

# Review Article: Effective Management of Opioid Withdrawal Symptoms: A Gateway to Opioid Dependence Treatment

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**Background and Objectives:** The opioid crisis has taken an immense toll in the United States. On average, five lives are lost to an opioid overdose every hour of the day; estimated costs associated with opioid misuse exceed \$500 billion annually. Illicit opioid discontinuation is the first step in the treatment of opioid use disorder (OUD), and transition to an opioid agonist may initiate treatment. However, discontinuation to abstinence from either OUD directly or following agonist treatment results in severely distressing opioid withdrawal symptoms (OWS).

**Methods:** This review evaluated studies on the etiology, burden, and management of OWS.

**Results:** Noradrenergic hyperactivity generates many OWS. These OWS can cause patients to relapse during early opioid discontinuation. While agonist therapies are generally first-line for moderate or severe OUD and reduce OWS, prescribing restrictions can limit their availability.

**Discussion and Conclusions:** Non-opioid medications to treat OWS provides a gateway into long-term treatment with naltrexone or psychosocial therapies. For opioid dependent patients without OUD, non-opioid treatments like  $\alpha$ -2 adrenergic agonists can facilitate opioid tapering.

**Scientific Significance:** For the millions who are physically dependent on opioids, new treatments for OWS can enhance recovery from OUD and prevent relapse. (© 2019 The Authors. *The American Journal on Addictions* Published by Wiley Periodicals, Inc.;28:55–62)

*Soft hangs the opiate in the brain, And lulling soothes the edge of pain, Till harshest sound, far off or near, Sings floating in its mellow sphere.*

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From “An Opium Fantasy” by Maria White Lowell, published 1855.

## INTRODUCTION

Opium and its derivatives are among the earliest medicinal compounds known to man, with first use traced back more than 5,000 years.<sup>1</sup> 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 treatments were available for the opioid withdrawal symptoms (OWS) that inevitably follow abrupt discontinuation of opioids.<sup>2</sup>

Today US healthcare 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. The cost of this crisis is immense whether measured in human lives or US dollars. Based on estimates from 2016, 12 million Americans misuse opioids; and for approximately 2 million Americans, misuse was severe enough to be categorized as an opioid use disorder (OUD).<sup>3</sup> On average, 5 Americans died of an opioid overdose every hour, contributing to a decrease in the average life expectancy for 2016.<sup>4,5</sup> The financial cost of the morbidity and mortality associated with opioid misuse was recently

estimated at 504 billion dollars annually.<sup>6</sup> Clearly, OUD is a current public health crisis.

## 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 Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* (Table 1). Presence of 2–3 criteria is considered mild, 4–5 moderate, and 6 or more is severe on the OUD spectrum.<sup>7</sup> The aberrant psychosocial behaviors associated with OUD are critical for distinguishing OUD from appropriate medical use of opioids, such as in patients with cancer who need analgesia for chronic pain. While patients undertreated for pain may occasionally escalate opioid dosing, patients exhibiting multiple aberrant behaviors, or sometimes a single serious behavior (such as forging a prescription) are more likely to fall into the OUD diagnosis.<sup>8</sup> Differentiating physiological dependence with OUD depends on the patient meeting the DSM-5 criteria, and most OUD patients 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.<sup>9</sup> 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.<sup>10,11</sup> Improvements in treatment of the OWS has the potential to increase entry into OUD treatment programs that require opioid abstinence such as many criminal justice or residential programs and naltrexone with outpatients.

## 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. Withdrawal from buprenorphine, a long-acting opioid, can be less severe than withdrawal from short-acting opioids and of similar duration. Withdrawal from methadone also produces milder symptoms; however, they may last 2 weeks or more.<sup>12</sup>

The types of symptoms experienced may vary from patient to patient but are similar regardless of the type of opioid used (ie, long- vs short-acting). Table 2 lists commonly reported OWS that occur acutely after opioid discontinuation.

Although OWS will generally resolve after 5–14 days (depending on the half-life of the opioid), the distress in the first few days after discontinuation is severe. Without adequate treatment, many patients are unable to complete opioid

**TABLE 1.** DSM-5 criteria for OUD<sup>7</sup>

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period of time than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A lot of time is spent in activities to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance<sup>a</sup> as defined by either of the following:
  - (a) A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
  - (b) A markedly diminished effect with continued use of the same amount of an opioid.
11. Withdrawal<sup>a</sup>

*DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; OUD, opioid use disorder.*

Severity: Mild, 2–3 symptoms; moderate, 4–5 symptoms; severe, 6 or more symptoms.

