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Assessing Pain in Persons with Opioid Use Disorder: Approaches, Techniques, and Special Considerations

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Abstract

Pain and opioid use disorder (OUD) are inextricably linked, as the former can be a risk factor for the development of the latter, and over a third of persons with OUD suffer concomitant chronic pain. Assessing pain among people with OUD is challenging, be-cause ongoing opioid use brings changes in pain responses and most pain assess-ment tools have not been validated for this population. In this narrative review, we dis-cuss the fundamentals of pain assessment for populations with OUD. First, we de-scribe biological, psychological, and social aspects of the pain experience among people with OUD, as well as how opioid-related phenomena and healthcare dispari-ties in this population may contribute to the pain experience. Second, we review meth-ods to assess pain including: (1) traditional self-reported methods, such visual analog scales, and structured questionnaires; (2) behavioral observations and physiological indicators; (3) and laboratory-based approaches, such as functional brain imaging, electroencephalography, and quantitative sensory testing. These methods are consid-ered from a perspective that encompasses both pain and OUD. Finally, we discuss strategies for improving pain assessment in persons with OUD and implications for future research, including educational strategies for multidisciplinary teams. Substan-tial gaps persist in our knowledge, particularly regarding the applicability of current pain assessment methods to persons with OUD, as well as the generalizability of the existing results from adjacent populations. As research linking pain and OUD evolves, considering the needs of diverse populations with complex psychosocial back-grounds, we will be better equipped to reduce these gaps.

1. INTRODUCTION

The convergence between pain and opioid use disorder (OUD) continues to be a complex problem and significant public health concern. Pain is a pervasive issue, with over half of the U.S. adult population reporting some form of pain within the last three months[1]. More specifically, chronic pain, defined as persisting pain lasting over three months, affects over 100 million adults in the U.S., and chronic low back pain ranks as one of the 10 leading causes of reduction in disability-adjusted life years[2, 3]. Considering health care, forensic, production loss, and life loss costs, the economic burden of chronic pain has exceeded $600 billion annually[4].

In parallel, the consequences of the OUD continue to escalate amidst the opioid crisis, as we witness consecutive yearly records for fatal opioid overdoses and opioid-related hospitalizations in the U.S., now above 60,000 opioid-involved overdose deaths per year[5]. Pain is pivotal to this crisis, particularly as the initial wave of the opioid epidemic was the result of inadequately prescribed opioids for chronic pain[6]. An added layer of complexity is the pervasive stigma associated with OUD, often resulting in labeling patients with pain as "opioid-seeking." This hampers appropriate medical care in the context of acute and chronic pain[7]. Such is the need for specialized care that considers the consequences of co-occurring pain and OUD, for which

clinicians and other stakeholders have been attempting to develop innovative strategies, including specialized clinics that are capable of jointly managing pain and OUD[2, 3, 8, 9]. A persistent challenge, however, is distinguishing between pain-related and OUD-related phenomena, due to their clinical and neurobiological similarities[10].

Several approaches have been used to assess both acute and chronic pain among persons with OUD. For example, Delorme and colleagues recently conducted a meta-analysis to evaluate the prevalence of chronic pain among persons with OUD receiving buprenorphine or methadone[11]. The analysis included 23 studies, using a variety of pain assessment tools, with the Brief Pain Inventory (BPI) most frequently used (n=12). Four studies relied on a simple binary question, asking about the presence or absence of pain. One study utilized a pain numerical rating scale[12, 13], while another combined the BPI questionnaire with a numerical rating scale[14]. A unique approach was taken in one study, where a custom-made questionnaire was used to gauge pain levels[15]. The other two determined the presence of chronic pain based on the prescription or dispensation of analgesic medication longitudinally. This wide variation in assessment tools illustrates the lack of consensus in methods used to understand and quantify the experience of chronic pain among patients with OUD, highlighting the need for empirically-supported consensus in this area.

In this narrative review, we discuss the fundamental approaches to pain measurement in persons with OUD. First, we describe biological, psychological, and social aspects of the pain experience among people with OUD. Our discussion ranges from molecular opioid-related phenomena to healthcare disparities. Second, we review methods to assess pain including: (1) traditional self-reported methods, such as visual analog scales and structured questionnaires; (2) behavioral observations (e.g., antalgic and pain-avoidant behaviors) and physiological indicators (e.g., heart rate, blood pressure); (3) and laboratory-based approaches such as functional brain imaging, electroencephalography, and quantitative sensory testing. We discuss the influence of relevant clinical phenomena in the assessment of pain among persons with OUD, including tolerance, heightened pain sensitivity (i.e., hyperalgesia), and pain exacerbated by opioid withdrawal. Finally, we will outline strategies for improving pain assessment in OUD and implications for future research.

2. THE COMPLEXITY OF PAIN ASSESSMENT IN OPIOID USE DISORDER

Biological aspects of pain in persons with opioid use disorder

2.1.1 The normal physiology of acute pain

Pain is a complex and multifaceted experience, intertwining sensory, affective, cognitive, and behavioral dimensions. Nociception is the sensory nervous system process of encoding noxious or tissue-damaging stimuli, involving the activation of peripheral nociceptors, which in turn communicate through synapses with the central nervous system[16]. Acute pain can produce autonomic responses, frequently leading to increases in blood pressure, cardiac output, respiratory and heart rate. Thus, the experience of acute pain involves a visceral sympathetic reaction that informs the organism it must avoid or withdraw from a source of discomfort or damage[17]. Ascending neural pathways carry sensory information from the periphery through the spine to corticolimbic regions; descending pathways, conversely, modulate the pain experience as they relay physical and emotional signals down the spinal cord[18].

2.1.2 Pain chronification from a biological perspective

As pain becomes chronic, the persistent activation of neural circuitry responsible for emotional processing can lead to further psychological and physical consequences, thereby worsening the perception of pain and its functional impact over time[18]. Neurobiologically, pain chronification requires disruptions in multiple complex pathways crucial for the neural processing of the pain experience. The mechanisms behind these disruptions are diverse[19-21]. At the cellular level, they involve glutamate excitotoxicity and reductions in inhibitory gamma-aminobutyric acid (GABA) levels, intensifying pain sensitivity in the periphery[22]. At the central nervous system level, shifts occur in the activation patterns of brain sensory cortical areas, gradually stressing limbic areas over time[22]. Eventually, this progression leads to neuroplastic changes, manifesting as a pathological rewiring of brain and spinal cord circuitry[22]. Notably, the activation of limbic areas

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plays a pivotal role in driving the development and escalation of chronic pain[22]. This process occurs through emotional activation, triggering the conversion of an acute sensory experience into an emotional, chronic and, debilitating one. Consequently, the individual's experience of reality and decision-making become heavily impacted by the pain experience[21]. The fundamental link between pain and OUD stems from disruptions in the endogenous opioid system, which significantly influence the cellular and central nervous system changes described, with inappropriate neuronal rewiring and neuroplastic changes as a result, leading to perpetuation of pain and reward system imbalances[19, 20].

2.1.3 The role of opioids in modifying the experiencing of pain

Opioids have profound analgesic properties, reliably reducing both physical pain and psychological distress[23]. Molecularly, they bind to G-protein coupled opioid receptor subtypes(e.g., mu-μ, delta-δ, and kappa-ϰ) in multiple brain and spinal regions[23]. Each receptor type activates different cellular pathways, leading to varied physiological effects. The μ -opioid receptor is the primary target for most clinically used opioids and is chiefly responsible for their analgesic effects. The activation of the μ receptor generally leads to a decrease in the release of certain neurotransmitters including substance P, glutamate, and GABA[23]. In pain pathways, this results in the hyperpolarization of post-synaptic neurons, which thereby reduces synaptic activity and the inter-neuron communication of pain signals[23]. Secondary effects include reductions in blood pressure, heart rate, respiratory rate, as well as drowsiness[24]. Centrally, opioids agonists' actions at the opioid receptor level have euphoria-inducing and anxiolytic properties limiting one's awareness or appreciation of painful stimuli[25].

