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Learning from Addiction: Craving of Prescription Opioids in Chronic Pain Sufferers

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Abstract

Prescription opioids are a primary driver of opioid-related deaths. Although craving is a substantial component of OUD, the degree to which craving leads to misuse among chronic pain patients on long-term prescription opioids is unknown. A clear understanding of the factors that lead to misuse in this vulnerable population is needed for the development of safe and effective practices for opioid taper.

This narrative review summarizes the relevant literature on the role of craving in addiction and chronic pain through epidemiological and behavioral studies. The first part of this review examines the role of craving in predicting opioid use/misuse in individuals with chronic pain with and without OUD. The second part covers methods on how craving is evaluated experimentally using both subjective and objective measures and provides related findings. The overall goal of this review is to facilitate the development of a population-specific description of craving in those who use opioids to control chronic pain and to describe how it may be mechanistically linked to patterns of opioid (mis)use.

Keywords

craving; opioid use disorder; chronic pain; cue-reactivity; dot-probe; insula

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1. Introduction

Opioid overdose deaths in the United States are higher than any other drug-related death and have now reached epidemic proportions. Prescription opioids remain a primary driver of opioid-related deaths (CDC, 2021b; Mattson et al., 2021). Although the national opioid prescribing rate fell between 2012 and 2020 from 81.3 to 43.3 prescriptions per 100 people, prescribing rates remain as many as 9 times higher in select counties, signaling an ongoing crisis in several U.S. regions (CDC, 2021a). Reliable markers of disordered or dangerous use in opioid users with chronic pain are needed. Identifying such markers is of paramount importance to the safety of our nation's service people, given that 50-60% of Veterans have chronic pain and 11% take opioids chronically (Rosenberg et al., 2018).

One of the hallmark symptoms clinicians use to help identify disordered substance use is craving, as evidenced by its recent addition to the diagnostic criteria for addictive disorders in the Diagnostic and Statistical Manual of Mental Disorders (APA, 2013). While not necessary for diagnosis, subsequent investigations into craving have supported its psychometric validity (Kervran et al., 2020; Murphy et al., 2014) and predictive utility (Cavicchioli et al., 2020; McHugh et al., 2014; Tsui et al., 2014; Tsui et al., 2016; Vafaie and Kober, 2022). However, very little work has examined these relationships in those who use opioids for chronic pain. As noted in a 2018 public meeting hosted by the US Food and Drug Administration (FDA) (Kakko et al., 2019; Zheng et al., 2021), while craving is a substantial component of opioid use disorder (OUD) and is considered one of the diagnostic criteria for OUD (CDC, 2020), the degree to which craving plays a role in the patterns of opioid consumption among patients with chronic pain is not yet known. Understanding the utility of targeting craving and/or reducing craving in patients who use opioids for pain control may therefore be critical for effective treatment development, and may also aid in understanding whether craving is a reliable marker of those at high risk for opioid related harm.

Individuals with substance use describe the subjective experience of craving as having an "urge," "hunger," or "desire" to use a substance. The concept of craving is subjective and complex, with heterogeneous etiologies (e.g., affective, physiological, conditioned) (Gossop et al., 1990; Skinner and Aubin, 2010) and numerous between- and within- person and contextual moderators (see Figure 1)(e.g., (Bresin and Verona, 2021; Browne et al., 2016; Heckman et al., 2013; Parisi et al., 2022a; Parisi et al., 2022b; Serre et al., 2015; Toor et al., 2022). As such, how to effectively measure and target craving is still incompletely understood (Kleykamp et al., 2019). Although we are early in our understanding of how craving impacts opioid use in those with chronic pain, research thus far suggests that drug craving increases with exposure to stress, drug cues related to opioid use, and ease of access to opioids (Preston et al., 2017; Sinha, 2001). Recent studies have also demonstrated that craving may be intricately linked to emotional distress, depression, and catastrophizing (Parisi et al., 2022a; Parisi et al., 2022b; Toor et al., 2022). Considering that all these factors are often present in chronic pain patients who use opioids for pain control (i.e., stress due to pain, cues at home related to pill consumption, prescription-mediated access, and depression due to decreased function), it stands to reason that craving may be a substantial risk for continuing or escalating opioid use among chronic pain patients. Therefore, as the field

continues to build an interdisciplinary understanding of this construct and its measurements, it is critical to continue to develop population-specific descriptions of craving and how it may be mechanistically linked to patterns of opioid use in those with chronic pain.

2. Neurobiological Mechanisms of Craving

Craving is thought to have heterogeneous etiologies and has been demonstrated to have widespread neurobiological underpinnings (Kleykamp et al., 2019). The neurobiology behind craving has been elegantly described in detail elsewhere (e.g., (Paulus and Stewart, 2014)) and is not the focus of the current work. Briefly, the experience of craving is related to both wanting and liking, both of which are manifested in the human reward system (Berridge and Kringelbach, 2015). The amount of wanting one experiences for a substance depends on the brain's in-the-moment dopaminergic mesolimbic incentive salience circuit reactivity, as well as on the stable learned association value of the conditioned stimulus (Berridge and Kringelbach, 2015). In contrast, the amount of liking one experiences for a substance is associated mostly with the more diffuse system that produces the hedonic experience of reward (Berridge and Kringelbach, 2015). The incentive-sensitization theory proposes that, as a drug is taken repeatedly, mesolimbic dopaminergic sensitization occurs and results in amplified "wanting" in response to conditioned drug cues, *without* a concurrent increase in "liking." In other words, a central process of addiction results as cues associated with drug use trigger a strong motivational drive to engage in drug use (i.e., amplified "wanting"), even in the case of downregulated opioid receptors (i.e., tolerance, or lack of hedonic response) (Robinson and Berridge, 1993).

Perhaps most relevant to individuals with chronic pain is the well-described relationship between craving and interoception (Gray and Critchley, 2007), or the perception of the physiological condition of the entire body (Craig, 2002; Craig, 2015) on both subjective and neural levels. The model posits that interoceptive feedback of bodily responses (autonomic arousal) influences feelings and affective experiences, and can lead to a feedback loop of motivated behavior (Gray and Critchley, 2007). Thus, interoception plays a pivotal role in drug seeking behaviors (Gray and Critchley, 2007; Naqvi et al., 2014), which are motivated by craving (Litt et al., 2000; Ramirez and Miranda, 2014). In support of an interoceptive mechanism of craving, studies show that craving is negatively associated with indices of interoceptive awareness, i.e., the lower the interoceptive awareness in those with substance use, the more craving for that substance is reported (Çöl et al., 2016). In addition, craving is reduced following interoceptive awareness training (Price et al., 2019), which, in turn, improves self-reported interoceptive awareness (Mehling et al., 2012). On the neural level, craving has also been associated with activity and connectivity within the insula cortex, which is considered part of the interoceptive sensory cortex (Craig, 2002). Seminal lesion work in humans has shown that craving for smoking is uniquely associated with the insula, especially on the left side (Naqvi and Bechara, 2010; Naqvi et al., 2014; Naqvi et al., 2007). Several neuroimaging studies using Positron Emission Tomography (PET) and functional fMRI (fMRI) studies have shown that the feeling of craving for opiates, alcohol, food, cocaine, and cigarettes directly correlates with activation in the insula (Brody et al., 2002; Kilts et al., 2001; Myrick et al., 2004; Sell et al., 1999). Additionally, increased insula activation to gambling cues has been observed in a treatment-seeking group with gambling

disorder (Limbrick-Oldfield et al., 2017). This study specifically showed a relationship between insula activity and craving intensity ratings (Limbrick-Oldfield et al., 2017). However, some studies have failed to observe significant insula related activation during cue reactivity (e.g., (Xiao et al., 2006), see Figure 2), which is used to objectively assess craving (*see Section 4.6*), underscoring the heterogeneous etiologies of the construct. It is relevant here, as studies in chronic pain support disruption in interoceptive processing, both behaviorally and neurally (Baliki et al., 2012; Bultitude and Rafal, 2010; Di Lernia et al., 2016; Fritz et al., 2016; Hashmi et al., 2013; Lu et al., 2016; Mehling et al., 2013; Shizuma et al., 2021; Tsay et al., 2015).

Furthermore, it appears that interoceptive feelings are related to both wanting and liking (Berridge and Kringelbach, 2015; Paulus and Stewart, 2014). Although, while wanting is expressed in the interoceptive sensation of craving/urges, liking is regarded as an interoceptive sensation of physical pleasure (Pace-Schott et al., 2019). It is plausible that compared to wanting, which occurs in the presence of a feedback loop, liking may be a less relevant construct in those with chronic pain and OUD who are looking for relief from pain, or relief from craving.

To the best of our knowledge, networks for wanting vs. liking and degree to which opioid consumption in chronic pain users relates to these networks has not been studied. However, there is evidence to suggest that chronic pain itself damages reward processes (Baliki et al., 2010; Baliki et al., 2012; Elman and Borsook, 2016), and dulls these “wanting” and “liking” sensations, which then has significant effects on hedonic sensory impact and reward-induced motivation (Liu et al., 2019). It is possible that these processes may be even further damaged when opioid consumption is also involved, but further studies concerning incentive salience theory in a chronic pain and opioid use population are warranted to fully understand the impact of these diseases.