<sup>a</sup>This criterion is not met for individuals taking opioids solely under appropriate medical supervision.

**TABLE 2.** Opioid withdrawal symptoms<sup>13,14</sup>

|                                       |                        |
|---------------------------------------|------------------------|
| • Aches/pain                          | • Hot flashes/chills   |
| • Muscle spasms/twitching/<br>tension | • Heart pounding       |
| • Tremor                              | • Lacrimation          |
| • Abdominal cramps                    | • Sweating             |
| • Nausea/vomiting/diarrhea            | • Rhinorrhea           |
| • Anxiety/restlessness                | • Pupillary dilatation |
| • Irritability                        | • Yawning              |
| • Insomnia                            | • Gooseflesh           |

discontinuation.<sup>15,16</sup> While pain relief, relaxation, self-medication of depression and anxiety, or pleasure-seeking may be the initial reason for use of opioids, with prolonged use, avoidance of OWS often becomes the most powerful force driving continued use.<sup>10</sup>

*You don't get high after a while. You just need it so you're not sick. You have to have that balance. There are some days where you're so dope sick, you can't even get out of bed.*<sup>17</sup>

In a study that included patients with chronic pain, 56.5% of patients initially using prescription opioids for pain relief reported the primary reason for continuing use was to avoid OWS.<sup>11</sup> In another study of opioid analgesic misuse, OWS were most frequently cited as the reason for transitioning from opioid analgesics to heroin,<sup>18</sup> presumably because of its greater availability and lower cost.<sup>19</sup>

*Heroin is like a dark word. It's like a danger. Like, heroin is the worst drug a person can do, but when you get sick from Percocet, you are so sick you don't care. You just want that sickness to be gone.*<sup>18</sup>

Conversely, patients also report OWS as a primary motivating force for seeking OUD treatment.<sup>20</sup> Effective treatment of OWS may stabilize patients and set the stage for motivating patients to discontinue opioid use and enter longer term treatment.

*Right before I entered my first treatment program, I was not 'getting high' any more, I was purely seeking the drug to stay well. I was tired of being addicted but could not stop using on my own. I would get into the withdraw symptoms and need to use because I would get too sick. I would beg, borrow or steal just to be able to get money to get opioids. . .*<sup>20</sup>

## 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. Opioid-induced changes in mesolimbic reward circuits (including the ventral tegmental area and its projections to nucleus accumbens, prefrontal cortex, and amygdala) are believed to underlie the pathophysiology of opioid craving, compulsive use, and depression during OWS. The insomnia in OWS is driven through the ascending reticular activating system originating in the brainstem, thalamus, and hypothalamus. However, many of the physical dependence symptoms during opioid withdrawal are generated primarily by changes in a different brain pathway—the locus coeruleus (LC) in the brainstem and its projections, which include projections to the reticular activating system.<sup>21</sup>

The LC contains norepinephrine (NE) neurons and has major inputs to the prefrontal cortex, hippocampus, and amygdala.<sup>21</sup> The LC is involved in regulation of attention, vigilance, and autonomic nervous system function. When an opioid drug binds to  $\mu$ -opioid receptors on LC neurons, enzymes in the cyclic adenosine monophosphate (cAMP) pathway are inhibited, LC neurons decrease their firing rate, and less NE is released. This results in acute opioid effects, including drowsiness and reduced blood pressure, respiration, and muscle tone. After repeated use of opioids, LC neurons adapt to this opioid inhibition by increasing enzyme supply and activity causing the cAMP pathway to be upregulated and produce “normal” levels of cAMP. Thus, LC firing rate and NE release return to normal levels. However, once opioid tolerance has developed, abrupt cessation of opioids causes the LC to become hyperactive. Too much cAMP is produced, and excessive quantities of NE are released for days or weeks until LC neurons readapt to the absence of opioids. This noradrenergic hyperactivity is the primary neurobiologic underpinning of acute OWS (Table 2).<sup>9,22</sup>

## 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.<sup>18</sup>

Once OUD or opioid physical dependence is recognized and the patient requests or consents to treatment, a long-term treatment strategy must be defined. OUD is a chronic disorder and often requires long-term or even life-long treatment. The treatment goal will guide OWS treatment strategies.

