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EDITORIAL

Pain in the management of opioid use disorder

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Sunil Sirohi[1]
Amit K Tiwari[2]

[1]Laboratory of Endocrine and Neuropsychiatric Disorders, Division of Basic Pharmaceutical Sciences, College of Pharmacy, Xavier University of Louisiana, New Orleans, LA, [2]Department of Pharmacology and Experimental Therapeutics, College of Pharmacy and Pharmaceutical Sciences, University of Toledo, Toledo, OH, USA

Opioids remain the drug of choice for the clinical management of moderate to severe pain. However, in addition to their most effective analgesic actions, opioids also produce a sense of well-being and euphoria, which may trigger significant concerns associated with their use.[1] In fact, there has been an alarming increase in prescription opioid use, abuse and illicit use; and according to the National Center for Health Statistics, the total number of deaths related to opioid overdose has more than tripled from 2011 to 2014.[2–5] Although representing 5.0 % of the global population, studies report that Americans consume 80% of the global opioid supply,[3] and the United States is experiencing an opioid abuse epidemic.[6] Considering this unprecedented rise in opioid consumption, the United States Centers for Disease Control and Prevention has listed prescription opioid overdose among one of the 10 most important public health problems in all the 50 states.[7]

Opioid use disorder (OUD) is defined as a repeated manifestation of 2 or more of 11 problems (e.g., strong desire to use an opioid, use of an opioid in increased amounts, continued opioid use despite negative consequences and withdrawal when the dose of an opioid is decreased) within a 12-month period.[8] Recent studies report a shocking increase in emergency room visits and individuals seeking treatment for OUD.[9] Various pharmacotherapies exist for the detoxification or long-term management of OUD, including opioid antagonists (naltrexone), partial agonists (buprenorphine), opioid agonists (methadone), alpha-2 adrenergic agonists (clonidine) and psychosocial interventions. A detailed account of these interventions is reviewed elsewhere.[10,11] While these medications have better efficacy in the management of OUD compared to non-medication interventions, treatment requires long-term management, and a high rate of relapse is a significant concern posttreatment.[10,12–14]

A growing body of literature suggests a higher prevalence of chronic pain in OUD patients, and approximately 50% of patients maintained on methadone or buprenorphine have been reported to experience chronic pain.[15–18] In addition, heightened psychiatric problems are associated with increased pain intensity in OUD patients receiving opioid agonist-assisted treatment (OAAT).[16] Furthermore, in patients receiving OAAT, chronic pain is associated with poor abstinence rate,[19,20] however, no association has been reported by others.[21,22] Drug craving, defined as an intense urge for a drug experienced previously,[23] is a clinically relevant phenomenon that precedes drug-seeking behavior and has a potential to trigger relapse.[24,25] Craving has been shown to predict lapse to opioid use in patients receiving treatment for OUD,[26,27] and a recent study reported that among

Correspondence: Sunil Sirohi
Laboratory of Endocrine and Neuropsychiatric Disorders, Division of Basic Pharmaceutical Sciences, College of Pharmacy, Xavier University of Louisiana, 1 Drexel Drive, New Orleans, LA 70125, USA
Tel +1 504 520 5471
Email ssirohi@xula.edu

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patients treated for OUD, those with chronic pain had higher opioid craving.[28] Very relevant to the management of OUD is the abnormal pain sensitivity, associated with craving, persisting for months following abstinence,[29] which may adversely impact the treatment outcomes and contribute to relapse.

Opioids remain the most powerful and effective medications for the treatment of chronic pain associated with various medical illnesses.[30] First reported in patients receiving repeated morphine injections,[31] a paradoxical state of heightened pain sensitivity called opioid-induced hyperalgesia (OIH) emerges following chronic opioid therapy, potentially as a consequence of neuroadaptations in the nociceptive pathways.[32,33] In this subset of the population, OUD is highly prevalent and even higher doses of opioids are ineffective in controlling pain, a phenomenon collectively referred to as opioid overuse pain syndrome.[34–36] OIH has also been documented after rapid titration with intravenous morphine in cancer patients.[37] Studies have shown that one in five cancer patients is at significant risk of developing OUD, and this risk is much higher when combined with alcohol and smoking.[38] Although OIH and tolerance appear to share similar symptoms (i.e., reduced analgesic response to opioid treatment), OIH distinctly differs from tolerance. Whereas an increase in opioid doses may overcome tolerance, this similar approach might intensify pain intensity in a patient with OIH.[32] Furthermore, in patients receiving opioid medication for chronic pain, the self-reported craving has been reported to predict aberrant use of prescription opioids.[39] In short, chronic opioid therapy may induce a state of increased pain intensity, which may facilitate opioid overuse/misuse and development of OUD.

OUD and chronic pain may be best framed as a syndrome. Furthermore, certain psychiatric pathologies are frequently comorbid with chronic pain, which can further intensify pain symptoms.[40,41] As a result, in patients receiving opioid agonist therapy for chronic pain and/or OUD, undertreated or untreated pain conditions may have adverse consequences.[28] Therefore, patients receiving OAAT for OUD should be screened for pain conditions, and chronic pain must be considered as an additional target for treatment. This, however, could be challenging due to the lack of well-accepted and specific protocols to assess and treat chronic pain in OUD patients receiving OAAT. Furthermore, even well-experienced practitioners express concerns over diagnostic and clinical decision making in the management of chronic pain comorbid with OUD.[42–44] A significant disparity in pain management under these conditions may also stem from prioritizing treatment for either OUD or chronic pain.[42] It is important to understand that OUD and chronic pain may be a result of neuroadaptations in the nociceptive circuitry following prolonged opioid exposure. Insufficient understanding of this interplay coupled with inadequate management of either condition could contribute to relapse and treatment failure. Considering this complex, intertwined relationship between chronic pain and OUD, a multidisciplinary approach of treating both the states is warranted. Providing necessary training, which emphasizes the critical interaction among chronic pain, opioid dependence and tolerance, could equip clinicians to address these unmet needs. In the case, providing a comprehensive treatment plan is not feasible in one clinical setting; OUD treatment providers must work closely with pain clinicians to ensure that both chronic pain and addiction components are addressed completely. In addition, managing comorbid psychiatric complications that may regulate chronic pain state may be necessary to maximize treatment benefits. Further research is necessary to evaluate novel screening, protocols and improved medications to treat chronic pain in OUD patients receiving OAAT. Although challenging, an appropriate evaluation and treatment strategy that adequately treats pain conditions in this population may hold promise in the successful management of OUD with better outcomes.

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