

Management Of Opioid Withdrawal Symptoms with Opioid Use Disorder

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Abstract—Opioids are a mainstay in acute pain management and produce their effects and side effects (e.g., tolerance, opioid-use disorder and immune suppression) by interaction with opioid receptors.

Opioids are class of drugs that include the illegal drug heroin, synthetic opioids such as fentanyl, and pain relievers available legally by prescription, such as oxycodone (OxyContin), hydrocodone (Vicodin), codeine, morphine, and many others.

According to the brain opioid theory of social attachment, endogenous opioids, specially μ -opioids, are released by experiences of social bonding and mediate the pleasant feelings stemming from social bonding and affiliation

Index Terms—Analgesics-non-narcotic, analgesics-opioid, opioid-related disorders, receptors-opioid.

I. INTRODUCTION

- Opium and its derivatives are among the earliest medicinal compounds known to man, with first use traced back more than 5,000 years.
- Opiates were available over-the-counter” in the United States in the early 20th century and were widely used for treatment of headache, toothache, diarrhea, insomnia, anxiety, cough, and other common ailments.
- This unrestricted access led to widespread opioid overuse and misuse. In the late 1800s, opioid dependence prevalence rose to levels of an opioid crisis that rivals that of today.
- Federal restrictions on opioid access in the early 1900s led to significant suffering and death from illicit access to opioids, because in part no effective treatment were available for the opioid withdrawal symptoms (OWS) that inevitably follow abrupt discontinuation of opioids.
- Today US health care providers find themselves in the midst of another opioid crisis, OWS have safe and effective treatments available.

- While increased restrictions on opioid prescribing have begun to take effect, opioid dependence continues at record levels due to multiple factors including continued over-prescribing and diversion of these family and friends’ licit supplies.
- Other contributors are the low prices of street heroin and its augmentation using illicit fentanyl, which has extremely high potency and low cost of production compared morphine⁽¹⁾

II. HISTORICAL OVERVIEW

Opioids had been used for pain relief for thousands of years before William Morton demonstrated the 1846. The leap from analgesia to anesthesia temporarily reduced the clinical use of opioids as analgesics in the United Kingdom and the United States. However, opioids were soon once again included in the practice of anesthesiology but as an adjunct to inhalational agents.

A. Opioids in the 19th Century:

In addition to Morton’s ether demonstration in 1846, other occurrences in the 19th century are of historic importance. Friedrich Serturmer isolated morphine from opium in 1803. Codeine (methyilmorphine), molecular formula C₁₈H₂₁NO₃, was isolated from opium in 1832. Eventually, 20 pharmacologically active alkaloids in opium were reported. Codeine remains the most commonly used opioid derivative today, either alone or combined with dextromethorphan as an antitussive.