Dependence on opioids occurs in a variety of patient types and clinical situations, which leads to different patient preferences and treatment strategies. Table 3 lists factors that will influence the approach to treatment.

Regardless of the ultimate treatment goal, management of acute OWS is the first step during opioid discontinuation or dose reduction. For patients using short-acting opioids, OWS will emerge within 18–24 hours of the first missed dose. Failure to recognize and manage OWS may cause patients to abandon their recovery attempt at the outset while effective OWS treatment serves as a bridge to longer-term treatment. However, a detailed discussion of OUD treatment after the early phase of opioid withdrawal is beyond the scope of this review (for review, see ref.<sup>23</sup>). For patients whose treatment goal is maintenance with opioid agonist therapy (OAT) (eg, methadone or buprenorphine), these drugs are ideally started during early opioid withdrawal because they are effective for relieving acute OWS as well as for long-term treatment of OUD. OAT is generally recommended as first line for patients with moderate or severe OUD.<sup>24</sup> While a slow tapering of the OAT dosage over weeks or months can also substantially reduce OWS, final discontinuation of OAT will lead to expression of OWS, which can benefit from the medications reviewed in this paper. Studies have compared these dosage tapers to other approaches, but details of these dosage tapers are not covered in this paper.

Several clinical situations are inappropriate for OAT, or OAT may be unavailable due to geographical, legal, or other restrictions in provider availability. These situations are important to recognize in order to maximize successful treatment of OWS and to promote continuing treatment of OUD or tapering of opioids (Table 4). The clinical scenarios

described below are not a comprehensive list of inappropriate situations for using OAT, but focus on some common situations where non-opioid treatments for OWS may be desirable.

### Physically Dependent on Opioids Without 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. They do not meet the diagnostic criteria for moderate or severe OUD but may experience distressing OWS that will impede them from stopping opioids.

As the dangers of long-term opioid analgesic use are becoming apparent, the practice of treating chronic non-cancer pain with opioids is no longer acceptable aside from a minority of situations where benefits outweigh risks.<sup>25,26</sup> For many patients, cessation of opioid analgesia may be in their best interest not only to avoid progression to OUD but also because opioids may become less effective over time and can even increase pain sensitivity.<sup>27</sup> However, convincing patients with pain to stop opioids is often difficult, especially in those maintained on opioids for years.<sup>23</sup> Patients may understandably misinterpret opioid tolerance and hyperalgesia as a need for continued use or for higher doses of opioids. Additionally, pain and hyperalgesia are symptoms that commonly occur during opioid withdrawal,<sup>28</sup> again reinforcing patients' fears that they must use opioids to avoid pain and discomfort. These

**TABLE 3.** Overview of considerations in OUD treatment

| Patient type   | OUD characteristics   | Treatment goals <sup>a</sup>   |
|--|---|--|
| <ul style="list-style-type: none"> <li>● Opioid analgesic misusers/abusers               <ul style="list-style-type: none"> <li>○ Short-acting</li> <li>○ Long-acting</li> </ul> </li> <li>● Heroin/illicit opioid users</li> <li>● Post-opioid overdose (naloxone treated)</li> <li>● Users of opioid-based maintenance therapy for OUD</li> <li>● Patients with chronic pain</li> <li>● With opioid tolerance or hyperalgesia</li> <li>● No longer requiring opioid analgesia</li> </ul> | <ul style="list-style-type: none"> <li>● Physical dependence only<sup>b</sup></li> <li>● Mild OUD</li> <li>● Moderate/severe OUD</li> </ul> | <ul style="list-style-type: none"> <li>● Maintenance therapy               <ul style="list-style-type: none"> <li>○ Opioid agonist (buprenorphine, methadone)</li> <li>○ Opioid antagonist (naltrexone)</li> </ul> </li> <li>● Transition from opioid-based maintenance to opioid-free</li> <li>● Opioid dose reduction/taper               <ul style="list-style-type: none"> <li>○ With transition to opioid-free</li> <li>○ With maintenance of reduced dose</li> </ul> </li> <li>● Opioid-free               <ul style="list-style-type: none"> <li>○ Residential program</li> <li>○ Psychosocial counseling</li> <li>○ Self-help and 12-step programs</li> </ul> </li> <li>● Transition to opioid-free analgesia or no analgesia</li> </ul> |

OUD, opioid use disorder.