3. Opioid Craving in Chronic Pain

Although patients with chronic (non-cancer) pain are at specific risk of developing opioid use disorders, craving of prescription opioids in those with chronic pain on long-term prescription opioid therapy is still poorly understood (Toor et al., 2022; Wasan et al., 2009; Wasan et al., 2012). 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 (Garland et al., 2013a; Parisi et al., 2022a; Skinner and Aubin, 2010). For example, Garland et al.’s (2013) model of chronic pain and opioid addiction posits that individuals crave opioids to maintain psychological well-being when experiencing recurrent pain (Ashrafioun, 2016; Garland et al., 2013a). Nevertheless, it remains unclear to what extent craving is indicative of prescription opioid misuse since those without opioid addiction have also reported craving (Toor et al., 2022). Conversely, some chronic pain patients with opioid misuse report no craving (Toor et al., 2022). This is relevant, since recent evidence suggests that opioid tapering among chronic pain patients does not seem to result in increased pain, i.e., subjective pain does not worsen (Darnall et al., 2018). In other words, if a taper does not increase subjective pain, it may be the case that residual craving persists to threaten taper in opioid use. If craving relates to continued

opioid consumption in this population, similar to other substance use disorders (Allen et al., 2008; Crits-Christoph et al., 2007; Heinz et al., 2009; Heinz et al., 2005; Kober, 2014; Kober and Mell, 2015), targeting craving and its underlying mechanisms may be of particular value for treatment development (Garland et al., 2019b) as well as identifying patients at risk for overdose. As yet, the interplay of these factors is unclear, as recent work suggests that the relationship between craving and opioid intake is complex in those on low prescription opioid therapy with severe pain (Toor et al., 2022), and self-reported craving of opioids is generally low, even in chronic pain patients with co-morbid OUD (Parikh et al., 2022).

Several studies have examined whether craving of other addictive drugs at study entry predicts outcomes following treatment, with some studies supporting this association (e.g., (Allen et al., 2008; Anton et al., 1996; Bordnick and Schmitz, 1998; Monti et al., 1999; O'Connor et al., 1991; Robbins and Ehrman, 1998; Robinson et al., 2011; Sinha, 2011; Weiss et al., 1997)), some finding no association (e.g., (Ahmadi et al., 2009; Dreifuss et al., 2013)), and others finding associations only for particular types of craving (e.g., stress-induced craving (Sinha et al., 2006)). In addition, treatment related change in craving is often an outcome measure in randomized controlled trials of interventions for substance abuse (e.g., (Bjornestad et al., 2020). A recent meta-analysis of 237 studies examined the predictive utility of prospectively measured craving (i.e., cue exposure, physiological cue reactivity, cue-induced craving, and self-reported craving) to predict drug use and relapse (Vafaie and Kober, 2022). Authors made the important discovery that a 1-unit increase in craving more than doubled the likelihood of drug use or relapse (Vafaie and Kober, 2022). However, while this study included 9 studies of OUD individuals, no study focused on participants with chronic pain. To our knowledge, there are no randomized clinical trials that report the predictive value of craving on opioid use among chronic pain patients. There have been recent trials in individuals with chronic pain and co-morbid OUD that have shown the effectiveness of a treatment comprising training in mindfulness, reappraisal, and savoring positive experiences compared supportive group psychotherapy (control condition) on outcome measures including opioid misuse, pain severity, and opioid craving (Cooperman et al., 2021; Garland et al., 2019b; Garland et al., 2022; Parisi et al., 2022a), yet these studies provide no conclusive evidence as to whether craving moderated opioid taper outcomes (e.g., craving was not a statistical predictor of treatment outcome). Understanding whether pre-treatment craving predicts treatment outcomes and tracking the impact of opioid use interventions on craving may be important to aid our understanding of how treatments work in those with chronic pain and opioid use disorders. Furthermore, as chronic pain patients make up a major proportion of those with opioid misuse, controlled trials investigating the relationship between treatment and craving, and other potential moderators of this relationship, may provide important insights as to how to best support recovery in these individuals. In sum, thoughtful assessment of craving, exploration of its relationship with opioid use patterns, as well as moderating factors are needed in those who manage chronic pain with prescription opioids.

4. Tools used to Assess Opioid Use/Misuse and Craving

Comprehensive assessment of craving in pain patients is not currently standard practice, especially for those with chronic pain on long-term opioid therapy. Existing measures of

opioid use that assess craving directly (i.e., ask individuals to rate craving intensity) are extremely limited, and often only include a single item to assess craving, if any. We now catalogue and briefly describe tools used to assess opioid craving as well as their limitations: (1) Subjective assessment (i.e., self-assessment and clinician report) (Table 1), (2) ecological momentary assessments (EMA) (Table 2), and (3) objective assessments (i.e., cue reactivity, dot probe tasks) (Table 3), and follow each type of measure with a narrative summary based on findings using those measures.

4.1 Subjective assessment

4.1.1 Self-Report Measures That Measure Craving—*The Opioid Craving Scale* is a modification of the Cocaine Craving Scale (Weiss et al., 1995; Weiss et al., 1997; Weiss et al., 2003) and is the most commonly used measure for opioid craving (McHugh et al., 2014; Wasan et al., 2012). This scale consists of three items rated on a visual analogue scale from "0 – not at all" to "10 – extremely": (1) How much do you currently crave opiates? (rated from not at all to extremely), (2) In the past week, please rate how strong your desire to use opiates has been when something in the environment has reminded you of opiates (rated from no desire to extremely strong), and (3) Please imagine yourself in the environment in which you previously used opiates…what is the likelihood that you would use opiates today? (rated from not at all to I'm sure I would use). The scale demonstrated internal consistency, reliability, and concurrent and predictive validity in both clinical and research settings (McHugh et al., 2014). Strengths of this measure include differentiation of phasic (mood induction component) and tonic (longstanding background) craving. Limitations include a lack of attempts to assess craving in the context of pain or negative affect or mood, and (given that these items were not developed for those using opioids for chronic pain management) the possibility that there may be more sensitive or specific questions that predict opioid use behaviors.

Craving Visual Analog Scale (VAS). This scale assesses opioid craving using a single item numeric scale (Rosenberg, 2009; Tsui et al., 2016). Participants are asked to indicate how much craving they have experienced during the past week, with responses anchored at "0 = no craving at all" to "10 - strongest craving ever". Any response greater than zero is normally considered positive for opioid craving. However, some studies used a dichotomous outcome (yes/no), as the degree of craving is often skewed (Zheng et al., 2021), which may limit this scale's predictive power.

Revised Screener and Opioid Assessment for Patients with Pain 2 (SOAPP-R; score > 18 for misuse) (Butler et al., 2008). The SOAPP-R is a 24-item, self-administered screening instrument used to assess suitability of long-term opioid therapy for chronic pain patients and help determine risk potential for future opioid misuse. Items are rated 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, addresses craving, i.e., "How often have you felt a craving for medication?" Higher SOAPP-R scores were found to be significantly associated with greater desire to take morphine again, less feeling down and feeling bad,

and greater reductions in sensory low back pain intensity following morphine administration in chronic back pain patients. This latter effect was due primarily to SOAPP-R content assessing medication-specific attitudes and behavior (Bruehl et al., 2015). The face validity of items and the perception of patient input potentially limiting access to pain medication is a limitation of the scale (Butler et al., 2008). An additional shortcoming of the scale is that it contains a single item to measure craving to assess frequency (not intensity), and this item is not specifically tied to the other criteria (i.e., feeling down and bad, desire to take morphine, pain intensity) that might precipitate craving. Similarly to VAS described above, this measure of craving has been used in a dichotomous manner (yes/no) (Toor et al., 2022).

Desires for Drug Questionnaire; scores range from 7 to 49 for the Desire-and-Intention subscale and 4 to 28 on the Negative Reinforcement subscale. The DDQ, originally written for heroin craving (Franken et al., 2002), was adapted to assess craving at the present moment (i.e., "now") for prescription opioids. Respondents were asked to indicate their level of agreement with each of 13 items using a seven-point Likert Scale, so that higher scores indicated stronger craving. Three subscales are calculated: (1) Desire-and-Intention (i.e., the desire and intention to use prescription opioids), (2) Negative Reinforcement (i.e., craving for the relief from negative states), and (3) Control (i.e., perceived control over use). Among individuals on opioid replacement therapy (~80-% chronic pain) internal consistency reliabilities were .90 for the Desire-and-Intention subscale, .80 for the Negative Reinforcement subscale, and .54 for the Control subscale. The major strength of this scale is that it assesses precipitants of craving (expectation of relief, desire, intent), but it confounds desire and intent into one scale and does not assess other cue-induced or contextual factors.

Obsessive Compulsive Drinking Scale-Revised (OCDS-R) is a 10-item, revised version of the original OCDS (Anton et al., 1995) that is adapted to assess behavioral and cognitive aspects of craving and asks about experiences such as the frequency of obsessive thoughts of drug use, amount of distress associated with thoughts of drug use, amount of time spent using drugs, drug-related interference in daily activities, and perceived degree of control over drug use over the last (Morgan et al., 2004). Scores range from "0 – never" to "4 – all the time". Higher scores on the OCDS-R suggest more obsessive thoughts and compulsive behaviors associated with prescription opioids. Although it does not assess craving directly the internal consistency in opioid users with chronic pain is high, and it relates to cue-reactivity indices in opioid users with chronic pain (Garland et al., 2013b; Garland et al., 2017; Morgan et al., 2004). It is unclear whether ratings on this scale relate to neural response to opioid cues.