B. OPIOID USE DISORDER

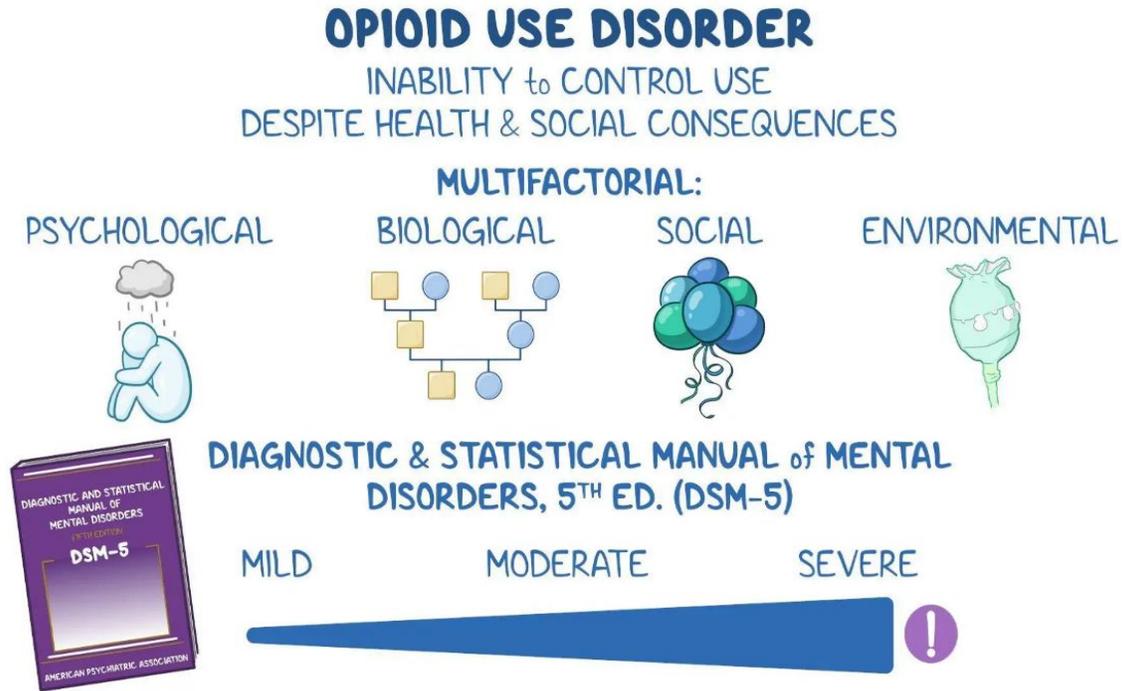
- OUD is a treatable and relapsing chronic illness, with a limited success rate if merely treated with a detoxification.
- The severity of OUD is defined by varying levels of problematic opioid misuse in the Diagnostic

and statical Manual of Mental Disorders, Fifth Edition (DSM-5).

- Presence of 2-3 criteria is considered mild, 4-5 moderate, and 6 or more is sever on the OUD are critical for distinguishing OUD from appropriate medical use of opioids, such as in while patients undertreated for pain may occasionally escalate opioid dosing, patients exhibiting multiple aberrant behaviors, or sometimes a single serious behavior are more likely to fall into the OUD diagnosis.
- Differentiating physiological dependence with OUD depends on the patient meeting the DSM-5 criteria, and most OUD patient meet six or more of these criteria.
- Medically managed OWS is typically the treatment of choice for physiological dependence

without OUD and may be followed by restarting the same opioid analgesics that were needed before physiological dependence and its side effects or medical risks from respiratory depression prohibited further opioid dose escalation.

- Chronic use of opioids whether as a part of OUD or for legitimate medical use as analgesia leads to tolerance to their effects and distressing OWS when opioids are discontinued or dosage is reduced⁽²⁾
- These OWS begin soon after opioid discontinuation, are often severe, and may motivate patients to restart opioids in the early days after opioid discontinuation or prevent them from attempting to stop opioids at all.