<sup>a</sup>Psychosocial counseling and self-help programs also are recommended in addition to other treatments (eg, maintenance therapy, dose reduction) in patients with OUD.; <sup>b</sup>Physical dependence only (does not meet criteria for OUD but may lead to OUD).

**TABLE 4.** Circumstances where OAT may not be preferred for OWS

| OAT undesirable/inappropriate/inadequate   | OAT unavailable   |
|--|---|
| <ul style="list-style-type: none"> <li>● Mild OUD or physical dependence only               <ul style="list-style-type: none"> <li>○ Patients with chronic pain</li> </ul> </li> <li>● Prior to treatment with naltrexone<sup>a</sup></li> <li>● Patients desiring opioid-free therapy</li> <li>● Tapering off OAT maintenance during the lowest dosages before discontinuation</li> <li>● During OAT induction with buprenorphine when the previous opioid dose has been beyond about 80 mg of methadone daily</li> </ul> | <ul style="list-style-type: none"> <li>● Rural and other areas without OAT access</li> <li>● Post overdose in naloxone-treated patients</li> <li>● Criminal justice system</li> </ul> |

OAT, opioid agonist therapy; OUD, opioid use disorder; OWS, opioid withdrawal symptoms.

<sup>a</sup>As a bridge to naltrexone (opioid-receptor antagonist) during opioid-free withdrawal or during/following OAT-assisted withdrawal.

patients may especially benefit from education on the effects of opioid tolerance.

Although most patients using opioid analgesics long term for non-cancer pain do not meet OUD criteria, one study found that 45% displayed aberrant behaviors associated with OUD,<sup>29</sup> and another study found that the lifetime prevalence of OUD as defined by the *DSM-5* was 35%.<sup>30</sup> Intervention to prevent progression of physical dependence to OUD is key. Centers for Disease Control and Prevention guidelines recommend slowly tapering opioid analgesics with a transition to non-opioid pain management.<sup>25</sup> Non-opioid medications are useful to treat OWS that emerge during opioid dose tapering in patients with mild OUD or physical dependence.

### Tolerance to Opioid Analgesia in Patients With Cancer and Chronic Pain

Up to 90% of patients with advanced cancer experience pain, and opioid analgesia is considered the cornerstone of treatment.<sup>31</sup> However, like any patient having chronic pain, opioid tolerance and hyperalgesia can occur in patients with cancer, and it is a challenge to manage. Switching to a different opioid or dose reduction or withdrawal of the opioid analgesic is a recommended strategy.<sup>32</sup> If opioid doses are reduced or opioids discontinued temporarily, opioid analgesia may become effective again at lower doses. Other therapies including non-opioid medications should be increased during this period of an opioid “reset” back to a non-tolerant state, in which analgesia will again be possible with lower opioid doses.<sup>33</sup> These non-opioid medications include the newly FDA approved  $\alpha$ -2 adrenergic agonist lofexidine, but also have included off-label use of benzodiazepines (prazepam, oxazepam), anti-diarrhea agents like anticholinergics (biperiden) or loperamide, sedating antidepressants (trazadone) and sedating atypical antipsychotics (quetiapine). High doses of either benzodiazepines or the opioid loperamide can be abused, however. Managing tolerance and hyperalgesia with opioid withdrawal or rotation is complex and best handled by a pain medicine specialist. Decreasing tolerance to opioids increases risk for overdose upon restarting opioids.

