co-morbid psychiatric diagnoses. Several important findings were observed. First, prescription opioid craving was generally low with 66.44% of the sample reporting no craving and only 33.56% of the sample reporting any level of craving. Second, we found that Veteran patients with chronic pain who reported any craving had significantly higher daily opioid prescriptions (i.e., MEDD), higher potential for misuse, and greater incidence of OUD diagnosis. Third, our findings show that psychological factors, such as history of a depression diagnosis, differed between craving groups, yet we found no relationship between daily opioid prescriptions (i.e., MEDD) and psychological factors, irrespective of the craving status. Importantly, we found that craving had little clinical effect on the reported chronic pain, in that both groups, on average, reported "severe" pain. Finally, using a Random Forest classifier, we found that the highest contribution to reported craving was the severity of depressive symptoms and pain-related disability. Additionally, this showed that the reported daily pain had less contribution, and that sex had the lowest importance in our sample. Overall, our findings display that craving among Veterans with chronic pain who are prescribed opioids for pain is complex. While lowering craving symptoms may potentially improve psychological measures and vice versa, further studies need to determine the role of opioid craving in prescription opioid tapering in this population.

Prescription Opioid Craving, Misuse, and Morphine Equivalent Daily Dose (MEDD)

Sixty six percent of the sample reported no craving of prescription opioids, consistent with craving distributions found in other chronic pain studies [42]. As in other studies [15], we used the SOAPP-R to assess risk potential for future opioid misuse. We found that, on average, those who reported craving indicated possible risk of future opioid misuse, while the N-CRV group scored in the range of no risk for future opioid misuse, suggesting that craving, as reported on the SOAPP-R, is predictive of potential medication misuse [42]. Consistent with this, we found a significant difference in the frequencies of OUD among the craving groups, with the CRV group reporting a significantly higher OUD rate. Our findings potentially suggest that not having craving may be protective from potential opioid misuse, consistent with a similar study [42]. However, given that approximately half of those who scored positively for risk of future opioid misuse in our study also reported no craving, suggests that misuse of opioids and craving of prescription opioids may have a more

complex relationship. Nevertheless, we found that the daily MEDD was significantly higher for those reporting craving compared to those who did not, throughout the investigated time frame of 12 months, suggesting the relationship between the presence/absence of craving and daily opioid prescription. It is of note, however, that the difference in MEDD between the N-CRV and CRV groups (N-CRV: $M = 29.3$; CRV: $M = 38.2$) may translate variably in clinical terms, depending on the specific opioid; for instance, this difference in MEDD could be equivalent to the difference of a low-dose pill (e.g., a 5-milligram change in oxycodone). In the context of addiction, craving is often a salient predictive factor in continued drug and alcohol use for patients in treatment for dependence [17; 36]. Our findings suggest that in those with chronic pain who are not prescribed medications for opioid use disorder (MOUD), craving of prescription opioids is not only minimal, but may also not drive the compulsive use or misuse of prescription opioids. Our results reinforce the need to better understand the relationship between prescription opioid craving, prescribed opioid doses, and misuse among those with chronic pain.

Pain, Psychological Factors, and Prescription Opioid Craving

We found several associations between pain and psychological measures among the groups, suggesting that craving and pain-related emotion may be influenced by each other, as demonstrated in previous research [41; 43]. Negative reinforcement models of drug addiction pose that prescription opioids are particularly reinforcing since besides relieving pain, they help attenuate pain-related emotions and negative experiences [14; 35]. Consistent with other work [44], we found little influence of chronic pain on the reported craving, as both groups, on average, report moderate-severe pain. Although we found little association between craving and reported pain in our sample, our findings support the relationship between emotional well-being and craving [14]. Depression scores, as assessed by the PHQ-9, indicated a statistically significant increase in the CRV group compared to the N-CRV group and the lifetime diagnosis of major depression was higher in the CRV group, aligning with the negative affect and psychiatric co-morbidity models of prescription opioid craving [25; 26; 40; 43]. These models were further supported using computer-based classification methods in which a random forest model ranked the predictors in order of their contribution to predicting craving group in our study. The highest contribution to reporting craving and higher prescription opioid use was the severity of depressive symptoms and pain-related disability with the reported pain having lower importance. This again suggests that craving is more likely related to psychological symptoms and particularly to depression. Our model showed fair to good fit, as craving of opioids in our sample, even in those who reported craving, was low (average craving rated between “seldom” and “sometimes”). Of note, however, the degree of craving is difficult to assess, especially through a single-item measure, and patients may conceal their actual level of craving in such measures [46].