Continued opioid use, whether motivated by pain or OUD, can lead to the neuroadaptive developments of tolerance and physical dependence, necessitating higher doses to achieve the same effects over time and resulting in withdrawal symptoms upon drug cessation. Chronic opioid exposure triggers modifications in the quantity and responsiveness of opioid receptors, a process known as receptor downregulation and desensitization[26]. As a consequence, receptors become internalized or less reactive, contributing to the phenomenon of tolerance[26].

Human studies utilizing pain laboratory models have shown that individuals maintained on full-agonist opioids such as methadone for the treatment of OUD exhibit increased sensitivity and decreased tolerance to painful stimuli, as evidenced by studies conducted by the investigative teams of Clark, Compton, and Wachholtz[27-29]. Interestingly, Athanasos and colleagues found that despite inducing respiratory depression in some participants, high doses of morphine failed to enhance pain tolerance in methadone-maintained patients[30]. Additionally, Compton and colleagues reported that neither buprenorphine nor methadone treatments improved pain sensitivity for participants with OUD[28]. In a systematic review of 225 participants on opioid agonist therapy for OUD, De Aquino and colleagues found that the majority of participants do not experience analgesia despite receiving opioid doses up to 20 times greater than those used to treat acute pain in opioid-naïve participants[31]. Conversely, they remained vulnerable to respiratory depression despite receiving medications for OUD — suggesting tolerance to analgesic effects cannot be equated with tolerance to adverse effects from opioids. This intricate interplay of physiological changes underscores the complexities associated with opioid-induced neuroadaptations and pain management in individuals with OUD.

Psychological aspects of chronic pain in opioid use disorder

The presence of pain can significant worsen one's quality of life. As a multifaceted phenomenon, it also brings wide-ranging consequences. For instance, mobility, sleep, concentration, mood, and overall physical functioning are negatively impacted by ongoing pain. Various psychological factors can worsen the pain experience, including negative expectancy (i.e., behaving in an avoidant manner as if expecting the pain to worse) or perceived controllability (i.e., sense of lack of control over their pain increases the perception of intensity). These factors bring additional repercussions, such as social isolation and avoiding physical activities or *kinesiophobia* (from the Greek terms "kinesis" [movement] and phobia [fear]). Collectively, these components of the pain experience can converge, and the individual may refrain from usual enjoyable activities and roles, contributing to depression, anxiety, and lower quality of life[32, 33].

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Physical pain and emotional pain intersect and can synergistically influence not only the overall experience of pain itself, but also influence co-occurring psychopathology (e.g., mood disorders and trauma-related disorders)[34]. For example, mood disorders predict both non-medical opioid use and the increased likelihood for developing chronic pain conditions[35, 36]. Persons with chronic pain are also more likely to be diagnosed with mood disorders and may be at higher risk of developing OUD[37, 38]; although there are conflicting data in the literature regarding the risk of progression to OUD[39]. However, despite the considerable overlap between these conditions, the influence of co-occurring psychopathology on the assessment of pain among people with OUD remains largely unaccounted for in most clinical settings.

Other important psychological factors that contribute to the pain experience in persons with chronic pain include pain catastrophizing and attentional bias[40]. Pain catastrophizing involves ruminative thoughts about pain, and a sense of hopelessness regarding pain improvement resulting in an amplification of pain[41]. Studied in both acute pain (e.g., whiplash injury after motor vehicle accidents) and chronic pain[42-44] (e.g., fibromyalgia[45], low back pain[46, 47]), pain catastrophizing is a risk factor for poorer pain treatment prognosis and outcomes in persons with OUD, as well as a predictor of pain chronicity[48]. Attentional bias refers to a cognitive fixation in which attention is automatically captured by pain- or opioid-related cues, serving as motivation for further medication use[49, 50]. In other words, as patients with chronic pain engage in re-occurring opioid use, pain (e.g., experiencing external or interoceptive painful stimuli) and opioid-related cues (e.g., pill bottles) can trigger craving and perceived worsening of pain. Clinically, it has been suggested that attentional bias may precede drug use in persons with OUD and be an early warning signal of return to non-medical opioid use[51].

Research shows that persons with OUD tend to experience pervasive anhedonia and dysphoria with consequences such as increased sensitivity to social rejection, reward deficiency, and heightened pain experience[52-54], contributing to opioid craving and further non-medical opioid use[53, 55, 56]. This dysphoria or *hyperkatifeia* (from the Greek term "katifeia" [dejection]) is referred to as encompassing negative emotional symptoms such as irritability, anxiety, and unease that derive from dysregulation of brain reward and stress systems, and has been demonstrated to worsen during protracted abstinence and seems to facilitate relapse[57].

Further exemplifying the clinical relevance of these chronic pain-related psychological factors, emerging evidence demonstrates that interventions addressing both the physical consequences of pain and long-term opioid use, and the maladaptive psychological patterns, such as pain catastrophizing, produce superior clinical outcomes[58]. As an example from an adjacent long-term opioid use population, Martinson and colleagues studied 77 veterans with multiple chronic pain conditions in the primary care setting and offered six, 50-minute sessions of cognitive behavioral therapy for pain[59]. Approximately 52% of participants had long-term opioid use. They suggest that this psychological behavioral intervention significantly improves pain symptoms, physical function, family stability, sleep quality, satisfactions with outcomes of care, pain-related anxiety, generalized anxiety, pain catastrophizing, and depressed mood. As seen in most studies encompassing pain and long-term opioid use, a limitation of this study is that it does not formally assess for OUD, thus, we suggest careful extrapolation of these findings from long-term opioid use populations to those living with OUD.

In summary, the psychological consequences of both chronic pain and OUD, especially when compounded by negative coping strategies and thought patterns, can make pain feel overwhelming for persons with co-occurring OUD and chronic pain. The perception of pain in these patients is influenced by these significant psychological factors, which can be accurately assessed for and are amenable to effective interventions.

Social aspects influencing pain assessment in persons with OUD

As the fields of pain research and treatment have progressed towards an adoption of a biopsychosocial model as an alternative to a purely biomedical approach, social aspects in clinical evaluations and pain assessments have garnered growing interest[60]. This model argues that social factors (e.g., racial-ethnic disparities, social support networks, access to health care) are often as important as biological determinants in the origin,

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exacerbation, and maintenance of pain.

2.3.1 The role of social support networks

Social support, defined as the perception of availability of other people in one's social networks, appears to play a central role in one's ability to cope with pain[61]. For instance, people with chronic pain who report high levels of social support experience less clinical pain intensity, distress related to pain, and less mood-disorder comorbidities than those with less support[61-63]. Moreover, higher levels of social support have been shown to reduce the occurrence of pain catastrophizing in a cohort of 74 persons with spinal cord injury[64]. Likewise, another study of 168 older adults with various forms of chronic pain showed that high social support, as measured with the Formal Social Support for Autonomy and Dependence in Pain Inventory, positively impacts not only the pain experience itself and decrease pain-related disability, but also favors higher levels of function autonomy and independence[65].

Although social connections appear to positively influence the outcomes of OUD treatment[66], (i.e., increased medication adherence, time in treatment, number of drug-free urine samples), thus far there are no specific studies specifically investigating the effect of social-support networks for patients with co-occurring OUD and chronic pain. However, given the clear benefits resulting from high levels of social support for people with pain or OUD, it is likely to be a benefit for those with both conditions.