### Opioid Agonist Therapy Is Undesirable or Unavailable to the Patient

Although buprenorphine and methadone are considered essential medications for moderate or severe OUD, they are not appropriate in all situations. Patient preference for non-opioid versus opioid treatment, previous failure with opioid agonists for OUD treatment, and risks and benefits for the individual patient based on their psychiatric and medical history are among the factors to be considered when choosing OUD therapy.<sup>24</sup>

Additionally, buprenorphine and methadone are controlled substances and not available in all settings. Buprenorphine prescribers are required to have training about using buprenorphine to acquire a Drug Enforcement Administration waiver; methadone can only be obtained through federally certified treatment programs.<sup>24</sup> Rural areas are especially underserved as far as access to physicians able to prescribe OAT, and anti-opioid attitudes within the criminal justice system limit access to OAT.<sup>34,35</sup> Non-opioid treatment of OWS provides a more easily accessible option and time for transition to a qualified naltrexone or OAT provider or other long-term treatment provider. We strongly stress the very high risk of treating OWS without medication because of potential severe medical complications like dehydration from vomiting and diarrhea, as well as dropout and overdose soon after dropout from residential treatment. Thus, OWS should be medically managed in residential (non-medical) treatment programs that may be hesitant or even opposed to using medications.

### Opioid Agonist Therapy Is Inadequate Alone or No Longer Desired

It is critical to minimize OWS during early opioid withdrawal as patients are medically and emotionally fragile and have a limited alliance with the treater leading to drop out of treatment at this time. Concomitant use of non-opioid medications during buprenorphine induction is frequently underused to ameliorate any buprenorphine-precipitated OWS.<sup>36</sup>

For stable patients wishing to discontinue methadone or buprenorphine maintenance therapy, a detailed and

personalized discussion with the patient needs to address the decision to discontinue OAT including how this change will impact their emotional and physical health, their family, and their employment. Following this decision, specific plans should cover using medications to alleviate resulting OWS, and what are the strategies post-discontinuation to minimize the risk of relapse. We recommend very slow tapering of the OAT with use of non-opioid medications to ease OWS and discussion of opioid antagonist induction to prevent relapse to opioid use and dependence.<sup>24</sup>

### Transition to Naltrexone Treatment

Extended-release naltrexone, an opioid receptor antagonist administered as monthly injections, is a US Food and Drug Administration (FDA)-approved option for OUD maintenance treatment and may be a good option for motivated patients who desire opioid-free maintenance therapy. However, to avoid naltrexone-precipitated withdrawal, the manufacturer recommends a minimum 7- to 10-day opioid-free period before naltrexone induction.<sup>37</sup> Few patients are able to achieve this goal without medical assistance and a variety of opioid discontinuation protocols have been employed using short courses of buprenorphine in combination with non-opioid adjunctive medications and sometimes with increasing (but low) doses of naltrexone.<sup>16,38</sup> For patients with lower levels of opioid dependence, non-opioid therapy alone may be adequate to treat OWS after opioid discontinuation or during opioid taper. These adjunctive medications should be started before the OWS begin, and then they are continued on a standing basis, rather than as needed. However, dosage increases may be needed if OWS symptoms emerge during the withdrawal period. Continuing adjunctive non-opioid medication use during the first few weeks of naltrexone therapy is helpful for treatment of residual OWS that occur during stabilization.<sup>38</sup>

### Post-Opioid Overdose

Naloxone administration for opioid overdose saves many lives but may also result in precipitating the OWS. Laypersons or emergency medical services can administer standard naloxone doses but without the ability to titrate. Higher naloxone standard doses have become available recently because of failures of lower doses to overcome overdoses with large quantities of opioids or potent opioids such as fentanyl. Use of excessive naloxone doses, while unavoidable, will also produce distressing OWS.<sup>39</sup> Use of non-opioid medications may provide relief for OWS and are available in an emergency room setting. The ability to keep a patient comfortable during the immediate post-overdose period may provide a critical entryway into further OUD treatment. While buprenorphine has been suggested to reverse overdoses, its slow onset of action, potential to enhance opioid toxicity, and long duration of action compared to naloxone make its risk relatively high. Starting buprenorphine in the emergency department has been examined as an effective intervention, but only after an acute overdose has been fully managed, and after the patient is able to provide full informed consent to buprenorphine treatment.

## MANAGEMENT OF OPIOID WITHDRAWAL SYMPTOMS: NON-OPIOID PHARMACOLOGICAL OPTIONS

$\alpha$ -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.