Urge to Use Scale: The Urge to Use Scale is used to assess the urge to use heroin and non-heroin opioids, modified by Cousins et al (2016) from the Penn Alcohol Craving Scale (PACS) (Cousins et al., 2016; Flannery et al., 1999). Along with the OCDS, the PACS is one of the most widely used measures of craving in alcohol research. Questions concerning urge to use within the past week (referred to as "during this period") include "How often have you thought about using or how good using would make you feel during this period?", "At its most severe point, how strong was your urge to use during this period?", "How much time have you spent thinking about using or about how good using would make you feel during this period?", "How difficult would it have been to resist taking or using during

this period of time if you had known drugs were in your house?", and "Keeping in mind your responses to the previous questions, please rate your overall drug urge to use for the stated period of time" (Cousins et al., 2016). Answer responses follow the format of "Not at all" to "Would not be able to resist", and each question is rated on scale from 0 to 6. This scale is a recent modification of the PACS, and so has not yet been widely used to assess craving, which is a possible limitation. This scale includes frequency, total time, strength, and control-over urges, but does not assess cue induced, context-related craving, and does not link craving to drug use.

4.1.2 Self-Report Measures of Craving-related Constructs—*Pain Medication Expectancy Questionnaire (PMEQ)*.

The PMEQ is a 38-item measure designed to assess outcome expectancies of prescription opioids (Ilgen et al., 2011). Respondents are asked to rate the likelihood from 1 ("Not at all likely") to 10 ("Very likely") that they would use a pain medication for each of the 38 reasons divided into three subscales: (1) pleasure/social enhancement, (2) pain reduction, and (3) negative experience reduction. Higher scores suggest greater endorsement of prescription opioid use outcome expectancies. Internal consistency reliability in opioid users with chronic pain was .98 for the pleasure/social enhancement subscale, .92 for the pain subscale, and .97 for the negative experience reduction subscale. Even though PMEQ does not assess craving directly, this scale provides objective information on the triggers for opioid consumption, which can be used for treatment development. Expectancies of positive opioid effects are positively related to craving, although effect sizes are notably small (Grusser et al., 2007).

4.1.3 Measures of Use Severity—*Current Opioid Misuse Measure (COMM)*

(COMM > 9 for aberrant medication-related behaviors) is a self-report measure to monitor chronic pain patients on opioid therapy and evaluate the potential for misuse (Butler et al., 2010; Chou, 2009). The COMM was developed to track patient status over time, so items included in the COMM can be used repeatedly to provide an estimate of a patient's "current" status. The COMM contains 17 items rated from 0= "never" to 4= "very often" and items capture a 30-day time period (i.e., "in the past 30 days,"). The 17 items are summed to create a total score. Craving is not assessed by this scale directly, yet a proxy to *wanting* is measured by item #6: *How much of your time was spent thinking about opioid medications (having enough, taking them, dosing schedule, etc.)?* The reliability and predictive validity of COMM is highly significant (AUC =.79-.81). Reliability (coefficient α) ranges from 0.83-.86. The COMM-9 is a brief electronically administered 9-item form of the COMM using a 5-point Likert scale. ROC analyses revealed areas under the curve (AUC) of .79, .77, and .78 for the COMM-9, suggesting that accuracy is similar to the original 17-item COMM (McCaffrey et al., 2019). The COMM appears to be a reliable and valid screening tool to help detect current aberrant drug-related behavior among chronic pain patients. Cut-off points of 9 and 13 on the COMM-9 have been used to indicate opioid misuse among patients with chronic pain (Garland et al., 2019b; Hanley and Garland, 2020; Hudak et al., 2022; Moeller et al., 2020; Parisi et al., 2022a; Parisi et al., 2022b). With only a single item to assess craving related behaviors, it is unclear how reliable the scale would be in establishing an association between craving and opioid use.

Prescription Opioid Misuse Index: The Prescription Opioid Misuse Index (Knisely et al., 2008) was originally developed to assess OxyContin misuse in patients treated for chronic pain. It includes 6 items: “Do you ever use more of your medication, that is, take a higher dose, than is prescribed for you?”, “Do you ever use your medication more often, that is, shorten the time between doses, than is prescribed for you?”, “Do you ever need early refills for your pain medication?”, “Do you ever feel high or get a buzz after using your pain medication?”, “Do you ever take your pain medication because you are upset, using the medication to relieve or cope with problems other than pain?”, and “Have you ever gone to multiple physicians, including emergency room doctors, seeking more of your pain medication?” (Knisely et al., 2008). Responses are “yes/no” formatted. Although it doesn’t directly assess craving of opioid medication, it assesses potential misuse and behaviors that relate to craving (Hanley and Garland, 2020; Parikh et al., 2022). Nevertheless, the main limitation of this questionnaire is that it was originally created for a specific population of OxyContin users, and more studies are necessary to assess its validity across other prescription opioid users (Knisely et al., 2008).

4.1.4 Clinician Administered Measures of Use Severity—*Addiction Severity Index (ASI)*:

This scale quantifies drug use and psychiatric severity indices over the past 30 days (McLellan et al., 1980; Rosen et al., 2000). It is conducted by a trained interviewer and takes about one hour to complete. Composite scores that range from 0 (no endorsement of any problems) to 1 (maximal endorsement of all problems). Question topics include medical status, employment and support, drug use, legal status, family/social status, and psychiatric status. There is a single, open-ended item inquiring “How many days in the past 30 have you experienced drug problems?” wherein suggested coded responses include “craving.” Two scores are generated from a complete ASI: a severity rating and a composite score. The test has been put through validity studies and content, criterion, and construct validity have all been determined to be successful (Leonhard et al., 2000), including in opioid users with chronic pain (Saffier et al., 2007). A self-reported version, the ASI-SR, shows good reliability with clinician-rated versions (Leonhard et al., 2000; Ljungvall et al., 2020).

Prescription Drug Use Questionnaire (PDUQ; score > 11 for misuse, suspected substance use disorder). This 42-item structured interview is probably the most well-developed abuse-misuse assessment instrument for pain patients at this time (Savage, 2002). The PDUQ is a 20-minute interview during which the patient is asked about his or her pain condition, opioid use patterns, social and family factors, family history of pain and substance abuse, and psychiatric history. It is suggested that subjects who score below 11 do not meet criteria for a substance use disorder, while those with a score of 11 or greater show signs of a substance use disorder. A self-reported version of PDUQ (31-item) shows good concurrent and predictive validity with clinician-rated versions (Compton et al., 2008). PDUQ demonstrates acceptable internal consistency (Banta-Green et al., 2009; Garland et al., 2018). While the questionnaire does not directly ask about craving of medications, it demonstrates consistency in predicting prescription drug misuse.

Prescription Opioid Therapy Questionnaire (POTQ) This 11-item scale, adapted from the Physician Questionnaire of Aberrant Drug Behavior (Michna et al., 2004), is normally completed by the treating clinician to assess misuse of opioids and has been used in chronic

pain (Butler et al., 2010). The items reflect the behaviors outlined by Chabal and colleagues (Chabal et al., 1997) that are associated with substance abuse. Providers answer yes or no to eleven questions indicative of misuse of opioids, including multiple unsanctioned dose escalations, episodes of lost or stolen prescriptions, frequent unscheduled visits to the pain center or emergency room, excessive phone calls, and inflexibility around treatment options. The POTQ has been found to be significantly correlated with the PDUQ and abnormal urine screens ($p<0.01$) as an external measure of its validity (Butler et al., 2004). Patients' ratings of craving opioid medication have also been found to be significantly correlated with physicians' ratings on the POTQ (Wasan et al., 2009). Patients who were positively rated on two or more of the items met criteria for prescription opioid misuse, as indicated in previous investigations (Butler et al., 2004; Wasan et al., 2007). A positive rating on the POTQ is given to anyone who has two or more physician-rated aberrant behaviors (Butler et al., 2008). A positive rating from the urine screens is given to anyone with evidence of having taken an illicit substance (e.g., cocaine) or an additional opioid medication that was not prescribed. While this interview does not include questions concerning craving, it is often paired with question #11 on the SOAPP-R for craving of prescription medications (Wasan et al., 2009).

In summary, subjective measures (self-report and clinician report) assess craving and aspects of craving through a variety of approaches, including measures developed for other substances of abuse and re-purposed for opioid use. Variable scales to assess craving in OUD have been utilized and there is no single accepted gold standard measure currently available, which adds to lack of conceptual coherence and heterogeneity of findings. There is neither an established measure that appears most clinically useful in those who are prescribed opioids for chronic pain management, as there may be important differences between the two groups. In addition, some global limitations of all subjective opioid misuse scales are worth mentioning. For example, (1) sensitivity to patient underreporting, (2) time-linked assessment of craving and its proximity to cues and subsequent opioid use, and (3) positive/negative affect at the time that they are completing the assessment. Endorsing use/misuse of controlled substances may be problematic. Thus, craving-specific assessment, without questions associated with misuse may be important to utilize, especially within specific populations or select settings. For instance, measures that ask about illicit behaviors like drug use and driving can be problematic if participants fear that access to ongoing medication may be limited due to their responses, or, if they fear the consequences of disclosure may be too great, e.g., individuals with children, active-duty service personnel who fear disciplinary action, or Veterans who fear disability benefits may be withheld if they disclose certain health-related behaviors.