Methods for assessment of social support networks have been well described by Bryant and colleagues[67] and interactive tools such as the Columbia Social Support Network Map have been created to simplify this assessment[68]. Social workers are well-equipped with knowledge and skills to assess levels of social support, highlighting the importance of multidisciplinary care for both chronic pain and OUD.

2.3.2 The role of racial-ethnic disparities

Barnett and colleagues used 2016-2019 Medicare claims data to identify racial-ethnic differences in the prescription and rates of use of medications to treat OUD (buprenorphine, intramuscular extended-release naltrexone) and prevent opioid overdose deaths (naloxone), as well as high-risk prescription medications (e.g., opioid analgesics and benzodiazepines)[69]. They found that Black persons are less likely to access buprenorphine and naloxone than non-Hispanic White (NHW) populations. This is particularly concerning, in that Black persons have experienced greater increases in opioid-involved overdose deaths than any other racial group, growing by a factor of 7.7 between 2010 and 2020[70].

Noted disparities in OUD treatment are mirrored by disparities in chronic pain treatment in minoritized patients living with OUD. Black and, to a degree, Hispanic adults have been shown to experience greater clinical pain severity and pain-related disability than NHW adults[71-73]. In laboratory models of pain, Black persons have been found to exhibit lower pain thresholds and lower tolerance of pain[74-80]. Growing evidence highlights that these racial differences in pain perception may result from the harmful effects of health-care disparities and societal racism in general.

At the mechanistic level, racism-related stress, or pervasive emotional distress caused by racial discrimination, may negatively affect pain perception through sleep disturbance and corticolimbic disfunction, as demonstrated by Letzen and colleagues[81]. The authors assessed the effects of race-related stress on the corticolimbic system, using positron emission tomography (PET) to evaluate the binding potential of μ-opioid receptors; actigraphy sleep variables were also measured[81]. An association was demonstrated between levels of exposure to racism and pain sensitivity through mechanisms of: (1) race-related stress, (2) sleep disturbances associated with race-related vigilance, and (3) corticolimbic opioid-receptor modulation changes. These findings emphasize the role of multi-disciplinary trauma-informed approach to pain treatment in racialized populations, as the experience of racism may worsen the experience of pain and be evident beyond physical domains[82].

In summary, biological, psychological, and social factors converge to impact the experience of chronic pain, challenging holistic pain assessments. For persons with OUD, this assessment is further complicated by

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opioid-related disruptions of pain pathways. For optimal clinical outcomes, it is imperative to undertake a comprehensive, multidisciplinary pain evaluation that can account for this complexity (**Figure 1**).

SPECIAL CONSIDERATIONS

Tolerance and hyperalgesia

Pain assessment in individuals with OUD can be complicated by the phenomena of tolerance and hyperalgesia, which are opioid-induced changes to pain systems that can result in increased analgesic demand by persons with pain[26]. Tolerance is characterized by a decreased response to an opioid over repeated administration, necessitating dose increases to achieve the previous magnitude of analgesic effects[26]. Opioid-induced hyperalgesia (OIH) is a paradoxical state of heightened pain sensitivity that is distinct from and superimposed on the painful condition[26, 83]. As people with chronic pain continue to deteriorate, increasing need for opioids at higher doses can indicate several diagnostic hypotheses. First, it may reflect untreated or inadequately treated pain that could indeed benefit from higher dose adjustments[84, 85]; second, it may signal the development of tolerance to the analgesic effects of the current opioid regimen[86, 87]; or third and alternatively, the dose escalation itself may be triggering OIH, in which case higher doses might, in fact, be detrimental[26, 83].

Multiple mechanisms likely underlie the development of tolerance and OIH. In some ways similar to mechanisms for pain chronification, these include NMDA-receptor activation, neuroadaptations in descending pain modulatory pathways, increased excitatory neuropeptides, and glial cell activation[85, 87, 88]. However, the precise etiology remains incompletely understood. Clinically, distinguishing between under-treated pain, tolerance to analgesic effects of opioids, and hyperalgesia is crucial yet challenging in persons with OUD. A comprehensive phenotyping of the pain experience exploring characteristics, timing, triggers, and radiation can determine if pain represents disease progression or an opioid-related effect. A trial of opioid dose reduction may also clarify if OIH is present[87]. Carefully weighing these pain-related factors helps clinicians to identify the source(s) of pain and optimize pain management in this complex clinical population.

3.2 Physical dependence and opioid withdrawal

In addition to tolerance and OIH, pain in patients with OUD can be complicated by the consequences of physical dependence, namely opioid withdrawal hyperalgesia[89-91]. Opioid withdrawal is commonly assessed using standardized scales such as the Clinical Opiate Withdrawal Scale (COWS)[92], the Subjective Opioid Withdrawal Scale[93], and the Objective Opioid Withdrawal Scale (OOWS)[93]. These tools evaluate self-reported symptoms and observer-rated signs of opioid withdrawal, including anxiety or irritability, perspiration or sweating, tearing or lacrimation, runny nose or rhinorrhea, goosebumps or piloerection, restlessness, as well as the presence of specific types of pain itself (e.g., abdominal pain and cramps).

However, there is considerable overlap between the symptoms of opioid withdrawal and those associated with poorly treated chronic pain. For example, feelings of irritability[94], anxiety[95], and restlessness[96] can be associated with chronic pain as well as opioid withdrawal. This overlapping symptomatology makes it challenging to differentiate etiology, potentially leading to inadequately treated pain in clinical practice. Hence, clinicians must consider the possibility of undertreated pain when evaluating opioid withdrawal, especially in patients with known OUD. **Figure 2** provides clinical pain assessment parameters to distinguish between opioid hyperalgesia, tolerance, and withdrawal. Such differential assessment can prevent premature diagnostic closures that negatively affect pain-related functioning.

4. METHODS OF PAIN ASSESSMENT

Pain is a wholly subjective experience; thus, objective assessment is hindered. Traditionally, pain has been evaluated using three main approaches: patient self-report, behavioral observations, and physiologic indicators. In addition, there is growing evidence for the use of psychophysical, neurophysiological, and neuroimaging techniques to objectively complement those assessments **(Table 1).** However, accurately applying these modalities in patients with OUD requires nuanced understanding of their respective strengths and limitations, particularly considering the biopsychosocial and opioid-related variables of interest.

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Notably, the pain assessment tools utilized in various observational and randomized controlled trials evaluating both acute and chronic forms of pain in individuals with OUD are often inconsistent, as there is limited evidence to justify the choice of one tool over another, reflecting the need to develop consensus on optimal evaluation methods for this complex population. Additionally, although the psychometric properties of the assessment self-report scales have been widely reported[97-99], providing evidence of reliability and validity, psychometric evaluation is often absent for populations of persons with both pain and OUD.

4.1 Self-report measures

4.1.1 Visual Analogue Scale

The visual analogue scale (VAS) was first described by Hayes and colleagues[100] as an instrument to quantify pain intensity. It features a linear scale ranging from "no pain" to "worst pain ever", and the individual marks the intensity of their pain on a 100 mm line. This scale has been commonly used in various populations (e.g., children[101], patients with chronic non-cancer pain[102], individuals with juvenile idiopathic arthritis[103]). In patients with OUD, several studies have utilized the VAS to assess pain[104-106]. Notably, similar VAS tools have been used to measure other opioid-related clinical phenomena, such as opioid craving and withdrawal[107, 108].

Several studies have examined the use of the VAS to assess pain in patients with OUD undergoing opioid switching or taper. For example, Muriel and colleagues conducted an observational study in 138 patients with OUD and co-occurring chronic pain undergoing a 6-month opioid taper[104]. They examined whether CYP2D6 (an enzyme involved in opioid metabolism) phenotypes (poor vs. extensive vs. ultrarapid metabolizers) affected the severity of opioid withdrawal symptoms and pain using VAS and the Opioid Withdrawal Scale (OWS). In the context of significant opioid tapering, CYP2D6 ultrarapid metabolizers demonstrated more severe opioid withdrawal symptoms and higher VAS pain scores compared to extensive and poor metabolizers. This suggests that the VAS may be used to quantify the severity of chronic pain experienced during opioid tapering[104].