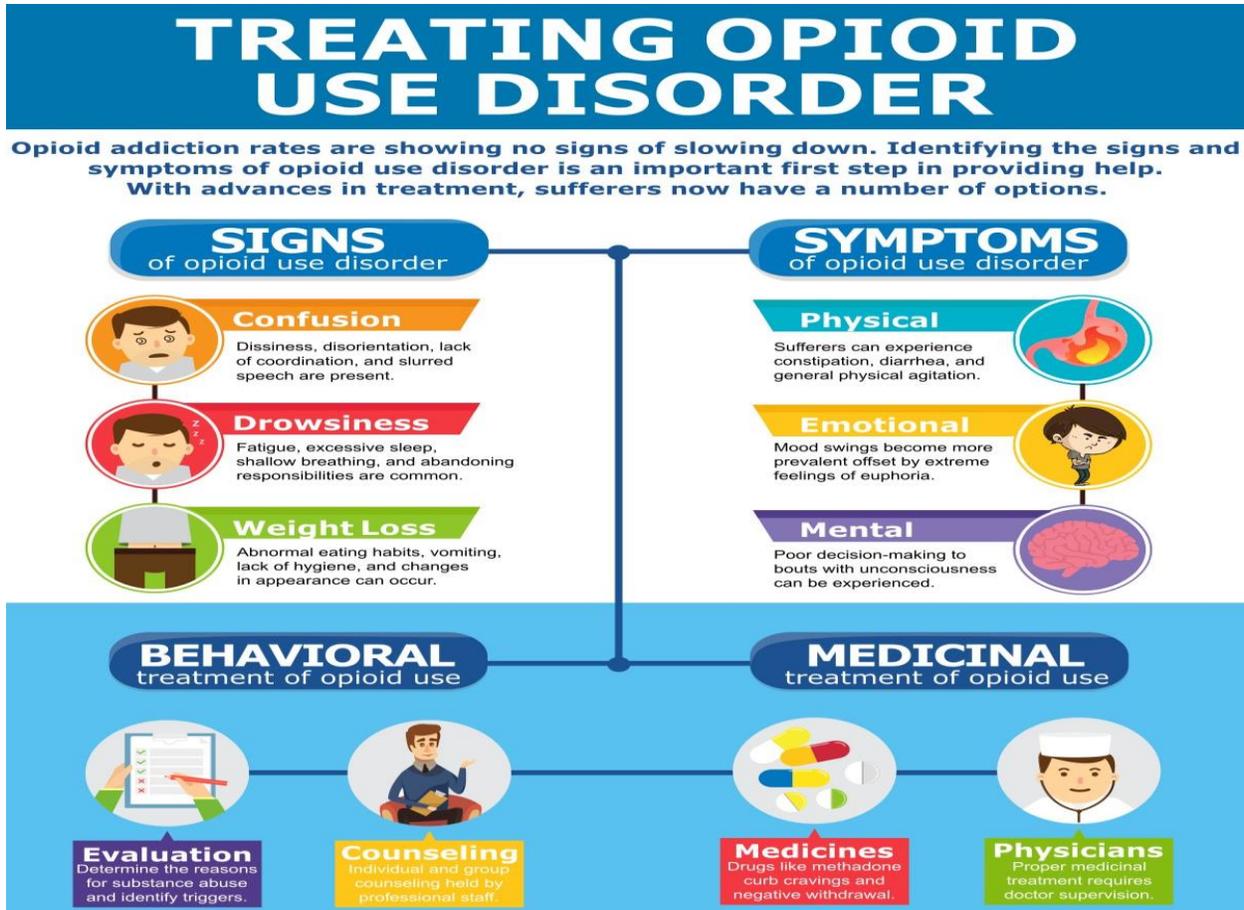


C. Burden of Opioid Withdrawal Symptoms

- The severity and duration of OWS varies as a function of the half-life of the opioid, the duration of opioid use, and patient-specific characteristics including health status.
- Abrupt cessation of short-acting opioids (eg, heroin, hydrocodone, and oxycodone) is associated with severe OWS that typically begin within 12 hours after a missed dose, peak at 36-72

hours, and gradually taper off over the following 4-7 days.

- Conversely, patients also report OWS as a primary motivating force for seeking OUD treatment.
- Effective treatment of OWS may stabilize patients and set the stage for motivating patients to discontinue opioid use and enter longer term treatment⁽³⁾



D. Etiology of Opioid Withdrawal Symptoms:

Repeated use of opioids leads to complex adaptations in the brain and other organs. These other organs include the gastrointestinal (GI) system, which has mu opioid receptors that contribute to diarrhea, nausea and vomiting. We address these GI symptoms and their treatment later in this paper.

Our initial focus is on the brain, and in a simplified view, changes can be ascribed to three major brain circuits that underlie different components of OUD⁽⁴⁾

E. Management of opioid withdrawal Symptoms: Clinical Scenarios:

Clinicians should strive for early diagnosis and treatment of OUD to avoid progression to a greater severity of the disorder. Very early recognition of physical dependence on opioids, prior to development of psychological dependence, could prevent OUD.

Patient education is helpful. Patients may be unaware that opioid physical dependence can develop within weeks of starting opioids and may initially attribute OWS to having a cold or the flu, rather than withdrawal of opioids, because the symptoms are so similar.