4.1.5 *Summary of studies that used* self-report *to assess craving in chronic pain—*

The majority of research examining craving in chronic pain patients using opioids (i.e., without OUD) has utilized self-report questionnaires, however, even these studies are scarce and somewhat inconclusive. Observational research examining craving among patients with chronic pain prescribed long-term opioid therapy has found that opioid craving is associated with various indices of prescription opioid misuse, including self-reported opioid misuse (Garland et al., 2014; Martel et al., 2014a; Wasan et al., 2009), physician-

rated opioid misuse (Wasan et al., 2012), and positive urine toxicology screens (Butler et al., 2009; Wasan et al., 2012). Furthermore, self-reported craving for medication was associated with aberrant drug behaviors with positive urine toxicology at 6-month follow-up interview (Wasan et al., 2009). These authors also found that among 455 patients prescribed opioids for pain, slightly less than half (45%) reported craving their prescription opioid, "seldom to very often." Importantly, the rate of opioid misuse in those who reported craving was twice as high as that of non-cravers (Wasan et al., 2009). This suggests that over half of chronic pain patients using opioids did not report craving (55%) and in those who did, a range of craving levels are present. However, even low levels of craving were an important indicator of problematic use. We found a similar pattern in a large sample of Veterans with chronic pain and prescription opioid use (Toor et al., 2022), where only 33.6% of Veterans reported craving, which was low but was, nevertheless, related to higher daily opioid doses(Toor et al., 2022). Yet another study examined self-reported craving in 62 patients with chronic pain who were at either high or low risk for opioid misuse as defined by their *Revised Screener and Opioid Assessment for Patients with Pain 2 (*SOAPP-R) score. They found that chronic pain patients in both high and low risk groups consistently endorsed craving, and the degree of self-reported craving significantly correlated with the desire to take more opioids, preoccupation with the next dose, *and mood*, as assessed using an adapted version of the 4-item revised Cocaine Craving Scale (Wasan et al., 2012). Indeed, other studies conducted in this area have indicated that opioid craving may be influenced by patient-specific variables such as negative affect (Martel et al., 2014a; Martel et al., 2014b; Wasan et al., 2012). Other moderating factors may include past history of substance use problems (Rosenblum et al., 2003), gender (Wasan et al 2009) (but see (Ashrafioun, 2016)), and the level of pain experienced by chronic pain patients (Martel et al., 2014a; Martel et al., 2014b). Understanding the moderating influence of mood, pain, and other factors on the relationship between craving and misuse in an important next step for this population (see Figure 1).

Perhaps surprisingly, the strength of the association between pain and craving has been modest. Correlations between measures of pain intensity and opioid craving are generally low, ranging from r = .04 to .13 (Garland et al., 2016; Martel et al., 2014a; Martel et al., 2014b). Similarly, a study in patients with chronic pain prescribed opioid therapy who were asked to provide daily reports of pain intensity and opioid craving for a period of 14 days found that the average daily level of opioid craving was generally low (i.e.,18.3 (SD = 18.1) out of 100) and that pain was only weakly associated with opioid craving in patients with chronic pain who used prescription opioids (r = 0.19) (Martel et al., 2016). These findings suggest that patients' symptoms of pain contribute only minimally to opioid craving, and thus the clinical significance of levels of opioid craving in chronic pain patients is still unclear (Toor et al., 2022). However, in another study in prescription opioid users (Franken et al., 2002), the authors found that participants who reported experiencing pain in the last three months had stronger craving of prescription opioids than those without pain during the same time interval. Others have also reported that desire and intention of using prescription opioids was significantly correlated with pain severity, $r(104) = .35$, $p < .001$, pain interference, $r(102) = .28$, $p < .01$, and number of pain locations, $r(104) = .20$, $p < .001$ (Ashrafioun, 2016). Likewise, craving for the relief from negative states scores were

significantly, though not as strongly, associated with both pain severity, $r(104) = .20$, $p < .05$, and pain interference, $r(102) = .23$, $p < .05$, but not with number of pain locations, $r(104) = .16$, $p > .05$ in this study (Ashrafioun, 2016), although it is unclear whether this scale captures pain-related, affectively moderated, or non-specific negative states. Yet another study in 105 adults on methadone or buprenorphine maintenance with and without chronic pain, found that chronic pain was associated with 3-fold higher odds of reporting craving in the past week, and the association was stronger in those with moderate-severe pain compared to mild pain – however the contribution of chronic pain to positive urine drug test was not statistically significant (Tsui et al., 2016). This suggests that higher pain is associated with higher craving, but not with the higher risk of opioid misuse. It is relevant to note that these study participants also reported depression, which once controlled, attenuated the relationship between chronic pain and opioid craving (Tsui et al., 2016), suggesting that mood/affect was a relevant moderator in this sample. Overall, the relationship between pain and craving levels appears to modest, with potentially important modifying factors such as negative affect.

Contrary to the mixed associations between opioid craving and pain symptoms noted in the literature, the detrimental effects of psychological traits and/or psychiatric co-morbidities on opioid craving are more robustly supported. Studies report that psychiatric co-morbidities are associated with heightened craving and increased opioid misuse in those with chronic low back pain (Wasan et al., 2015). The authors studied 81 patients with chronic low back pain and found that those with high levels of depression and anxiety symptoms, and those with “comorbid negative affect,” reported significantly more craving for opioids and were more likely to misuse opioids. Another study in 109 patients with chronic pain on long-term opioid prescription therapy examined self-reported catastrophizing, opioid craving, as well as pain intensity, and depressive symptoms using daily self-reported electronic questionnaires. The authors found that higher levels of self-reported opioid craving related to higher levels of catastrophizing even after controlling for demographic and psychological factors (Martel et al., 2014b). A recent systematic review specifically examined the risks of developing iatrogenic opioid use disorders in chronic pain patients with psychiatric comorbidities (van Rijswijk et al., 2019). They found that depression and anxiety significantly contributed to opioid craving and problematic opioid use, as well as to poor opioid treatment outcomes in chronic pain patients, as evidenced by less analgesia and more opioid side effects. These findings are similar to Toor et al. (2022) wherein self-reported craving of prescription opioids in chronic pain patients showed a small association with pain severity but was more strongly associated with depression (Toor et al., 2022). It has been hypothesized that in individuals with chronic pain and co-morbid depression, attempts to suppress distressing and intrusive thoughts may result in increased opioid craving (Garland et al., 2016). Therefore, craving for prescription opioids may be a salient risk factor for prescription opioid misuse specifically in those with concurrent high levels of negative affect, psychiatric comorbidities, or tendencies for cognitive distortion. Finally, while euphoric effects of opioids have been hypothesized to contribute to opioid craving (Frimerman et al., 2021) and in some studies opioid misuse (Bieber et al., 2008) in chronic pain, this association seems to be moderated by pain intensity, catastrophizing, and negative

affect (NA) (Frimerman et al., 2021). This further supports findings that prescription opioid use seems to be influenced more by mood and stress rather than pain (Blatt, 2022).

Available data suggests that the relationship between craving and opioid use is bidirectional, and that active opioid use is associated with more craving. Among individuals addicted to prescription opioids with chronic pain who were on opioid maintenance therapy, those who reported having used prescription opioids within the past seven days had significantly higher craving scores than those who reported having last used within the previous 31 to 90 days or having last used more than 90 days previously (Ashrafioun, 2016), similar to findings in illicit opioid users without chronic pain (Kowalczyk et al., 2018). In a complementary manner, craving also predicts opioid intake. A study in a large sample of individuals addicted to prescription opioids and undergoing substance use disorder treatment found a significant positive association between craving and opioid use in the following week (McHugh et al., 2014). Likewise, studies of other addictive substances also find that periods of use are linked to higher craving, and that craving increases prior to drug taking (Buckner et al., 2012; Catley et al., 2000; Epstein et al., 2010; Hopper et al., 2006; Kober, 2014; Litt et al., 2000; Marhe et al., 2013; Moore et al., 2014; O'Connell et al., 2004; Shiffman et al., 2002; Shiffman et al., 1996) (Buckner et al., 2012; Cooney et al., 2007; Holt et al., 2012; Johnson et al., 2009; Shiffman et al., 1997). While additional work in opioid users with chronic pain is necessary to understand the relationship between craving and opioid use, these findings for other drugs of abuse suggest that craving may be an important predictor and potential causal factor for use behaviors (e.g., (Shiffman et al., 1997)). Finally, the time course of *tonic* or background craving, which generally fades over increasing abstinence (Galloway et al., 2010; Hallgren et al., 2018) and *phasic* or cue-induced craving, which tends to increase over abstinence (Li et al., 2015; Zanda et al., 2021), is not yet well described in those who use opioids for chronic pain management. A better understanding of these different forms of craving in patients with chronic pain would clarify the causal role of craving in patterns of opioid use.

In summary, while there is evidence for a relationship between self-reported craving and problematic opioid use in chronic pain patients, it is unclear whether this relationship is dependent upon moderators such as mood and affect, gender, pain severity, or opioid type. There is evidence to suggest that in those with other mental health disorders, severity of psychiatric symptoms appears to be linked with higher craving and greater opioid (mis)use. Conversely, there is less compelling evidence that pain severity reinforces opioid craving and (mis)use. We also find that, as with other substance users, craving is both a predictor and an outcome of opioid use, suggesting a cycle of problematic use. Finally, there is evidence that prescription opioid users may differ from illicit heroin users in important ways with regards to craving, suggesting potentially different treatment targets for this sub-populations of users.

