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Craving of Prescription Opioids in Patients With Chronic Pain: A Longitudinal Outcomes Trial

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Abstract: Little is known about whether patients with chronic pain treated with opioids experience craving for their medications, whether contextual cues may influence craving, or if there is a relationship between craving and medication compliance. We hypothesized that craving for prescription opioids would be significantly correlated with the urge for more medication, preoccupation with the next dose, and current mood symptoms. We studied craving in 62 patients with chronic pain who were at low or high risk for opioid misuse, while they were enrolled in an RCT to improve prescription opioid medication compliance. Using electronic diaries, patients completed ratings of craving at monthly clinic visits and daily during a 14-day take-home period. Both groups consistently endorsed craving, whose levels were highly correlated ($P < .001$) with urge, preoccupation, and mood. The intervention to improve opioid compliance in the high-risk group was significantly associated with a rate of decrease in craving over time in comparison to a high-risk control group ($P < .05$). These findings indicate that craving is a potentially important psychological construct in pain patients prescribed opioids, regardless of their level of risk to misuse opioids. Targeting craving may be an important intervention to decrease misuse and improve prescription opioid compliance.

***Perspective:** Patients with noncancer pain can crave their prescription opioids, regardless of their risk for opioid misuse. We found craving to be highly correlated with the urge to take more medication, fluctuations in mood, and preoccupation with the next dose, and to diminish with a behavioral intervention to improve opioid compliance.*

***Key words:** Craving, noncancer pain, opioid therapy, opioid misuse, substance abuse.*

Craving has been described as a strong desire for or urge to imbibe psychoactive substances, such as drugs, alcohol, and tobacco.[9] Colloquially, in English-speaking cultures, craving something implies a lack of control over use of that substance.[9] Indeed, studies indicate that craving is a powerful predictor for relapse in heroin and cocaine.[15,19] Thus, important principles in the treatment of addiction and the prevention of relapse are the assessment of craving, attempts to extinguish it, and helping patients to cope with craving.[8,22] Craving can be thought of as a psychological reaction (with physiological underpinnings) to avoid the negative affect associated with drug withdrawal, such as dysphoria, anxiety, or anhedonia.[22]

Patients with chronic pain taking prescribed opioids, and not demonstrating signs of addiction, may experience psychoactive effects of the medication such as euphoria.[24] We have demonstrated in such patients that reports of craving for prescription opioids are associated with an elevated rate of opioid misuse.[21] Among 455

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patients prescribed opioids for pain, those who reported craving the medication (55%) had twice the rate of opioid misuse.

The American Academy of Pain Medicine (AAPM), The American Pain Society (APS), and The American Society of Addiction Medicine (ASAM) define prescription opioid addiction in patients with pain as "a primary, chronic, neurobiologic disease that is characterized by behaviors that include one of more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving."[17] These behaviors may be perpetuated by a physiologic drive that comes with using prescription opioids,[13] in which mesolimbic motivational circuits are "hijacked," creating a disorder of motivated behavior.[7,12] For many pain medicine and addiction specialists, this definition is preferred in patients prescribed opioids for pain over the Diagnostic and Statistical Manual (DSM-IV) definition of substance dependence, because unlike the DSM-IV definition, the criteria for prescription opioid addiction includes craving and does not include physical dependence. APS, AAPM, and ASAM define substance misuse in this patient group as the use of any drug in a manner other than how it is indicated or prescribed.[17] Substance abuse is defined as the use of any substance when such use is unlawful, or when such use is detrimental to the user or others.

Thus, opioid misuse may indicate a treatment adherence issue, or may signal a more serious addiction problem, if accompanied by a lack of control over use despite negative consequences. These distinctions can be blurred, and in a clinical pain medicine practice it is often unclear whether a patient is simply noncompliant with their medication or addicted. The presence of craving is central to this distinction in applying the addiction criteria. It remains unclear to what extent craving is indicative of prescription opioid addiction since those without opioid addiction have also reported some craving.[21] And yet, reports of craving are significantly associated with a substance use disorder.[6,19] Few studies have focused on craving among patients with pain-prescribed opioids and the relationship of craving to risk for opioid misuse. We know very little about what the components of craving may be and whether it changes over time, despite its importance in diagnosing prescription opioid addiction.

The purpose of this study is to characterize self-reports of craving in patients prescribed opioids for chronic pain and to examine the relationships between opioid compliance interventions, self-reports of craving, and opioid misuse. It was hypothesized that craving would be significantly associated with: 1) the desire to take more opioids; 2) preoccupation with the next dose; and 3) mood symptoms affecting the urge to take more mediation. We also hypothesized that report of craving would be reduced with frequent monitoring (urine screens and compliance checklists) and motivational counseling (individual and group sessions).

Methods

Participants, Study Design, and Eligibility

This was a prospective, longitudinal, descriptive, cohort study of craving for prescription opioids. This data was collected while subjects were enrolled in a randomized clinical trial (RCT) of a behavioral intervention to improve prescription opioid compliance (NCT# 00988962). Subjects were patients with noncancer pain treated in a pain medicine specialty clinic. Full details of the interventional study have been previously published.[10] A brief description of the RCT and the craving study methods are described below.

The Human Subjects Committee of Brigham and Women's Hospital (Boston, MA) approved this study's procedures and written informed consent was obtained from every subject. All patients were recruited through the Pain Management Center of Brigham and Women's Hospital. Patients with back or neck pain, with or without radicular symptoms, were recruited to participate in this 6-month trial. Subjects were divided into High Risk Experimental (HRE), High Risk Control (HRC), and Low Risk Control Groups (LRC, see Fig 1 for CONSORT diagram). Patients were eligible if they: 1) had chronic back or neck pain for >6 months' duration; 2) averaged 4 or greater on a pain intensity scale of 0 to 10 with medication; and (3) had been prescribed opioid therapy for pain for >6 months.

Patients were excluded from participation if they had: 1) a current diagnosis of cancer, any other malignant disease, acute osteomyelitis, or acute bone disease; 2) present or past DSM-IV diagnosis of schizophrenia, delusional disorder, psychotic disorder, or dissociative disorder; or (3) current substance dependence, addiction, or abuse of any kind within the past year (at enrollment, positive on the Mini International Neuropsychiatric Interview; M.I.N.I. v.5.0[18] and/or meeting the AAPM and ASAM criteria for prescription opioid addiction described above).

Chronic Opioid Treatment

Patients were evaluated by 1 of 5 board-certified pain medicine physicians who all had at least 5 years of consultant-level experience. Each subject received a complete history, physical, and review of radiological studies. All subjects were maintained on their current opioid medication and asked to remain on a stable dose throughout the study period. The physician evaluation included an assessment of the appropriateness of the current opioid dose(s) as well as the specific opioid used and adjustments were made, if indicated, prior to enrollment. All other adjuvant medication remained constant through the course of the 6-month trial. Prescriptions of immediate release (IR) opioids for breakthrough pain and long-acting opioids were based on physician decision. All prescription medications were carefully monitored by the study manager through the use of electronic diaries and monthly contacts. Medication was prescribed once per month unless decided otherwise by the treating physician.

Enrollment Criteria

Subjects were determined to be at high risk for prescription opioid misuse based on a positive indication on any of the following criteria: 1) their responses on the