Limitations

Several limitations of the present study should be noted. First, the study population was a well-characterized group of VA-enrolled veterans with chronic pain referred to the SFVAHCS Pain Clinic, however not generalizable to all veterans with chronic pain. Specifically, the sample consists largely of Caucasian males, of whom a third were either divorced or separated. Additionally, the subjects represented an older population, with the

mean age around 60 years old. Opioid misuse is associated with impulsivity and younger age [18], and it is possible that opioid craving may diminish with age [6], which further points to the need to understand craving of opioids among chronic pain sufferers. Possibly due to the VA's implementation of an opioid safety initiative in 2013, as well as prescribers' consideration of the 2016 Centers for Disease Control and Prevention's opioid prescribing guidance and 2017 Veterans Affairs/Department of Defense opioid prescribing guidance, the mean MEDD values steadily decreased throughout the years of this study's data. While our study only included data on VA-prescribed opioids and all subjects were Veterans enrolled in the SFVAHCS, it is possible that some of these patients received non-VA opioid prescriptions. Furthermore, diagnosis codes found in patient medical records may be unreliable or incorrectly labelled. We also did not have information on medication adherence or diversion; thus, doses of prescribed opioids may differ from consumed opioids. In addition, although the SOAPP-R is commonly used to assess craving [15] this measure has not been used across a wide variety of opioid users, indicating that more studies using the SOAPP-R on a robust population are needed to determine its validity [8]. Additionally, we used MEDD as a measure of daily opioid prescription. Despite the commonly accepted use of MEDD, several factors outside of MEDD calculations contribute to an individual's opioid risk and prescribing guidelines, such as genetic and metabolic factors, including pharmacogenetics, drug-drug and drug-disease interactions, patient age, body surface area, and organ dysfunction [13]. Finally, data on family history of opioid use/misuse and psychological characteristics, was not available, and would be important to examine in the future as genetics play an important role in substance abuse, craving of opioids, and major depression [19]. The strengths of the paper include a relatively large sample size of Veterans with chronic pain, which is important as Veterans have more severe pain and more problematic opioid use [30]. In addition, by utilizing retrospective analysis of both patient-reported outcomes and CDW data, we cross-referenced two separate datasets to paint a more complete picture of each patient.

In summary, craving is a complex concept among patients with chronic pain on prescription opioid therapy. Expanding upon the existing literature, which has limited support for the idea that craving of prescription opioids varies among patients with chronic pain, this study offers to fill some gaps in understanding whether a core symptom of OUD (i.e., craving) is present among patients with chronic pain on prescription opioids, and the degree to which craving reinforces prescription opioid use in these patients. Based on our study, craving is a driving factor in MEDD, but it is, in turn, driven by psychiatric distress, suggesting that treating an underlying disorder may potentially be more effective than prescribing an opioid patch, even in cases where the presenting symptom is pain. By better understanding the role of craving on patients' use of prescription opioids to control their pain, more effective interventions can be developed for supporting patients in opioid tapering and pain management.