Veldman and colleagues conducted an observational study examining the effects of switching 43 persons with OUD and co-occurring chronic pain from full μ-opioid receptor agonists to buprenorphine-naloxone[106]. Using the VAS, pain levels were measured at baseline, while on full agonists, and again two months after switching to buprenorphine-naloxone. Change scores indicated that patients showed a significant reduction in pain scores on the VAS following the transition; further, they also demonstrated increased pressure and electrical pain thresholds and tolerance, suggesting reduced hyperalgesia[106].

Taken together, these studies demonstrate that the VAS appears to be an acceptable and valid method for evaluating pain severity in populations with co-occurring OUD and chronic pain. Notably, the unidimensional nature of the VAS pain assessment portends significant limitations in elucidating the multifaceted experience of chronic pain in persons with OUD.

In an additional adjacent study, Nielsen and colleagues also employed the VAS to measure perceived pain severity in a randomized trial comparing ketamine to placebo for acute postoperative pain in 147 patients with chronic pain patients with a history of daily opioid use[105]. Evaluating VAS scores, the investigators found that ketamine reduced the need for opioids during the 24 hours after surgery compared to placebo. A follow-up pain assessment conducted six months post-surgery continued to show that patients treated with ketamine had greater improvements in pain relief as measured by the VAS compared to those who received the placebo[105]. Of note, it is unclear if these patients actually met diagnostic criteria for OUD, so caution is suggested in generalizing these findings to this population.

4.1.2 Numeric Rating Scale

The Numeric Rating Scale (NRS), first described by Downie and colleagues[109], is a numeric version of the VAS that asks individuals to choose a number from zero to 10 (or 20 or 100) to communicate their pain severity, with zero representing "no pain" and the higher number representing the "worst pain imaginable"[110]. Much like the VAS, the NRS is broadly utilized in both clinical and research settings due to its simplicity,

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and is a unidimensional operationalization of pain. Notably, as it only accepts discrete numerical responses, the NRS offers a less detailed pain gradation in comparison to the VAS[111]. In short, while the NRS, due to its simplicity, has demonstrated ease of application in some studies[112], its inherent limitations necessitate careful interpretation in persons with chronic pain and OUD.

Despite its widespread use, literature supporting the use of NRS for patients with comorbid OUD and chronic pain is sparse. Much like the VAS, the NRS relies on self-report, which must be appreciated in patients with OUD while also considering the potential for altered pain perception and tolerance due to neurobiological changes from long-term opioid use[113]. Opioid-induced hyperalgesia and the overlap between pain and withdrawal can also complicate assessment[87].

In an example of using the NRS for assessing pain in patients with OUD, Latif and colleagues conducted a cross-sectional study to assess the prevalence and characteristics of chronic pain among 560 persons with OUD receiving buprenorphine or methadone therapy in Norway[114]. An 11-point NRS was used to assess pain intensity in addition to a survey that captured pain duration, onset, triggers, sites, persistence, radiation, migration, triggers and medication effects. Chronic pain was reported by 55% of patients, and those with higher NRS pain scores were more likely to describe their pain as constant, migrating, not improved with analgesics, and triggered by stress and exercise. The study supports evidence that chronic pain is highly prevalent in persons with OUD and that the NRS has been used to successfully measure the severity of their pain.

4.1.3 Brief Pain Inventory

The Brief Pain Inventory (BPI) was developed in 1983 to assess pain in individuals with cancer[115]. Unlike the unidimensional VAS and NRS tools, not only does it capture pain severity (derived from the average of four NRS pain intensity questions)[116], but also calculates an accompanying pain interference score, derived from seven items which evaluate how pain affects ability to participate in activities of daily living. Together, these scores produce an overall rating between zero and 70, reflecting the intensity, chronicity, and functional impact of pain[115].

With a completion time of approximately five minutes, and multidimensional approach to pain assessment[117], the BPI is particularly valuable when assessing individuals with co-occurring OUD and chronic pain[114]. Notably, it has been endorsed by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) for use in chronic pain trials due to its "reliable, validated assessment of pain's impact on physical functioning"[118].

With respect to its applicability to persons with co-occurring OUD and chronic pain, the BPI was used by Hall and colleagues to assess the relationship between pain interference and central sensitization (an abnormal state of responsiveness of the nociceptive system)[119] in 141 patients with OUD[120]. Nearly 90% of participants reported chronic widespread pain, often meeting diagnostic criteria for fibromyalgia, and those with higher levels of central sensitization (assessed by the American College of Rheumatology Fibromyalgia Survey), were more likely to report BPI pain interference as a reason for delaying OUD treatment, continuing and escalating opioid use, and returning to non-medical opioid use. In short, the BPI assesses multiple dimensions of pain, providing a more comprehensive characterization than unidimensional intensity scales like the VAS or NRS as is appropriate for chronic, as opposed to acute, pain.

4.1.4 McGill Pain Questionnaire

The McGill Pain Questionnaire (MPQ) prompts persons with chronic pain to rate (0 = not at all, 1 = mild, 2 = moderately, and 3 = severe) the degree that they feel certain types of pain sensations (throbbing, tiring, heavy, stabbing, etc.)[121]. With three subscores (affective pain, sensory pain, and total pain), the MPQ attempts to capture how an individual's pain experience is divided into affective and sensory components[121].

De Aquino and colleagues used a 15-item version of the MPQ to assess the sensory and affective dimensions of an acute pain experience among methadone-maintained persons with OUD in a randomized, placebo-controlled study to investigate the acute analgesic effects of 10 mg or 20 mg of delta-9-tetrahydrocannabinol

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(THC)[122]. Participants reported significant relief on the MPQ to an experimental pain stimulus in the THC conditions, with predominant effects on sensory rather than affective components of the pain experience.

In another randomized trial conducted by Latif and colleagues, a Norwegian version of the Short-Form MPQ was used to evaluate chronic pain in 143 individuals with OUD randomized to either 12 weeks of naltrexone or buprenorphine[123]. No differences in MPQ chronic pain reports were found after patients transitioned from non-prescribed opioid use to either buprenorphine or naltrexone; additionally, a 36-week follow-up found no increase in MPQ pain scores for those continuing naltrexone or those switching from buprenorphine to naltrexone. These studies provide preliminary evidence of the utility of the MPQ in assessing pain in persons with OUD.

4.2 Behavioral Observation

Behavioral observations assess pain through the visual inspection of patients' responses or actions. These techniques are especially useful for those who may have difficulty self-reporting their pain, such as children[124], the critically ill[125], sedated patients[126], and individuals with cognitive impairment[127]. Other pain-related behavioral findings identified in the literature include changes in facial expressions, affect, agitation, irritability, and the use of self-soothing or distraction techniques[128]. For those with OUD, shifts in behavior related to pain may include social withdrawal, which has been identified as a potential consequence of chronic pain that may contribute to worsening OUD symptoms[129]. However, the literature specifically examining the role of these techniques in assessing pain among persons with OUD is insipient.

4.2.1 The role of technologies for behavioral observation in OUD

In addition to simple observation of pain-related behaviors, more objective tools have been employed to quantify several behaviors commonly associated with pain in individuals with OUD. Of note, an important limitation is that the following studies did not specifically assess pain, and therefore, these results need to be extrapolated with caution.