4.2 Ecological Momentary Assessments (EMA)

Ecological Momentary Assessment (EMA) allows researchers and healthcare professionals to collect environmentally dependent, personalized data at multiple points in time, often producing more accurate and dependable data than retrospective self-reports (May et al.,

2018). For the past approximately 20 years, the way that EMA is utilized has evolved rapidly alongside the invention of the smartphone. EMAs are distributed via a smartphone through preset, electronic alarm prompts that alert the participant that it is time to complete an online survey relevant to a researcher's aims and hypotheses.

Many recent studies have begun to take advantage of easy access to the internet to collect real-time data from participants. It is particularly useful for self-reporting chronic pain and addiction-related behaviors, because studies have found that retrospective reports of pain (e.g. when participants are asked to look back at their pain experience hours, days, or even weeks later) often result in higher pain intensity (Garcia-Palacios et al., 2014), while in addiction research real-time collection allows examination of the relationship between environmental factors and substance use (Kowalczyk et al., 2018). May et al. (2018) state that the three most beneficial aspects to EMA are 1) it can reduce biases from memory recall 2) it is done in participants' natural environments, resulting in more accurate, real-time reports of affect and experiences and 3) it allows for multiple collection time-points every day, giving more insight into the personal experience of each participant. These three aspects are extremely important to pain and addiction research because of the complexity and number of variables that influence how each individual experiences pain and/or urges. EMA provides an opportunity to collect data on a variety of factors that may affect craving, such as location, social environment, affect, stress, substance use, etc. (May et al., 2018). Assessing these aspects in real-time can lead to more accurate and reliable data to help describe the overall craving experience of the individual. EMA is becoming a gold standard for symptom evaluation in pain and addiction research, as assessing patients' symptoms in their natural environment in real time without the need for recall has substantially improved compliance and data validity (Salaffi et al., 2015; Shiffman, 2009).

Understanding individual variability in craving behaviors is particularly important, since craving varies among patients with chronic pain. As discussed, recent data indicate that craving in prescription opioid users with chronic pain may not be indicative of dependence, and dependence may not always include craving (Toor et al., 2022). EMA presents an unprecedented opportunity to understand individual variability in craving behaviors and triggers, as it assesses urges, cravings, and/or desires in their real environment throughout the day. Understanding the interplay of a variety of factors in the context of craving is critical for improving the predictive validity of craving and linking it to opioid use behaviors.

4.2.1 Summary of studies that used EMA to assess craving—Although several studies have used EMA technology to assess craving in opioid use disorders, there are very few studies specific to those with chronic pain and prescription opioid use (see Table 2 for details). Briefly, Wasan et al. (2012) (Wasan et al., 2012) examined self-reports of craving in patients prescribed opioids for chronic pain (n=62, treated for chronic neck and/or back pain with prescription opioid use longer than six months). Participants were considered high risk if they scored >18 on the SOAPP-R, if their physician had reported misuse, or if they had abnormal urine screens. EMA methods included monthly surveys, completed on personal digital assistant (PDA). Four questions, rated 0 to 1 on a visual analog scale were used to assess craving for prescription opioids in the past 24 hours. Questions asked

were: 1) How strong was your urge to take more opioid medication than prescribed? 2) How much did your mood or anxiety level affect any urge to take more opioid medication? 3) How often have you found yourself thinking about the next opioid dose? And 4) How much have you craved the medication?, which were based on the Cocaine Craving Scale (Weiss et al., 2003). Overall compliance for daily, take-home diaries was 95%, and in-clinic diaries was 89%. Craving was consistently endorsed (what was the rating?). In addition, all craving items from the four additional questions (based off the Cocaine Craving Scale) were highly correlated (.66-.82) with each other, but not correlated with pain level reports, once again suggesting that pain may not be a primary driver for reported craving. Wasan et al (2012) concluded that, overall, craving was significantly correlated with the urge to take more medication than prescribed, fluctuations in mood, and preoccupation with the next dose, as these three variables demonstrated significant correlation with craving. The authors acknowledge that they did not take assessments at randomly prompted times, and instead had pre-set times, which may have been a limitation to the study because it did not take ecological context into account (Wasan et al., 2012). This study suggests that it may be important to identify high risk subjects (e.g., using SOAPP-R or similar) to target those whose craving may significantly impact opioid use, that EMA and self-report show convergent validity, and that affect may be an important target for opioid users to decrease craving.

To further examine the relationship between opioid craving, opioid use, negative affect (NA) and chronic pain, Wasan et al (2015) (Wasan et al., 2015) examined 81 participants with mild, long-term chronic lower back pain (CLBP), but no history of long-term opioid use. These participants were characterized as having low, moderate, and high levels of NA, and were randomized to either oral opioid therapy or placebo drug groups and regularly assessed using EMA technology for mood and drug use behaviors. Results of EMA showed that NA group had a significantly higher rate of opioid misuse and craving (SOAPP-R score) than those in the low NA group, as well as more frequent neuropathic symptoms and significantly greater pain interference and more disability. Ninety percent of participants in the high NA group (that reported higher opioid craving) had a diagnosis of major depression with anxious features, had significantly higher pain catastrophizing and neuroticism scores, and more frequent histories of substance abuse. This study reinforces the relationship between various moderators and negative mood states in particular on opioid craving in chronic pain.

Garland and colleagues (Garland et al., 2019b) used EMA to examine the relationship between craving (defined by authors as ‘wanting and urge’) and positive and negative affect in thirty individuals with non-cancer chronic pain and OUD in methadone maintenance treatment. The EMA items were: ‘How much do you want to use opioids right now?’; ‘How strong of an urge do you have to use opioids right now?’; ‘How intense is your pain right now?’; ‘How unpleasant is your pain right now?’; ‘How much control do you have over your craving?’. The response rate was 62% in this study.

Subjects also were randomized into two OUD treatment groups: treatment as usual (TAU) and mindfulness-oriented recovery enhancement (MORE). Overall, the reported opioid craving was ~4/10 in this study. Results indicated that MORE participants had significantly decreased reported scores in opioid wanting and in opioid urge (44% decrease, $p<.001$,

50% decrease, p<.0001). Furthermore, participants in the MORE condition demonstrated significant reductions in momentary opioid craving, and their cravings were less intense than those in the TAU condition. They also reported being 1.3 times better able to control their cravings than those in TAU. Although this study didn't directly examine the role of craving in treatment oucomes, this study suggests that craving intensity may be selectively targeted by intervention, and that increases in positive affect may diminish opioid cravings - or that decreases in opioid cravings have a beneficial impact on mood - in prescription opioid using chronic pain patients. Another recent study by this group (Garland et al., 2022) found similar effects of mindfulness-based treatment on overall craving and opioid use reduction in chronic pain patients (n=250), yet no details on EMA craving data or whether craving was the mediator/moderator in treatment outcomes were provided. Likewise, another study by this group (Parisi et al., 2022a) used EMA technology to assess carving in patients with chronic pain on long-term opioid therapy (mean MEDD: ~70mg/day) and low risk for opioid misuse (COMM9<13, mean~8). Sixty-two participants completed up to 180 EMA measures delivered three times per day for the duration of the eight-week treatment. Single, validated items that paralleled those used to assess pre-to post-session changes measured current opioid craving ("How strong of an urge do you have to take your medication right now?") [(NRS) (0–10)]. EMA data showed significant Group (MORE vs. supportive group therapyl) × Time (pre/post) interaction for momentary opioid craving (B = − 0.003, SE = 0.001, p = .015), indicating that relative to control group, participants in the mindfulleness-based group experienced a modest but significant decrease in craving throughout the eight weeks of treatment. No further details on craving EMA and/or the relationship of craving on treatment outcomes were provided.

Most studies using EMA to assess craving, however, were conducted in opioid use disorder without chronic pain, or did not assess chronic pain (e.g., (Huhn et al., 2016; Kowalczyk et al., 2018; Panlilio et al., 2019); Table 2 for details). Strong associations between negative affect and craving for prescription opioids are supported in this work. In other workds, EMA reports of increased craving and increased negative affect were associated with opioid intake.

In summary, EMA offers several advantages to understanding opioid taking behaviors among opioid users with (and without) chronic pain. Nevertheless, one possible complication in using EMA to measure craving, is that EMA itself could act as a cue and bias subjective craving measures. It is important for future research to examine how to best design EMA to capture triggers for opioid intake and decrease potential opioid cue reactivity biases.

4.3 Objective evaluation of craving

4.3.1 Cue-elicited reactivity: Drug craving can be elicited by drug-cue exposure in the absence of instrumental rewards, thus, cue reactivity paradigms are widely used in the examination of addiction and craving in attempts to model real world cued craving experiences in a laboratory setting. Drug related cues may include witness of drug use, people with whom they previously used drugs, places where they used substances, emotional or physiological states that prompted drug use, and drug paraphernalia. Such cues reliably

lead to subjective craving experience (Carter and Tiffany, 1999; Niaura et al., 1988; Parisi et al., 2022b), and are thought to arise from associative learning during previous drug use (Childress et al., 1993). Cue reactivity paradigms have been widely used in understanding risk factors for addiction e.g., (Betts et al., 2021; Cooney et al., 1997; McHugh et al., 2014; Norberg et al., 2016; Paulus and Stewart, 2014; Rohsenow et al., 1992; Schacht et al., 2013; Seow et al., 2020), and neural and physiological measures of cue reactivity have been found to predict relapse across a range of substances (cigarette: (Carpenter et al., 2009; Niaura et al., 1989; Niaura et al., 1988; Payne et al., 2006; Powell et al., 2010; Waters et al., 2004); alcohol (Cooney et al., 1997; Litt et al., 2000)), and opioid use (Fatseas et al., 2011; Lubman et al., 2009). Interestingly, although cue reactivity elicited craving via environmental and proximal cues are typically most pronounced for the drug of choice (McHugh et al., 2016), for opioids, environmental contexts tend to elicit less craving when compared to proximal cues such as paraphernalia (e.g., (McHugh et al., 2016)). Since prescription drug cues in those with chronic pain are encountered on a regular basis, i.e., drug cues are everywhere, understanding cue-induced craving specific to chronic pain patients on long-term opioid use is of particular importance.