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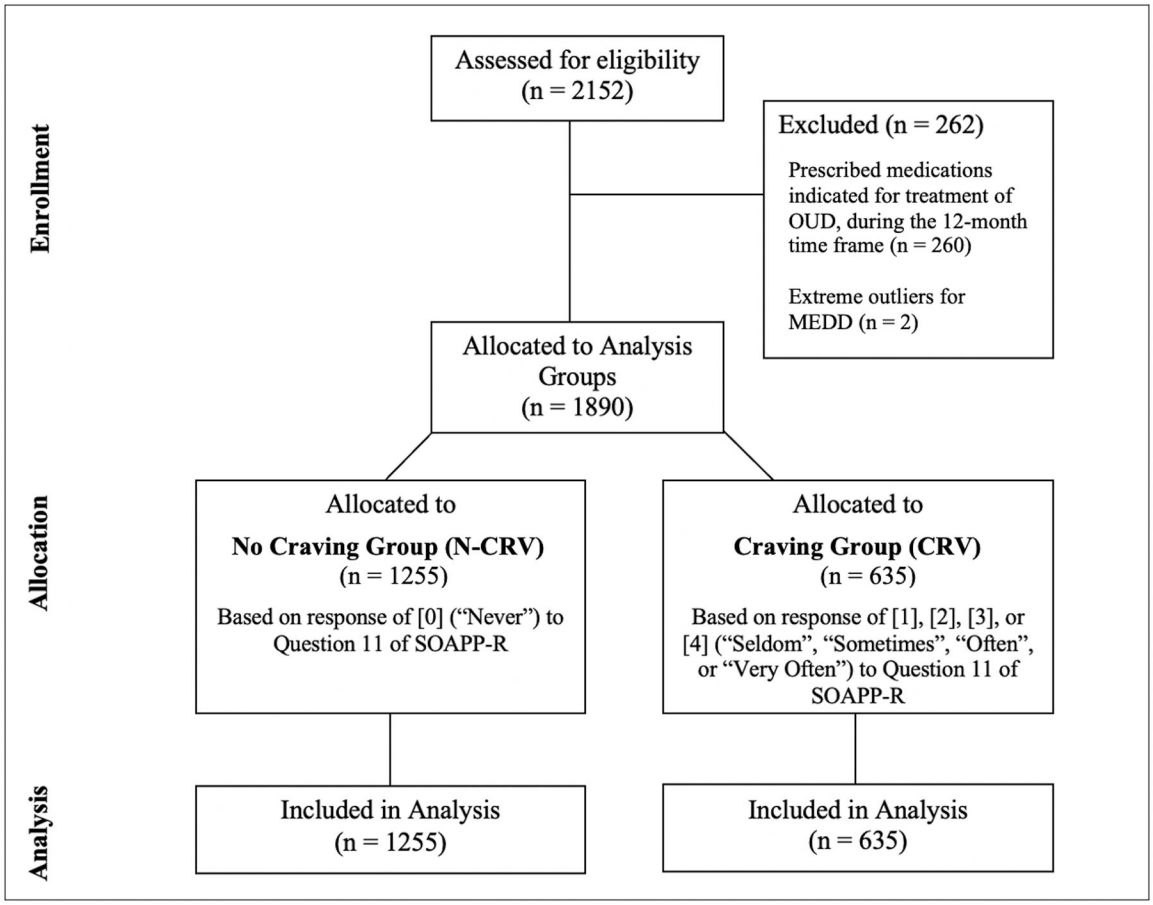