In a human laboratory study, Teeters and colleagues randomized 39 individuals with OUD to either a 15-minute laboratory stress or no-stress condition followed by exposure to opioid cues[130]. Opioid craving was measured, using a craving VAS before and after exposure to opioid cues, and sleep duration using the Pittsburgh Sleep Quality Index[131] and actigraphy. The study found that participants in the no-stress control group who reported shorter average nightly sleep duration had higher levels of opioid craving following opioid cue exposure. These suggest that poor sleep increases vulnerability to opioid craving, which could increase the perceived need for opioids to manage pain. As a final example, Salgado García and colleagues analyzed biosensor data from 46 patients who underwent dental surgery and received opioids after extraction. Based on metrics such as skin conductance and accelerometry, machine learning models could identify periods in which patients were using opioids with an accuracy of up to 83.7%[132].

Lambert and colleagues used sternal accelerometers to monitor involuntary movements in 23 patients undergoing opioid withdrawal, which has substantial clinical overlap with the pain experience[133]. The study revealed that patients exhibiting sinusoidal wave patterns in their accelerometry data, indicative of periodic leg bouncing and foot tapping, had worsening withdrawal symptoms, measured using the COWS. This finding suggests that accelerometry can identify those at risk of worsening opioid withdrawal. Bertz and colleagues also utilized actigraphy watches and electronic diaries to assess the sleep of 37 patients with OUD undergoing methadone or buprenorphine treatment[134]. Their findings suggested that patients experienced shorter sleep periods and delayed sleep timing during periods when they used non-prescribed opioids and cocaine based on urine drug screens. This suggests the potential for actigraphy to be useful in detecting return to non-medical substance use. Therefore, the ability to monitor behaviors quantitatively over time may also provide insights about pain trajectories and volatility, which have also been found to predict non-medical opioid use among persons with OUD[135].

4.3. Physiological indicators

Physiologic indicators of pain refer to measurable changes in the body that occur in response to acute

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painful stimuli. Some indicators include changes in vital signs (e.g., heart rate and blood pressure)[136], skin conductance, pupil dilation[137], and neurophysiological activity[138]. Similar to behavioral observation, these physiological changes have been shown to be useful in patients unable to adequately communicate pain, such as individuals receiving invasive forms of mechanical ventilation in critical care settings[139, 140]. For populations with OUD, they may be particularly helpful in the acute care setting, as these variables may offer clues into needs for higher opioid dosages in the setting of acute pain, particularly as people with OUD usually experience high opioid tolerance.

Respiratory rate is a commonly used physiological indicator of pain. A large observational study including 19,908 patients who called for emergency medical service due to pain, found that respiratory rate had the strongest correlation with patients' self-reported pain intensity compared to other vital signs[141]. This suggests that increased respiratory rate is a useful indicator of acute pain. It should be noted, however, that opioids directly depress respiratory activity by acting on opioid receptors in the brainstem[142], therefore, pain-induced increases in respiratory rate might be masked by an underlying opioid-induced respiratory depression. As such, careful interpretation of respiratory rate is required when using it to assess pain in this population, and it may be an unreliable indicator in isolation.

One of the most studied physiological indicators for acute pain assessment is heart rate variability (HRV). HRV refers to the variation in the time interval between consecutive heartbeats[143]. It is influenced by the autonomic nervous system, which regulates the body's response to pain and stress[144]. A study has shown that patients with OUD have lower resting-state high-frequency heart rate variability when compared to patients without OUD, suggesting a disturbed autonomic flexibility in the former[145]. Another study found that opioid withdrawal might induce a reduction in cardiac vagal tone, resulting in increased systolic blood pressure, heart rate, and decreases in heart rate variability[146]. Therefore, the autonomic sequelae of OUD might confound the interpretation of HRV for pain assessment. Still considering cardiovascular markers, blood pressure becomes an additional confounder in the assessment of pain among those using opioids chronically. Because of opioids vasodilating effects, we may not observe pain-related arterial hypertension frequently associated with acute pain[147, 148].

Thus, physiological indicators may not accurately reflect acute pain in patients with OUD due to opioid-induced physiological alterations. It's critical, therefore, to consider these potential confounders in pain assessment; integrating these indicators with self-report measures may offer a more comprehensive and precise pain assessment in this unique population.

4.4 Psychophysical, neurophysiological, and neuroimaging techniques

4.4.1 Quantitative Sensory Testing

Quantitative sensory testing (QST) of pain refers to a series of standardized techniques to quantify sensory experiences through various pain inducing assays. QST-induced nociceptive stimuli can include heat, cold, mechanical, or pressure[149]. Through controlled and calibrated administration of nociceptive stimuli, QST aims to reliably quantify pain and detect abnormalities in pain processing systems. Commonly used QST measures include single-point or static paradigms to a single stimulus, such as threshold (the weakest stimulus sufficient to cause pain) and tolerance (the maximum stimulus tolerated before pain becomes unbearable)[149].

In addition, multiple point or dynamic paradigms can measure central nervous system pain processing, by applying a supra-threshold pain stimuli and closely assessing the pain responses over a defined period of time[150]. Examples of dynamic QST include temporal summation and conditioned pain modulation. Temporal summation involves increased pain perception to repetitive noxious stimuli and reflects augmented spinal cord facilitation, while conditioned pain modulation refers to decreased pain from one stimulus due to a second simultaneous painful stimulus, reflecting descending inhibition[151]. By quantifying these processes, the QST can identify abnormalities in ascending and descending pain pathways. A full QST profile (e.g., batteries containing various modalities of sensory inputs) can typically be completed within an hour and brief (20-minute) batteries have been developed[149].

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Results from a study by Prosser and colleagues show that patients with a history of OUD had higher heat and pain thresholds compared to healthy controls, indicating reduced sensitivity to noxious stimuli[152]. These abnormal heat and pain perceptions persisted even after remission from opioids, which suggests that there may exist subgroups of individuals whose endophenotypes (e.g., aberrant pain modulatory systems) are associated with OUD[152]. Other studies have attempted to correlate QST's detection of hyperalgesia with genetic risks for the development of OUD, further verifying QST's clinical relevance[153-155]. Collectively, these studies support the notion that QST can help us gain insights into the multifaceted nature of pain.

Edwards and colleagues demonstrated that QST may be a predictive tool for identifying patients at high risk for OUD or those with OUD at risk for a worsening prognosis. A total of 91 participants were chronically prescribed at least 50 mg daily morphine milligram equivalents (MME) of non-specified full agonist opioids. Although rates of formally diagnosed OUD were not described in the study, several participants presented with opioid craving and tolerance, and some had already started non-medical opioid use, potentially qualifying for at least mild OUD. In this longitudinal study, participants classified as high-risk for non-medical opioid use exhibited increased pain sensitivity and decreased pain threshold and tolerance across multiple pain modalities, regardless of whether or not they already used opioids non-medically[156]. The high-risk group patients also presented with higher rates of hyperalgesia.

Echoing Edwards' findings, Compton and collaborators[157] identified differences in QST responses between patients with chronic pain who developed OUD after starting prescribed opioid therapy (n=20) and those who did not (n=20). In this cross-sectional study, they demonstrated worsened temporal summation results and increased pain sensitization among those patients who developed OUD. These results indicate that QST can identify pain phenotypes associated with a higher risk for the development of OUD.

Although QST has the potential to become a practical clinical tool for measuring pain responses in patients with OUD, it is not yet widely clinically available. Much of the existing research with QST and abnormal pain profiles provides strong associations with a risk of OUD, but there is little mechanistic understanding of these associations[149]. There are also several documented instances of interpersonal and intrapersonal variables that affect QST responses, such as age, gender, diet, mood, sleep, etc.[149] Further research into characterizing and understanding how QST is related to these variables is necessary before it can be implemented as a widely available clinical tool.