4.3.2 Summary of studies that used cue reactivity paradigms to assess craving—

There has been limited research utilizing cue reactivity paradigms in individuals with opioid use, especially in relation to chronic pain. To the best of our knowledge, only one group has examined cue-reactivity induced craving among individuals with chronic pain and prescription opioids (Garland et al., 2019a; Garland et al., 2018; Hanley and Garland, 2020; Parisi et al., 2022b). Garland and colleagues (Garland et al., 2018) sought to investigate the role of pain related cues as a conditioned stimulus to elicit a craving response using a cue-reactivity task in 30 opioid treated chronic pain patients (17/30 met criteria for opioid misuse). The task consisted of four blocks of 40 stimulus cue-prime pairs (i.e., control->drug, pain->drug, control->pain, and drug->pain) presented in randomized, counterbalanced order. At the beginning of the task and after each block, participants were asked to rate their level of opioid craving (1 = no opioid craving, 8 = extreme opioid craving). Researchers observed that HRV increased to a greater extent during the pain-opioid block compared to the control-opioid block for non-misusers compared to misusers, while HRV in misusers was elevated to all drug conditions regardless of pain stimulus. Craving ratings increased to a greater extent from baseline to the pain-drug block in misusers compared to non-misusers. Although pain pictures (instead of actual pain) may not have been sufficient to induce pain related craving in misusers, this study provides initial evidence that opioid-misusing patients with chronic pain exhibit a Pavlovian conditioned response towards prescription opioid cues when compared to non-misusing opioid individuals. Another study by this group in opioid misusing chronic pain sample (n=135; mean MEDD~70) examined how cue-reactivity measures (i.e., craving ratings, EEG late positive potential (LPP)) are modulated by treatment (i.e., Mindfulness-Oriented Recovery Enhancement (MORE)). Neutral, opioid, and natural reward images were used in the combined experiments. The authors report that opioid cues elicited significantly greater centroparietal LPP than neutral cues, again suggesting enhanced reactivity to opioid cues in those who misuses opioids for chronic pain. As this study focused on treatment effects, no other cue-reactivity data were provided (Garland et al., 2019a). In another study by

this group, the authors examined whether chronic pain patients receiving long-term opioid therapy (n=68; MEDD: mean±SD 92.34± 162.31) exhibited salivary cue-reactivity to their prescribed opioid (Hanley and Garland, 2020). The task consisted of two, 3-minute blocked conditions (i.e., opioid and neutral), each proceeded by a 3-minute resting baseline where participants sat quietly, without moving, and let their minds wander. To measure salivary reactivity, participants placed three dental cotton rolls in their mouth. In the opioid cue block, each participant was instructed to (1) hold a bottle of their most commonly used opioid medication 12” from their face, and look closely at it for one minute, (2) open their medication bottle’s lid and look closely at the medication inside the bottle for one minute, and (3) take out one pill, hold it 12” from their face, and look at it closely for one minute. In the neutral condition, participants completed the same set of procedures, but rather than using their prescribed opioid, participants withdrew paperclips from a generic unmarked bottle. At baseline, before, and after each block of the opioid medication reactivity task, participants rated their current pain (“How intense is your pain right now?”) and opioid craving. Self-reported craving and salivation following the opioid block was significantly higher compared to that following the neutral block. Importantly, the authors found that opioid cue-elicited craving was significantly and positively associated with opioid misuse ($r = .34$, $p = .004$), but was not significantly associated with opioid dose, duration of opioid use, or opioid cue-elicited salivation (Hanley and Garland, 2020). Another recent study by this group examined chronic pain patients on long-term opioid therapy with (n=145; MEDD: Mean± SD: 148.4 ± 261.2) and without (n=97; MEDD: Mean±SD: 122.5 ± 219.1) opioid misuse (COMM9>13 was used to indicated misuse) (Parisi et al., 2022b). Participants were presented with opioid and neutral cues images. After each block, participants rated their craving intensity in response to the question “How much do you want to take opioids right now?” on a five-button response box ranging from 1 (not at all) to 5 (extreme). Autonomic cue-reactivity were measured with high-frequency heart rate variability (HRV). This study found that exposure to opioid cues elicited craving, i.e., craving ratings was higher following opioid compared to neutral cues, but only in those with opioid misuse (Parisi et al., 2022b). In a related study by this group (Parikh et al., 2022), 87 veterans (74 males, 13 females) on long-term opioid therapy (33/87 with OUD diagnoses) performed novel opioid preference task (rather than a classical cue-reactivity paradigm). Participants were asked to view opioid-related images, as well as unpleasant, neutral, and blank images. On each trial, two images from these respective categories were presented side-by-side, and participants used continuous button-pressing for choosing one image over the other. The preference for the image category was indicated by the number of button presses and the higher number was coded as the “choice” for that trial. The authors found increased preference for opioid images only in those with OUD but that image choice was not related to subjective craving. Likewise, other studies by this group similarly showed increased opioid craving following opioid cues in chronic pain patients, particularly in those with opioid dependence and/or misuse (Garland and Howard, 2014). In one study opioid craving following viewing of neutral and opioid images was significantly associated with arousal ratings of opioid images ($r = .34$, $p = .006$) (Garland et al., 2013b). Taken together, these studies suggest that opioid cues induce subjective and objective (HRV, saliva) craving response, but this behavior is particularly related to opioid misuse among chronic pain patients. This supports the notion

that craving may not be the driver of continuous opioid intake in those with chronic pain that do not misuse opioids.

Cue-reactivity paradigms in opioid users without chronic pain may provide additional information about specific cue-elicited patterns linked to prescription opioid use (e.g., (McHugh et al., 2016). Detailed discussion of this literature is beyond the scope of this review, yet it brings interesting point regarding cue relevance. For example, images that depict primary routes of administration (needles vs. bottles) elicit stronger cravings within opioid-dependent participants based on their preferred route (McHugh et al., 2016). Likewise, traditional reactivity cues alone (visual stimuli) may be insufficient to fully present the complexity of addictive behavior in opioid users and a variety of cue presentation modalities, including imaginal, in vivo, audio, video, pictorial, and virtual reality techniques may be much more effective in eliciting subjective ratings and physiological responses (Back et al., 2014).These findings further imply that the development of personalized cues when studying cue-reactivity based craving may be especially important for certain drug use groups and that craving is particularly sensitive to the personal salience/specificity of drug-associated cues.

4.3.3 Dot-probe tasks: Attentional biases towards drug-related stimuli through dot-probe tasks may be another way to measure craving related constructs (e.g., salience). During the dot-probe task, participants are situated in front of a computer screen and asked to stare at a fixation cross on the center of the screen. Two stimuli, one of which is neutral and one of which is drug-related, appear randomly on either side of the screen. The stimuli are presented for a predetermined length of time (most commonly 500ms), before a dot is presented in the location of one former stimulus. Participants are instructed to indicate the location of this dot as quickly as possible, either via keyboard or response box. Latency is measured automatically by the computer. The fixation cross appears again for several seconds and then the cycle is repeated. Quicker reaction time to the dot when it occurs in the previous location of a drug stimulus is interpreted as attentional bias to drug cues.

4.3.4 Summary of studies that used dot-probe tasks to assess craving—To the best of our knowledge, only one group examined dot-probe tasks in chronic pain patients on long-term opioid therapy (LTOT) (Baker and Garland, 2019; Garland et al., 2014; Garland et al., 2013b; Garland and Howard, 2014; Garland et al., 2017). In Garland et al., (2013) (Garland et al., 2013b) opioid-dependent chronic pain patients (n = 32) and a comparison group of non-dependent opioid users with chronic pain (n = 33) completed a dot probe task designed to measure opioid attention bias. A set of 12 opioid images were chosen to represent a wide range of commonly prescribed opioids in a number of forms, including photos of pills (e.g., Oxycontin, Vicodin), pill bottles, crushed and powdered opioids for insufflation, and a syringe next to a vial of injectable morphine. Neutral images included 12 photos from the International Affective Picture System (Lang et al., 1997) depicting household items such as a rolling pin, rubber bands, a lamp, etc. Each pair of images was presented for either 200 or 2,000 ms. Participants were asked to press a computer key to indicate on which side of the screen the dot probe had appeared. Attentional bias was calculated as the difference in reaction time to the dot probe between neutral and opiate

related pictures. The authors found that opioid-dependent patients showed attentional bias towards opioid cues presented for 200 ms but not for cues presented for 2,000 ms, whereas non-dependent opioid users did not show such bias at either stimulus duration. Similar findings were observed in Garland et al., (2014) (Garland and Howard, 2014). Furthermore, among opioid-dependent and/or misusing individuals, 200 ms opioid attentional bias was significantly associated with opioid craving (Garland et al., 2013b; Garland and Howard, 2014). These findings suggest a heightened role of craving in chronic pain patients with opioid dependence and/or misuse. Interestingly, a study in current opiate users, ex-users, and non-users without chronic pain that used a similar paradigm (Constantinou et al., 2010) found greater attentional bias (i.e., shorter reaction times) in current opiate users towards heroin-related stimuli compared to ex-users and healthy non-users at both long and short exposures, unlike Garland et al. (2013) (Garland et al., 2013b). Conversely, in Frankland et al (2016) (Frankland et al., 2016), the authors found a significant attentional bias for drug cues at 200ms, a trend at 500 ms but not at 1,500 ms in participants who were opioid dependent – findings that closely matched those of Garland et al. (2013) (Garland et al., 2013b) and Garland and Howard (2014) (Garland et al., 2013b; Garland and Howard, 2014). These studies consistently demonstrate a bias at 200 ms which supports the view that early attentional processes preferentially direct processing resources toward drug cues, but these effects do not necessarily extend into longer and more elaborate processing of drug cues. These findings also demonstrate the bias in early attentional processes in opioid dependent subjects irrespective of chronic pain status.