F. Physically dependent on Opioids with Psychological dependence in patients with pain:

Repeated daily use of opioids may result in some level of physical dependence within days to weeks. With long-term use, opioid tolerance and physical dependence is inevitable.

Patients who initially had legitimate medical needs for opioid analgesia may find themselves physically dependent on opioids without the psychological component, and without a medical need to continue opioids⁽⁵⁾

G. Management of Opioid withdrawal symptoms: Non-Opioid Pharmacological Options:

α -2 adrenergic agonists and supportive medications targeted to specific symptoms provide the basis of non-opioid treatment.

However, as noted above a range of medications are commonly used off-label for symptomatic management of insomnia, diarrhea, anxiety, and other withdrawal symptoms.

These medications have included anticholinergics, antidepressants, antipsychotics, loperamide, and

benzodiazepines in spite of the abuse potential of these last two agents⁽⁶⁾

H. α -2 Adrenergic Agonists:

α -2 Adrenergic Agonists are the mainstay of non-opioid OWS treatment.

Their anti-adrenergic action through auto-receptor feedback inhibition specifically targets the constellation of symptoms generated by opioid withdrawal -induced noradrenergic hyperactivity⁽⁷⁾

I. Supportive Medication:

Supportive medications for residual OWS target particular symptoms. Insomnia is one of the most frequently reported OWS and sleep aids such as eszopiclone, zolpidem, or low doses of doxepin or trazadone are useful.⁽⁸⁾ Recommendations include nonsteroidal anti-inflammatory drugs and acetaminophen for musculoskeletal pain, and cyclobenzaprine or other anti-spasmodics for muscle spasms.

III. CONCLUSIONS

OUD and opioid physical dependence, a precursor to OUD, affect millions of Americans resulting in morbidity and an increasing number of opioid-overdose fatalities. Discontinuation of the problematic opioid often results in severe OWS, creating a barrier to opioid cessation and further OUD treatment. Effective treatment of OWS is a crucial first step on the pathway to successful OUD treatment. Although OAT treatment for OWS is desirable for many patients, non-opioid treatments are needed in a variety of situations that are not favourable for OAT or when OAT is inadequate alone. α -2 adrenergic agonists and supportive medications help fill this void and provide a gateway to further treatment. Future work needs to amplify and more carefully test these supplemental medications, particularly in combinations with lofexidine and with consideration for optimal matching of medication combinations with specific patients based on biomarkers such as genetic polymorphisms.

REFERENCES

- [1] Booth M. Opium: A History. New York,NY: St Martin's Press; 1996.
- [2] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th

edn. (DSM-5). Arlington, VA: American Psychiatric Association: 2013.

- [3] Passik SD, Krish KL. Assessing aberrant drug-taking behaviors in the patient with chronic pain. *Curr Pain Headache Rep.* 2004; 8:289-294.
- [4] Kosten TR, George TP. The neurobiology of opioid dependence:Implications for treatment. *Sci Pract Perspect.* 2002; 1:13-20.
- [5] Pappas S. Opioid crisis has frightening parallels to drug epidemic of late 1800's. Live Science website. <https://www.livescience.com/60559-opioid-crisis-echoes-epidemic-of-1800s.html> Published September 29,2017. Accessed March 6,2018.
- [6] Theisen K, Jacobs B, Macleod L, Davies B. The United States opioid epidemic: a review of the surgeon's contribution to it and health policy initiatives. *BJU Int.* 2018 Nov;122(5):754-759. [PubMed]
- [7] Højsted J, Sjøgren P. Addiction to opioids in chronic pain patients: a literature review. *Eur J Pain.* 2007 Jul;11(5):490-518. [PubMed]
- [8] 8. John WS, Zhu H, Mannelli P, Schwartz RP, Subramaniam GA, Wu LT. Prevalence, patterns, and correlates of multiple substance use disorders among adult primary care patients. *Drug Alcohol Depend.* 2018 Jun 01; 187:79-87. [PMC free article] [PubMed]