4.4.2 Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) captures changes in blood flow (as a proxy for brain activity) within the brain during a variety of states to provide insight into how the brain responds to certain stimuli and tasks[158]; it has also been used as a proxy of neural correlates of pain in the human brain[159]. Multiple studies have found that painful stimulation activates regions involved in the so-called "pain matrix" of the brain, including the primary and secondary somatosensory cortices, anterior cingulate cortex (ACC), and insula[160, 161]. Similarly, fMRI studies reveal not only alterations in brain activity associated with pain states but also specific abnormalities in regions related to reward and emotion regulation — such as the thalamus, striatum, and prefrontal[162, 163].

Focusing specifically on persons with OUD, a prospective, non-blinded, single-arm pilot study by Faraj and colleagues aimed to examine the effects of a 12-week virtual reality (VR) meditative intervention on chronic pain in 15 patients with OUD receiving methadone[164]. The VR-based intervention incorporated therapist-guided martial arts movements, breathing techniques, and meditation exercises using narration and VR technology. Patients completed 30-minute biweekly sessions that taught relaxation through coordinated upper body movements and breathing. During fMRI scans, patients first had a 10-minute resting state scan with their eyes closed. They then watched a 5-minute video designed to evoke mental states related to physical pain, as well as control, social, and mentalizing conditions. Before and after each biweekly intervention session, patients also rated their baseline chronic pain (BPI) and opioid craving on a 0-10 VAS. Results showed VAS ratings of pain, opioid craving, anxiety, and depression decreased significantly after each session compared to pre-session. The fMRI showed that after the 12-week meditation intervention, patients showed

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reduced activity in the postcentral gyrus, a region involved in processing physical pain sensations, when watching the two video tasks and also exhibited reduced postcentral gyrus connectivity with some other key pain neuromatrix regions, like the anterior cingulate cortex. This provides evidence for the usefulness of the fMRI in assessing the pain neuromatrix activation in individuals with OUD.

In an adjacent population, an experimental pilot study conducted by Dowdle and colleagues evaluated the pattern and amplitude of neural activity associated with acute pain in patients with chronic non-alcoholic pancreatitis who had been using prescription opioids daily for at least six months, compared to gender-matched non-opioid using healthy controls[165]. Twenty-eight participants underwent fMRI and completed the BPI and Current Opioid Misuse Measure to assess pain and opioid misuse. An individualized painful thermal stimulus equivalent to a pain rating of 7/10 was determined using a thermode on capsaicin-sensitized skin. During functional MRI scanning, participants underwent 3 runs of 14-second blocks of the personalized painful thermal stimulus alternating with 19-second blocks of a non-painful 32°C stimulus. Relative to controls, the patient group reported significantly higher pain scores on the BPI and showed significantly greater activity during acute pain in somatosensory cortex, anterior cingulate cortex, and occipital regions. The amplitude of ACC response correlated positively with opioid dose. In summary, this fMRI study demonstrated that compared to healthy controls, patients with chronic pain using prescription opioids have an amplified neural response to acute experimental pain, likely related to hyperalgesia, particularly in pain processing regions like somatosensory and cingulate cortex. Despite not studying people with OUD, as chronic prescription opioid use is different than the disorder, the authors suggest that the fMRI technique helped identify targets for future targeted-treatments pain among people with chronic opioid usage, including OUD.

As demonstrated in this section, few studies have used fMRI studies in patients with OUD have assessed pain as an outcome. Despite that, fMRI has the potential to elucidate brain dysfunction for OUD patients, allowing for a better understanding of their symptoms and experiences, which allows for the future development of treatments that target these symptoms and help maintain remission from opioids. It is important to note that fMRI may be particularly helpful for the measurement of pain-correlates, but not of pain experience itself, which is fundamentally subjective. It is limited in its ability to provide clinically relevant results for the understanding and treatment of OUD in its current state. Development of improved imaging techniques in the future is required to make substantial conclusions on pain and OUD treatment.

4.4.3 Electroencephalogram

Electroencephalogram (EEG) is a technique that measures changes in activity within brain systems and has been used to assess pain associated with evoked potentials (measurable electrical signals in the nervous system that originate from a controlled stimulus) and resting-state EEG[166-168]. EEG is readily available and relatively easy to use, although its uses in studies of OUD are limited[169]. EEG has been used to and evaluate OUD symptoms (e.g., impulsivity, emotional dysregulation, and reward sensitivity)[170-172] and co-occurring chronic pain, as well as assess who may benefit most from analgesics[173].

As sleep quality directly influences wellbeing and poor sleep worsens the experience of pain[174], the use of EEG for assessment of pain in patients with OUD presents as a promising, largely unexplored opportunity. For example, Lewis and colleagues[175] demonstrated, using EEG techniques, that heroin use suppressed REM sleep as well as deep non-REM sleep; notably, these findings were extended to methadone and morphine by Dimsdale and collaborators[176]. Discovery and validation of these abnormal sleep patterns in OUD patients through EEG provoked research into ameliorating these issues with novel treatments, subsequently reducing future risks of patient relapse[177]. EEG has proven to be a powerful tool in preclinical, human laboratory, and clinical research and has the potential to be a useful tool in diagnostics and risk assessment for patients with OUD in a clinical setting. The use of EEG in investigating how these measurements apply to pain for patients with OUD is limited and presents an opportunity for future biomarker research.

5. STRATEGIES FOR IMPROVING PAIN ASSESSMENT IN OPIOID USE DISORDER

5.1 Multidisciplinary pain assessment

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The enduring division of healthcare professionals who typically manage chronic pain and those who treat substance use disorders is a contributing factor to the potentially suboptimal care received by people living with co-occurring OUD and chronic pain[82]. Both pain and OUD treatment present complex clinical challenges that often coexist, necessitating a multifaceted approach to care. Thus, it is expected that the collaboration among professionals from various disciplines (e.g., physicians, nurses, psychologists, social workers, and addiction specialists) results in care that optimizes treatment outcomes and addresses the various facets of these intricate illnesses.

Despite this expectation, there are few studies examining the impact of multidisciplinary teams on pain and OUD outcomes, as well as the quality of the pain assessment provided, with most focusing only on pain-related outcomes but not addiction-related ones. Interdisciplinary pain clinics have been described for various pain conditions[178-183], including patients with co-morbid OUD, and have shown some evidence for reduced daily opioid requirements, pain intensity, and disability[184-186]. When integrated into primary care, these approaches appear to be supported by team members who see them as particularly helpful for comprehensive pain care and improving confidence and self-efficacy[187]. Similarly, specialized opioid treatment programs have integrated pain management as part of their OUD treatment, with positive preliminary results regarding treatment adherence, patient satisfaction, mood, and pain intensity[188, 189].

In cases where clinics have embraced interdisciplinary teams for assessing pain in persons OUD, they commonly integrate a comprehensive biopsychosocial evaluation and diverse, patient-centric treatment strategies, prioritizing functional outcomes and safety[183, 190]. By taking into account the individual's physical, psychological, and social dimensions, multidisciplinary teams can gain a comprehensive understanding of the patient's pain condition and needs, as well as related co-morbid opioid considerations, thereby facilitating multimodal assessments. This comprehensive approach enables the identification and management of pain triggers related to substance use, as well as addressing any barriers to treatment adherence or recovery. Moreover, the interdisciplinary nature of the team ensures that patients receive integrated care, potentially minimizing fragmentation in treatment plans and potentially improving treatment outcomes.

5.2 Training and education for healthcare providers

The significance of interprofessional education on pain assessment cannot be overstated. Particularly as assessing pain in individuals with OUD requires not only efficient, validated tools, but also professionals knowledgeable in the nuanced interactions between the two conditions. For a comprehensive review, it would be impossible to discuss assessments without considering the education of those doing the assessment,

Despite calls for action within undergraduate medical education to address pain as a multidimensional construct and to address biases in pain assessment[191], along with a strong desire to acquire pain-management and addiction-management skills, as indicated in stakeholder analyses[192], there have been limited formal evaluations of the effectiveness of these interventions in improving pain outcomes. Moreover, there is a scarcity of studies specifically designed to investigate the intersection between pain and OUD. From a students' perspective, clinical skill simulation laboratories have illuminated that medical students find cases involving these two interconnected diagnoses intricate and demanding[193].