Figure 1:
Consort Diagram of Study Flow

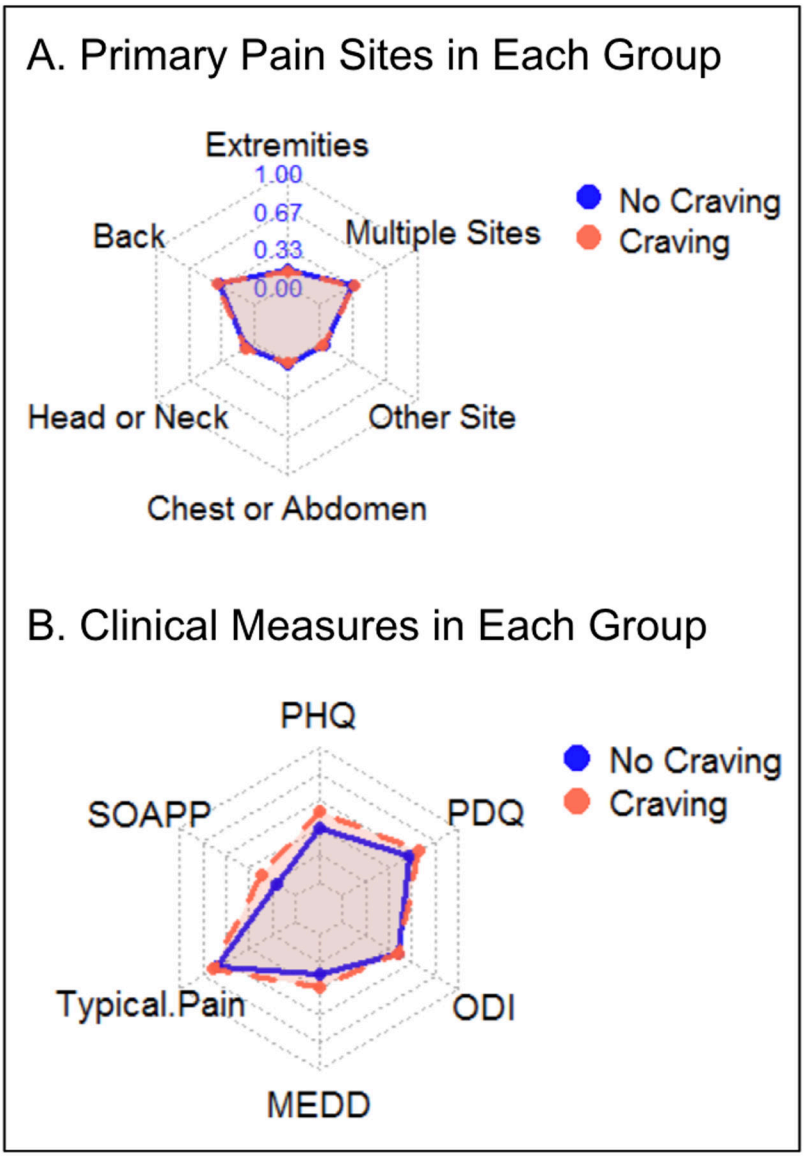

Figure 2: Graphical Representation of Patient Reported Outcomes.

A. Primary Pain Sites in Each Group (Top) shows that primary pain sites do not significantly differ among the craving groups (c.f. text for further details). Numbers (e.g., 0.33, 0.67) refer to percentages of each group responding with a particular pain site. Multiple Sites refers to patients that responded with more than one response to their primary pain site. Other Site refers to patients that responded with their primary pain site being other than head, neck, back, chest, abdomen, or extremities; **B. Clinical Measures in Each Group (Bottom)** shows some between group variation in clinical and psychological measures (c.f. text and Figure 3 for further details). The axes of each clinical measure represent their independent scales (e.g., pain levels range from 0–10; SOAPP-R scores range from 0–70). PHQ-9, Patient Health Questionnaire-9. MEDD, Morphine Equivalent Daily Dose. PDQ, Pain Disability Questionnaire. Typical.Pain, typical pain level reported. ODI,

Oswestry Disability Index. SOAPP-R, Screener and Opioid Assessment for Patients with Pain -Revised.