In a study conducted by Garland et al. (2014) (Garland et al., 2014), the authors used a dot-probe task to examine the effects of mindfulness-oriented enhancement (MORE) on reward responsiveness and opioid cue-reactivity. The paradigm was similar to (Garland et al., 2013b) and (Garland and Howard, 2014), again using 200ms and 2000ms durations. Three blocks of cues (opioid-related, pain-related, and pleasure-related) were presented, each paired with a neutral stimulus. The subjective opioid cue-reactivity relative to pre-stimulus baseline was assessed immediately after the opioid cue block on the dot probe task (VAS: “How much do you want your opioids right now?” anchored on a 10-point scale). Attentional bias was not reported in this study, but the investigators found that the MORE group had significantly greater reductions in opioid-cue reactivity in the dot-probe tasks than the support group, as well as significantly greater heart rate deceleration to natural reward cues correlated with subjective arousal to the same cues. Likewise, (Baker and Garland, 2019; Garland et al., 2017) used a dot-probe task in chronic pain patients on long-term opioid therapy. Attentional-biases to opioid images were not reported in these studies.

In summary, the majority of the studies discussed above show increased reactivity to opioid cues and increased attentional biases to opioid-related images in those with opioid dependence and/or misuse with or without chronic pain. This suggests that for chronic pain patients with prescription opioid misuse and omnipresent opioid cues, habituating to cues should be considered as part of a treatment strategy. However, it also appears that these tasks may be less sensitive to opioid salience/craving in chronic pain patients that are on long-term opioid therapy, but that have not experienced opioid misuse.

5. Conclusions and Future Directions

The first part of this review covers studies examining the role of craving in predicting opioid use/misuse in individuals with and without chronic pain. Overall, we found that there is a relative paucity of work describing the link between craving and patterns of opioid (mis)use in those who manage chronic pain with prescription opioids. Our preliminary conclusions are that craving does not appear to be a major presenting problem in many patients with chronic pain, however, when present, shows low to moderate associations with increased opioid related use. We suggest that future head-to-head comparisons of treatments for pain and opioid management include, at a minimum, pre- and post-treatment measures of craving to help understand its predictive value, and whether it is responsive to standard or experimental treatments. Observational studies show modest associations between craving and indices of opioid misuse, which may suggest that patient specific variables such as level and recency of pain contribute to these associations. Although we find little evidence that pain severity reinforces opioid craving and (mis)use in chronic pain patients, there is consistent support for the influence of psychological traits, psychiatric comorbidities, gender, and mood and anxiety symptoms on the presence and intensity of opioid craving in chronic pain patients. In other words, there is evidence to suggest that in those with other mental health disorders, severity of psychiatric symptoms appears to be linked with higher craving and greater opioid (mis)use. Importantly, these data suggest that future treatment targets should not only focus on pain but also on psychological distress in order to reduce craving and potential misuse. Our review also suggests that as with other drugs of abuse, craving appears to be both a predictor and an outcome of opioid use, although there appear to be important differences between those who engage in prescription misuse versus illicit opioid use. Specifically, illicit users demonstrate greater cue reactivity in response to opioid cues than prescription users, suggesting important mechanistic differences in craving between these two sub-populations. Future research comparing the characteristics of these groups may yield important insights for developing targeted treatments.

The second part of this review covers various methods used to evaluate craving both in the clinic and experimentally. Questionnaires used to assess craving in chronic pain have several limitations that should be addressed in future research. Single item assessments of craving fail to meaningfully operationalize craving and may suffer from poor reliability. Several measures do not attempt to assess craving specifically in the context of pain, which makes causal relationships difficult to assess. Other contextual factors or triggers are rarely assessed, such as negative affect or mood. Some craving scales are adapted from those developed to assess cocaine, alcohol or illicit heroin use. While these benefit from years of validation within other fields of addiction, they may miss important conceptual nuances in those using prescription opioids to treat chronic pain. Additionally, most scales do not differentiate between desire to use and intent to use, which could be an important factor for those on prescription pain maintenance, owing to their constant access to opioids. Additionally, some scales inquire about overlapping constructs (e.g., expectancies) but do not link them to urge to use. Finally, a major limitation for self-report measures of craving is that patient disclosure may limit access to prescription opioids or may threaten benefits or parental rights, thus presenting a major measurement confound. Therefore, anonymous

reporting might improve the validity of self-report measures of craving. EMA of craving addresses several limitations, such as retrospective bias in self-reported craving measures, and allows for real time assessment of craving as well as other contextual factors such as pain level, affect, mood, and environmental factors that may causally interact with craving. Coupled with the ability to provide de-identified reporting, EMA may provide both increased nuance (e.g., frequency, intensity, context, triggers, temporal precedence) as well as validity in craving measurement. However, EMA requires significant technical infrastructure, and poses data security challenges, making it less feasible to obtain in many settings. To date, few EMA studies in those with prescription opioid use and chronic pain have been conducted. Finally, objective measures of cue reactivity and attentional bias are lacking in those using prescription opioids to treat chronic pain. Initial results suggest that in response to visual cues of pain and opioids, opioid dependent users with a history of misuse and chronic pain demonstrate reduced HRV, a physiological marker of the capacity for self-regulation, as well as higher self-rated craving as compared to those without misuse. Cue reactivity studies in opioid users without chronic pain suggest that cues that represent the route of administration may be more salient, and thus suggest that personalization may be important to generate robust results in daily users. Previous work pointing to the importance of contextual factors and craving also suggests that designs that incorporate mood or contextual manipulations may be crucial to understanding craving in those with prescription opioid use and chronic pain.

Prescription opioid overdose accounts for a staggering number of deaths each year (CDC, 2021). While craving is considered a core symptom of substance use disorder, the way in which craving may contribute to problematic opioid use in the context of pain management is largely unknown. In this review we show that there are currently few well-controlled studies examining the contribution of craving to opioid misuse in those with chronic pain, and that the measures used to characterize craving are often insufficient to afford a mechanistic understanding of these relationships. Additional considerations for the measurement of craving, such as temporal resolution, context, mental health status, motivation, and personality may be important in understanding how craving relates to actual drug misuse in prescription-managed populations. We suggest that anonymous, electronic momentary assessment measurements, person- and context-specific assessment, and well-controlled study designs may significantly advance our ability to treat and predict the course of prescription opioid misuse in those with chronic pain.

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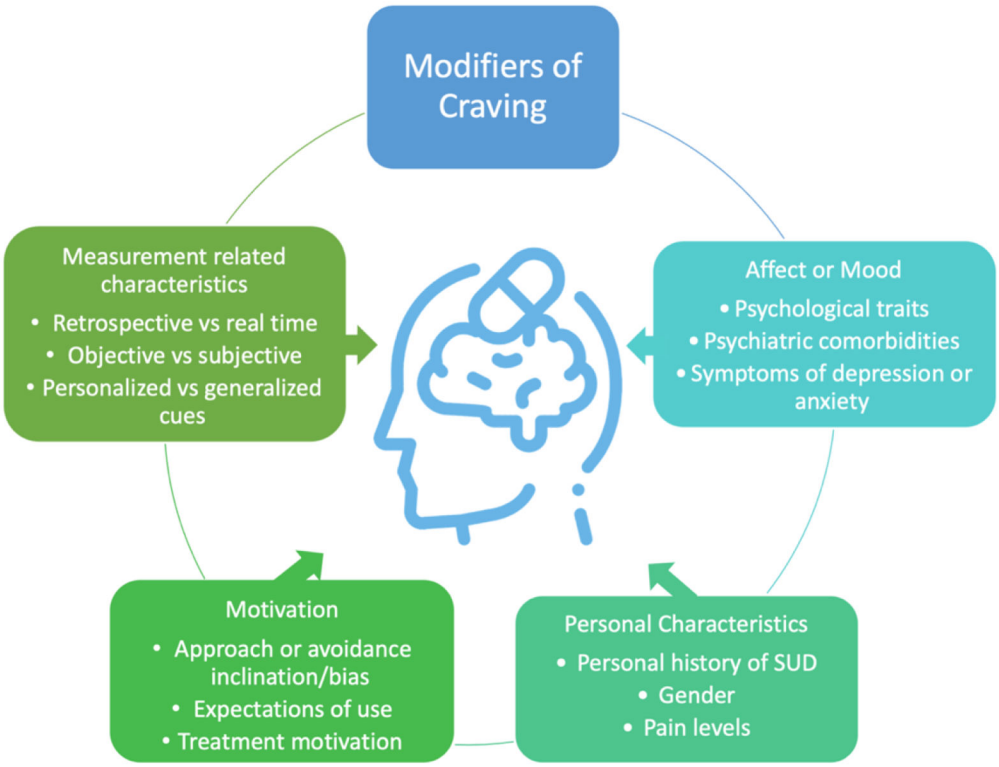
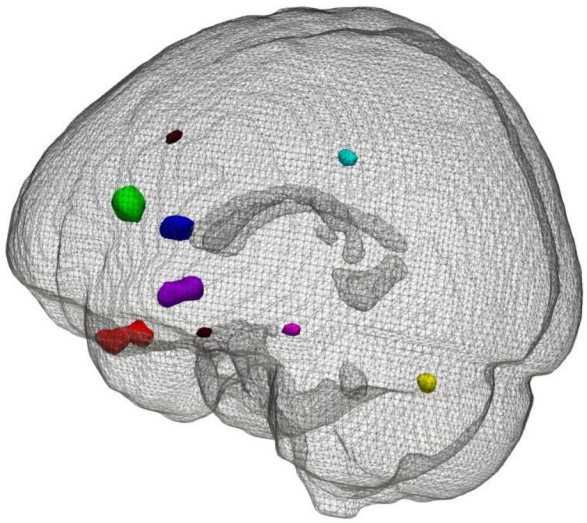