A recurrent criticism against numerous interprofessional continuing education initiatives is the dearth of assessments measuring tangible improvements in patient outcomes[194]. It is evident that medical students, for example, frequently receive inadequate instruction on pain and addiction management during their medical schooling[195, 196], although there exist several published model curricula that can be employed for both pain and OUD education[197-201]. For example, Stevens and colleagues developed a pain assessment and management curriculum for second-year medical students and compared them with the previous class which did not have access to the curriculum[202]. At the end of third year, both cohorts underwent a clinical skills examination considering different types of pain cases (acute, chronic, and terminal). More intervention students obtained basic (87.2% vs. 76.0%, p=.028) and comprehensive (75.2% vs. 60.9%, p=.051) descriptions of acute pain than control students. Students exposed to the curriculum more often asked about the impact of pain on functioning (40.7% vs. 25.8%, p=.027), advised changes of medication (97.3% vs. 38.7%, p<.001),

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and provided additional medication counseling (55.0% vs. 27.0%, p<.001). However, the authors did not comment on their curricula applications to OUD, exemplifying the scarcity of integrating the two issues.

Educational interventions such as the one described generally lead to enhancements in pain documentation, improvements in patient self-reported pain scores, and pain satisfaction levels[203]. Regrettably, while individual studies and resources exist for addressing pain and OUD separately, few have delved into the co-occurrence of these two conditions. To our knowledge, the scarcity of curricula considering both pain and OUD is pervasive throughout health-care professions beyond medicine, as we also could not find published examples in nursing, psychology, or social work literature.

A significant obstacle to effective pain management in persons with OUD is the prevailing stigma within healthcare systems and among individual providers towards this patient population, impacting patient encounters and treatment outcomes for chronic pain and OUD[204, 205]. Concerning in the previously referenced study by Sobel and colleagues is the early emergence of certain forms of stigma towards patients with OUD at an early stage of medical training[193]. Brief educational interventions hold the potential to significantly reduce stigmatizing beliefs, particularly regarding OUD, among medical professionals[201, 206]. By addressing stigma through education, healthcare providers may adopt an inclusive, patient-centered approach to evaluating and managing pain and OUD, enhancing patient engagement and outcomes.

7. FUTURE RESEARCH DIRECTIONS

In striving towards a more comprehensive and patient-centered approach to pain assessment, thereby improving pain treatment and fostering improved quality of life and outcomes for individuals with pain and OUD, we set out a brief research agenda for next steps on this topic.

First, validating pain scales tailored specifically to individuals with OUD remains an essential undertaking. Understanding how opioid use impacts pain perception is critical to developing accurate and reliable pain assessment tools that consider the unique characteristics of this population (including opioid-pain phenomena such as hyperalgesia, tolerance, and withdrawal. An additional direction includes the use of the data points obtained from these scales to inform patients and shared decision-making regarding medication changes and dose increases, as well as potentially quantifying the analgesic potential of each drug using multimodal methods.

Validating these assessments would involve evaluating their content validity to ensure they measure key pain domains relevant to this population, and its criterion validity by correlating each tool's scores against other pain measures. Construct validity would be assessed by correlating scores with related factors like depression and disability. Its responsiveness, or ability to detect changes over time or with treatment, must also be analyzed. Finally, these tools should demonstrate inter-rater reliability, ensuring consistent scores between different raters, and test-retest reliability to assess score consistency upon repeated administrations.

Second, assessing and validating various technologies and tools for the assessment of pain (e.g., QST, EEG, fMRI) and how they may impact clinical outcomes is needed. QST allows for a more precise evaluation of sensory perception and pain responses. Functional MRI and EEG can offer insights into the neural mechanisms underlying pain and chronic opioid effects, and how they intersect in OUD, with varying degrees of spatial and temporal resolution. Future research should investigate the neurobiological mechanisms underlying pain modulation in OUD and explore potential alterations in pain processing pathways, as these could inform objective methods of pain assessment, as well as using these technologies to expand the role of potential non-opioid analgesic strategies[207]. Integrating these cutting-edge technologies into pain and OUD care may someday allow for mechanistic-based treatment of pain rather than symptom-based management, the current panorama.

Third, we highlight the necessity to advance pain assessment approaches in minoritized populations. Historically biased approaches to pain assessments among these populations have repeatedly resulted in worse clinical outcomes[208]. Recognizing the impact of social stress and racism on the pain experience is essential to address disparities in treatment outcomes. Future research should delve into the social determinants of

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pain experiences, considering racism-related stress, cultural factors, social support networks, and stigma. By understanding these dynamics, healthcare professionals can develop culturally sensitive pain interventions that acknowledge and respect the diversity of experiences within these communities. The groundwork and methodological considerations for the elaboration of anti-racist pain research have been thoughtfully described in the three-part work by Morais and colleagues[208].

Finally, the expansion of pain assessment education for healthcare professionals and the use of multidisciplinary care for pain and addiction management present promising avenues for future research. Particularly refining the training of the professionals involved in the assessment of pain among patients with OUD is as important as improving the assessments themselves. Multidisciplinary education is necessary to guarantee that the various forms of assessments discussed in this manuscript are correctly and widely used.

CONCLUSION

Pain and OUD are complex clinical conditions with consequences that go beyond the biomedical into psychological and societal realms. When combined, the challenge of assessing and properly addressing pain in persons with OUD is magnified, as their pathophysiology, signs, and symptoms overlap and modify each other. In this review, we discussed how pain is a multidimensional biopsychosocial entity, adding nuance to the clinical presentation of OUD. Opioids are capable of modulating pain but can also produce phenomena that challenge their assessment such as hyperalgesia, tolerance, and withdrawal symptoms. For a substantial proportion of individuals with OUD, pain and opioid use become inexorably connected, thus, clinical, and experimental assessments of pain deserve special considerations. Pain inventories, scales, behavioral and physiological findings, as well as technology-based assessments have to be considered carefully, as opioid use and its phenomena reshape traditional assessment of pain in patients without OUD.

Unfortunately, research considering how pain and OUD are interconnected and how these assessments can be clinically used remains relatively undeveloped. For many of the pain assessment methods discussed in this review, there are few clinical trials exploring their applications for persons with OUD. Furthermore, an upstream deficit exists in medical education and multidisciplinary clinical approaches for the co-management of pain and addiction, with very few programs in the country discussing these combined issues. The ongoing opioid crisis demands more than passive acknowledgment; it calls for proactive, informed action. Beyond serving as a review of the available literature on the topic, we present this paper as a call-to-action, as the gaps in knowledge regarding pain assessment in patients with OUD are alarming. As research linking these two areas evolves, considering the needs of diverse populations with complex psychosocial backgrounds, and understanding the role that such psychosocial variables may play in the worsening of pain and OUD, we will be better equipped to reduce these gaps. Given the profound overlap between chronic pain and OUD—and the fact that the opioid epidemic's initial surge is closely tied to inadequate treatment of chronic pain—it becomes clear: our united commitment is essential. Together, pain and addiction clinicians and scientists must strive to improve the assessment of pain in persons with OUD, an important step to curtail the spiraling opioid crisis.

TABLE 1. Methods of pain assessment and considerations in patients with opioid use disorder: an overview.