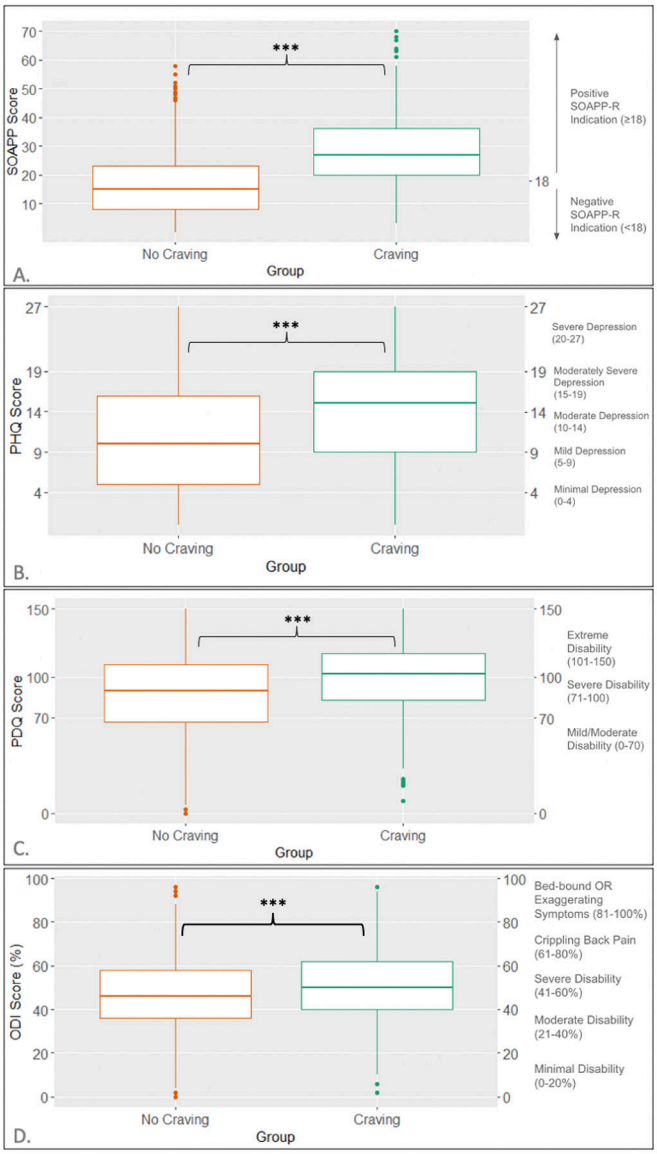

Figure 3: Boxplots Diagrams of Patient Reported Outcomes.

Score averages for each of the craving groups on **(A)** Screener and Opioid Assessment for Patients with Pain -Revised (SOAPP-R); **(B)** Patient Health Questionnaire-9 (PHQ-9); **(C)** Pain Disability Questionnaire (PDQ); **(D)** and Oswestry Disability Index (ODI) collected at the time of screening by the SFVAHCS Pain Service. Groups were determined based on each subject's response to SOAPP-R Question 11, "How often have you felt a craving for medication?" The no craving (N-CRV) group consisted of subjects that answered "Never [0]". The craving (CRV) group consisted of subjects that answered "Seldom [1]", "Sometimes [2]", "Often [3]", or "Very Often [4]". Error bars indicate SD. Clinical anchors for each scale are shown on the right. Note: *<0.05, ** <0.01, *** < 0.001.