Figure 1:
Potential Modifiers of Craving. Factors that may influence craving or impact the measurement of craving include: affect and/or mood, personal characteristics, motivations, and measurement related characteristics. The potential impact of these factors on craving are not yet well understood in individuals who manage chronic pain with opioids.



Area	#Voxels	CM x	CM y	CM z
Nucelus Accumbens (NAc)	99	-8.8	15.1	-10.1
Orbitofrontal Cortex (OFC)	93	6.3	41.8	-26.1
Dorsal Anterior Cingulte (dACC)	87	-10.7	38.7	14.9
Caudate	41	-5.9	22.6	10.2
Inferior Temporal Gyrus (ITG)	21	51.9	-44.5	-25
Inferior Temporal Gyrus (ITG)	13	-48.6	-43.8	-21.1
Superior Frontal Gyrus (SFG)	11	-16.5	22.9	36.7
Amygdala	10	-21.3	0.5	-23.5
Posterior Cingulate (PCC)	10	-9.2	-33.8	36

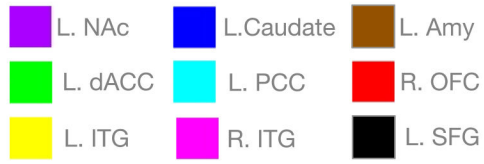


Figure 2:

Craving-related brain activation. Map (left) depicts term-based meta-analyses from Neurosynth (Yarkoni et al., 2011) (term: craving; association tests, download date: 11.04.2021). Note most left-side activation and lack of insula activation. Area and size of each cluster, as well as MNI coordinates are shown (top right). NAc – nucleus accumbens, dACC – dorsal anterior cingulate cortex, ITG – inferior temporal gyrus, PCC – posterior cingulate cortex, Amy – amygdala, OFC – orbitofrontal cortex, SFG – superior frontal gyrus.

Table 1:

Subjective Assessment of Craving and Craving-Related Constructs

Name	Authors	Year	# items	Craving Yes/No
Self-Report Measures that Measure Craving				
The Opioid Craving Scale	McHugh RK, Fitzmaurice GM, Carroll KM, Griffin ML, Hill KP, Wasan AD, & Weiss RD	2014	3	Yes
(Craving) Visual Analog Scale (VAS)	Rosenberg 2009 (e.g., Tsui et al., 2016)	2009	1	Yes
Revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R)	Butler SF, Fernandez K, Benoit C, Budman SH, & Jamison RN (e.g., Wasan et al., 2015)	2008	24	Yes
Desires for Drug Questionnaire	Franken IHA, Hendriks VM, & van den Brink W	2002	13	Yes
Obsessive Compulsive Drinking Scale-Revised (OCDS-R)	Morgan TK, Morgenstern J, Blanchard KA, Labouvie E, & Bux DA	2004	10	Yes
Urge to Use Scale	Cousins SJ, Radfar SR, Crèvecoeur-MacPhail D, Ang A, Darfler K, & Rawson RA	2015	5	No
Self-Report Measures of Craving-Related Constructs				
Current Opioid Misuse Measure (COMM)	Butler SF, Budman SH, Fernandez KC, Houle B, Benoit C, Katz N, & Jamison RN	2007	17	No
Pain Medication Expectancy Questionnaire (PMEQ)	Ilgen MA, Roeder KM, Webster L, Mowbray OP, Perron BE, Chermack ST, & Bohnert ASB	2011	38	No
Measures of Use Severity Frequently Employed in Studies of OUD				
Prescription Opioid Misuse Index	Kinsley JS, Janet S, Wunsch MJ, Cropsey KL, Campbell ED	2008	6	No
Clinician Administered Measures of Use Severity				
Addiction Severity Index (ASI)	McLellan AT, Luborsky L, O'Brien CP, & Woody GE	1980	NA	No
Prescription Drug Use Questionnaire (PDUQ)	Compton P, Darakjian J, & Miotto K	1998	42	No
Prescription Opioid Therapy Questionnaire (POTQ)	Butler SF, Fernandez K, Benoit C, Budman SH, Jamison RN	2008	11	No

Table 2:

Ecological Momentary Assessments Methods

Study	EMA Type	Frequency	Prompt Time	Questions	Compliance (%)
Chronic pain					
Wasan et al., 2012	Personal Digital Assistant (PDA)	1x/day for 14 days	Not specified	BPI, medication, pain location, pain intensity, craving	95
Wasan et al., 2015	Not specified	1x/day for 7 days	Not specified	Average pain level (0-10), # of medications taken daily	Not specified
Garland et al., 2019b	Smartphone prompt	2x/day for 56 days	Random between 9AM-9PM	Craving +/− affect, pain intensity	62
Garland et al., 2022	Smartphone prompt	1x/day for 8 weeks	Not specified	Opioid Craving scale 0-10	Not specified
Parisi et al., 2022a	Not specified	3x/day for 56 days	Not specified	Urge, affect, pain intensity (0-10)	70
No reported chronic pain					
Huhn et al., 2016	Smartphone prompt	4x/day for 12 days	Alarm at morning, noon, mid-afternoon, and evening	Craving (frequency and intensity intensity), +/− affect	Not specified
Kowalczyk et al., 2018	Portable Electronic Device	4x/day for 20 weeks	Randomly prompted during waking period	Craving, +/− affect	79
Panlilio et al., 2019	Smartphone or Personal Digital Assistant	16-18 days	Randomly prompted, participant initiated, end of day	Craving, +/− affect, stress level, hassles experienced	89

Table 3:

Objective Measures to Assess Craving

Study	Stimulus Modality	Stimulus Type	Subjective Outcome		Objective Outcome	
Cue-Reactivity						
Garland et al., 2013b $	Images	Neutral Opioid	Yes	Arousal [1 = completely unaroused - 9 = completely]	No	
Garland and Howard., 2014 $	Images	Neutral Opioid	Yes	How much do you want your opioids right now?" anchored on a 10-point scale (1 = not at all, 10 = extremely)	No	
Garland et al., 2018	Images	Neutral, opioid, pain	Yes	1 = no opioid craving, 8 = extreme opioid craving]	Yes	HRV
Garland et al., 2019a	Images	neutral, opioid, reward	Yes	How much are you craving opioids right now?" (1 = not at all, 5 = extremely)	Yes	EEG/LPP
Hanley and Garland, 2020	Pill bottles	Opioid (prescribed opioids) Neutral (unmarked bottle)	Yes	("How much do you want to take opioids right now?") 11-point NRS (0 = not at all, 10 = extremely)	Yes	Salivary reactivity
Parisi et al., 2022b	Images	Neutral Opioid	Yes	How much do you want to take opioids right now?" on a five-button response box ranging from 1 (not at all) to 5 (extreme)	Yes	HRV
Parikh et al., 2022	Images	Neutral Opioid Unpleasant Blank	Yes	Self-report opioid craving [VAS: 0-100]	No	
Dot-Probe						
Garland et al., 2013b	Images	Neutral Opioid	Yes	Arousal [1 = completely unaroused - 9 = completely]	Yes	RT
Garland and Howard, 2014	Images	Neutral Opioid	Yes	How much do you want your opioids right now?" anchored on a 10-point scale (1 = not at all, 10 = extremely)	Yes	RT
Garland et al., 2014	Images	Neutral, opioid, Pain, pleasure	Yes	How much do you want your opioids right now?" anchored on a 10-point scale (1 = not at all, 10 = extremely)	Not Reported	
Garland et al., 2017	Images	Neutral Opioid		Not Reported		Not Reported
Baker and Garland, 2019	Images	Neutral Opioid		Not Reported		Not Reported

$ - included under both, cue-reactivity and dot-probe as it combines subjective measures of cue-reactivity and attentional bias