Instrument	Description	Advantages	Disadvantages	Considerations in OUD	Study Examples
Self-Report Instruments	**Self-Report Instruments**	**Self-Report Instruments**	**Self-Report Instruments**	**Self-Report Instruments**	**Self-Report Instruments**

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Instrument	Description	Advantages	Disadvantages	Considerations in OUD	Study Examples
Visual Analogue Scale (VAS) 1921	A 10-cm line ranging from "no pain to "worst pain imaginable". The patient marks a point on the line to indicate their pain level	- Allows for a wide range of responses, and can be used for non-verbal communication of pain - Sensitive to small changes[209]	- Relies on patients' subjective perception - Cannot be administered verbally - Difficult conceptualization for some patients. - Unidimensional	Subjective pain reporting may be affected by tolerance and hyperalgesia	Muriel et al. (2023)[104] Nielsen et al. (2017)[105] Veldman et al. (2022)[106]
Numeric Rating Scale (NRS) 1978	Patients rate their pain on a scale from 0 (no pain) to 10 (worst possible pain)	- Simple and easy to use - Can be performed verbally in telephone interviews[210]	- Relies on patients' subjective perception - May lack sensitivity due to restricted range[211] - Unidimensional	Restricted range may fail to capture nuances for patients with altered pain perception	Latiff et al. (2021)[114]
Brief Pain Inventory (BPI) 1982	Questionnaire that measures both intensity of pain (sensory dimension) and interference of pain (reactive dimension)	- Multidimensional - Assesses functionality impairments - Short and simple format	- Longer to complete than the VAS or NRS	Useful for capturing multidimensional nature of pain in OUD patients, including functional impairment	Hall et al. (2022)[120]
McGill Pain Questionnaire 1999	Questionnaire that measures multiple pain domains	- Multidimensional - Assesses impairments in function, mood, social life, and sleep	- Longer to complete than the BPI	Useful for capturing details regarding the nature of pain in OUD patients, beyond functional impairments	De Aquino et al. (2023)[122] Latif et al. (2019)[123]
Clinical, Psychophysical, Neurophysiological, and Neuroimaging Techniques	**Clinical, Psychophysical, Neurophysiological, and Neuroimaging Techniques**	**Clinical, Psychophysical, Neurophysiological, and Neuroimaging Techniques**	**Clinical, Psychophysical, Neurophysiological, and Neuroimaging Techniques**	**Clinical, Psychophysical, Neurophysiological, and Neuroimaging Techniques**	**Clinical, Psychophysical, Neurophysiological, and Neuroimaging Techniques**

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Instrument	Description	Advantages	Disadvantages	Considerations in OUD	Study Examples
Behavioral Observations	Observable pain-related behaviors such as facial expressions, body language, changes in interpersonal interactions and changes in activity level as measured by actigraphy and pedometers	- Not self-reported - Useful for patients unable to communicate	- Behaviors can be ambiguous - Difficult to quantify - Prone to observer bias[126]	Opioid-induced hyperalgesia can complicate interpretation of behavioral reactions to pain stimuli	Teeters et al. (2021)[130] Salgado García et al. (2022)[132] Lambert et al. (2022)[133] Bertz et al. (2019)[134]
Physiological Indicators	Objective measures of bodily function such as heart rate, blood pressure, and respiratory rate	- Not self-reported - Useful for patients unable to communicate	- Nonspecific - Many factors can influence physiological responses - Equipment required	Opioid-induced physiological changes, and withdrawal may confound interpretation	Roberts et al. (2022)[145] Levin et al. (2019)[146]
Quantitative Sensory Testing (QST)	Series of standardized tests that quantify sensory experiences. Can use heat, cold, mechanical, or pressure stimuli	- QST is useful for pain phenotyping, assessing threshold, tolerance, habituation, and summation - Helpful to diagnose hyperalgesia	- Not yet optimized for daily clinical usual - Clinical usability data is incipient	QST is a rising tool for assessing opioid phenomena, but its use is yet limited to research settings	Prosser et al. (2018)[152] Edwards et al. (2011)[156] Compton et al. (2020)[157]
Functional MRI	Brain imaging that captures changes in blood flow as a proxy for brain activity.	- Can provide insight into which brain areas respond to certain stimuli and tasks - May serve for validation of therapy responses	- Correlation of brain activation does not necessarily imply a causal relationship - Less available, higher costs	Limited clinically relevant results for the understanding and treatment of OUD in its current state. Findings may be used as biomarkers in the future.	Faraj et al. (2021)[164]

Instrument	Description	Advantages	Disadvantages	Considerations in OUD	Study Examples
Electroencephalogram (EEG)	Technique using measurable electrical signals in the nervous system that originate from a controlled stimulus	- Relatively cheap and easy to employ, readily available - Can be used with other measures in a singular session (e.g., actigraphy)	- Does not provide the same spatial resolution and anatomical localization as neuroimaging - Gathers superficial cortical electrical activation, not inclusive of deeper brain structures.	Emerging use as a biomarker in OUD studies, for example as a predictor of opioid analgesic response	Huhn et al. (2022)[177]

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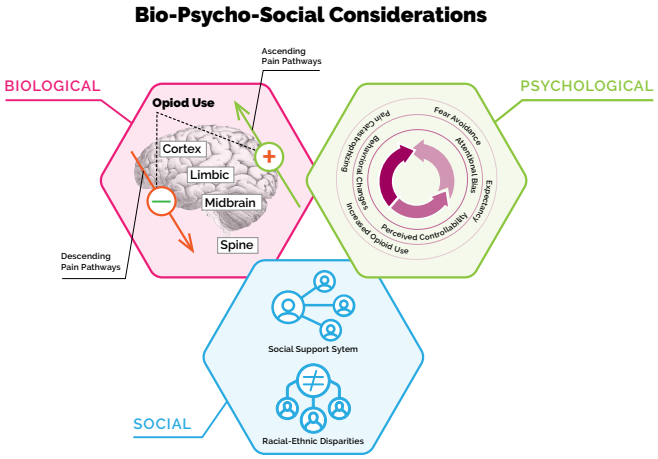
FIGURE LEGENDS

Figure 1. Biopsychosocial considerations in the assessment of pain for persons with opioid use disorder.

Pain and opioid use disorder are multidimensional entities. Biologically, ascending pain pathways carry neural signals from the spine and periphery to the corticolimbic system, which in turn, through descending pathways, modulate the actual physical and emotional experience of pain. Opioids may disrupt such pathways, increasing pain perception (hyperalgesia) and hindering modulatory input. Psychological aspects may alter these perceptions and lead to behaviors and thoughts patterns which in turn, can worsen or improve that experience. Finally, social support networks are a cornerstone of this assessment, as support can improve or worsen outcomes for both OUD and pain treatment. It is also important to acknowledge the role that healthcare disparities may play both in the perception of pain as well as on its treatment.

Figure 2. Opioid-induced hyperalgesia, tolerance, and withdrawal as important considerations for pain assessment in opioid use disorder.

The illustrated table describes the hallmarks to differentiate opioid-related phenomena. Patients with hyperalgesia tend to experience pain symptoms that are different than their original presentation, worsening with increased opioid use. Tolerance leads to worsening pain due to desensitization, but the pain is often similar to the initial symptom and tends to improve with additional opioids. Finally, those patients experiencing withdrawal develop certain signs and symptoms otherwise described in opioid withdrawal assessment instruments, such as the Clinical Opioid Withdrawal Scale (COWS).



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	HYPERALGESIA	TOLERANCE	WITHDRAWAL
MECHANISM	**Sensitization** of pain pathways	**Desensitization** of pain pathways	**Unoccupied opioid receptors**
TIMING	Generally described in **long term**, **high dose** opioid use		Dose reduction or **discontinuation**
RESPONSE	**Worsens** with higher opioid dosages	**Improves** with higher opioid dosages	
SYMPTOMS	**Different** from original pain	**Original** pain worsening	Body **aches**, increased pain **sensitivity**, and psychological **distress**