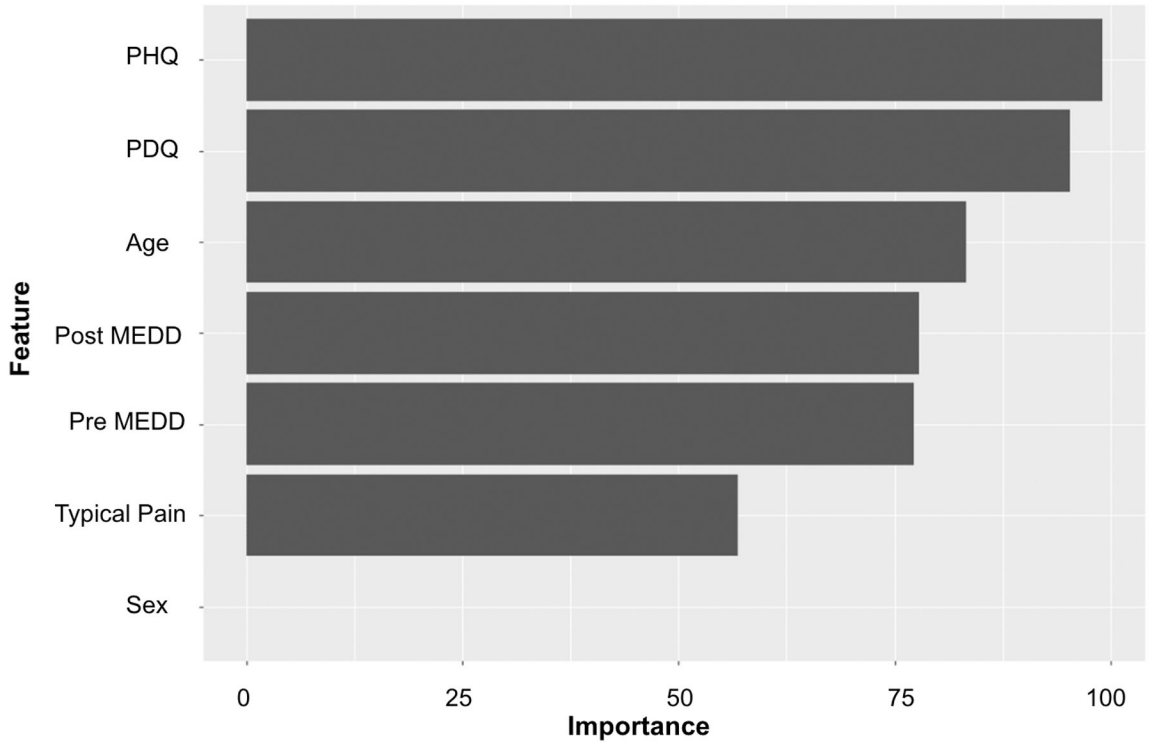

Figure 4: Bar Chart of Relative Importance of Variables in Decision Tree Classification Model.
PHQ-9, Patient Health Questionnaire-9. PDQ, Pain Disability Questionnaire. Post MEDD, Morphine Equivalent Daily Dose from up to 6 months after the subject's assessment date. Pre MEDD, Morphine Equivalent Daily Dose from up to 6 months prior to the subject's assessment date. Typical.Pain, typical pain level reported.

Table 1:

Veteran Sample Demographic Characteristics (n=1890)

	No Craving (N-CRV)(N = 1255)	Craving (CRV) (N = 635)	T/W-value, *p*
Age – mean (σ)	59.15 (14.36)	59.98 (12.75)	388045[a], $p = 0.352$
Sex – no. of participants (%)			420927[a], **$p < 0.001$**
Male	1103 (87.9)	594 (93.5)	
Race – no. of participants (%)			−0.375[b], $p = 0.707$
African American	181 (14.4)	80 (12.6)	
White	847 (67.5)	440 (69.3)	
Hispanic	73 (5.82)	29 (4.57)	
Asian	21 (1.67)	19 (2.99)	
American Indian	20 (1.59)	8 (1.26)	
Other	49 (3.90)	31 (4.88)	
Mixed	64 (5.10)	28 (4.41)	
Marital status – no. of participants (%)			−0.993[b], $p = 0.321$
Never married	193 (15.4)	94 (14.8)	
Married	482 (38.4)	240 (37.9)	
Living with someone but not married	109 (8.69)	49 (7.73)	
Divorced or separated	386 (30.8)	200 (31.6)	
Widowed	66 (5.26)	37 (5.84)	
Other	19 (1.51)	14 (2.21)	
Employment status – no. of participants (%)			385576[a], $p = 0.238$
Full-time	168 (13.4)	57 (8.98)	
Part-time	85 (6.77)	38 (5.98)	
Unemployed, not interested in returning to work	13 (1.04)	13 (2.05)	
Unemployed, looking for work	54 (4.30)	20 (3.15)	
Unemployed, disabled	399 (31.8)	243 (38.3)	
Retired, due to pain	215 (17.1)	115 (18.1)	
Retired, not due to pain	218 (17.4)	74 (11.7)	
Other	102 (8.13)	75 (11.8)	
Claims filed related to pain – no. of participants (%)			391045[a], $p = 0.494$
Workers' compensation	28 (2.23)	13 (2.05)	
Personal injury (unrelated to work)	16 (1.27)	13 (2.05)	
Social Security Disability Insurance (SSDI)	167 (13.3)	101 (15.9)	
Other insurance	17 (1.35)	10 (1.57)	
VA Service Connection	392 (31.2)	173 (27.2)	
None	339 (27.0)	137 (21.6)	
Other	296 (23.6)	188 (29.6)	
Mean Morphine Equivalent Daily Dose (MEDD)	25.2 (27.9)	33.6 (35.4)	324251[a], **$p < 0.001$**

[a] Mann-Whitney U Test, used as a non-parametric test for data not normally distributed.

[b] Independent Samples T-Test, used as a parametric test for normally distributed data.

Bold indicates results significantly different ($p < 0.05$) between the two craving groups. Percentages may not add to 100% due to rounding. Sub-categories marked as “other” refer to patients that responded with more than one option to a demographic question.