### $\alpha$ -2 Adrenergic Agonists

$\alpha$ -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.<sup>23</sup> In a 2016 meta-analysis, Gowing et al. reviewed studies comparing  $\alpha$ -2 adrenergic agonists with placebo, with each other, and with decreasing doses of methadone for opioid withdrawal. Most of these studies evaluated clonidine or lofexidine, but other agents include guanfacine and tizanidine.<sup>40</sup>  $\alpha$ -2 adrenergic agonists were superior to placebo for decreasing the severity of OWS and for completing withdrawal to an opioid-free state. These agents showed no significant difference in efficacy from decreasing doses of methadone. Withdrawal severity peaked earlier but resolved sooner with  $\alpha$ -2 adrenergic agonists compared with methadone. Efficacy differences between clonidine and lofexidine were not detected; hypotension was more problematic with clonidine than with lofexidine.<sup>40</sup>

Clonidine is FDA-approved for hypertension and attention-deficit/hyperactivity disorder treatment and is used off-label for treatment of OWS. No new studies of clonidine for OWS treatment have been published since those included in the 2016 meta-analysis noted above.<sup>40</sup> However, a recent evaluator-blinded study of clonidine versus morphine for neonatal abstinence syndrome found clonidine, but not morphine, significantly improved infants' neurobehavioral performance after 2–4 weeks of treatment and clonidine-treated infants required a significantly shorter duration of treatment.<sup>41</sup>

There is no established dosing regimen for clonidine due to its lack of FDA approval for OWS; the maximum daily doses in clonidine studies ranged from .9 to 1.35 mg with dosing 3–4 times per day.<sup>40</sup> As a general rule, for mild withdrawal, clonidine .3 to .6mg daily is typical. For more severe withdrawal, doses up to 1.2 mg daily may be appropriate. Clonidine should be given in divided doses of .1 to .2 mg per dose and can be repeated as often as hourly if needed.<sup>23</sup> A clonidine-experienced physician may titrate clonidine aggressively to get anxiety and other OWS quickly controlled. An instrument that measures OWS severity, such as the Clinical Opiate Withdrawal Scale<sup>13</sup> or Short Opiate Withdrawal Scale of Gossop,<sup>14</sup> can be used to aid clonidine dosing decisions.

Lofexidine has been approved in the United Kingdom and used for treatment of OWS since 1992. Although originally developed as an anti-hypertensive, this indication was abandoned due to lack of expected efficacy in clinical trials.<sup>42</sup> Two recently published double-blind Phase 3 trials of abrupt withdrawal of short-acting opioids were not included in the 2016 Gowing et al. meta-analysis.<sup>40,43,44</sup> In the 8-day trial, lofexidine 3.2 mg daily was superior to placebo for both co-primary endpoints: reduction in severity of OWS on day 3 and length of time patients remained in the trial. In the 7-day trial, mean daily reduction in OWS severity over 7 days was the primary endpoint: lofexidine 2.4 and 3.2 mg daily were superior to placebo. Lofexidine-treated patients were also significantly more likely to complete this trial. Hypotension was among the most common lofexidine-associated adverse event in both trials, but rarely required study discontinuation.<sup>43,44</sup>

The published Phase 3 trials of lofexidine for FDA registration dosed lofexidine at 2.4 and 3.2 mg daily (.6 or .8 mg QID).<sup>43,44</sup> The FDA approved lofexidine in May 2018 and it is the first non-opioid medication indicated for treatment of OWS in the United States.<sup>45</sup> Important safety considerations in using any of these  $\alpha$ -2-adrenergic agonists include orthostatic hypotension and potential fainting or falling, which appears to be significantly less frequent with lofexidine, and dosage adjustment with clonidine particularly, which is not required with the FDA's approved fixed daily dosing of lofexidine.

### Supportive Medications

Supportive medications for residual OWS target particular symptoms. Insomnia is one of the most frequently reported OWS<sup>44</sup> and sleep aids such as eszopiclone, zolpidem, or low doses of doxepin or trazadone are useful. Recommendations include nonsteroidal anti-inflammatory drugs and acetaminophen for musculoskeletal pain, and cyclobenzaprine or other anti-spasmodics for muscle spasms. Medications helpful for nausea include ondansetron, prochlorperazine, and metoclopramide; for diarrhea, loperamide, and bismuth are recommended. Increased oral hydration is important in patients with nausea and vomiting. While the OWS is generally not fatal, death can occur, if rehydration is poorly managed, which has occurred in criminal justice settings. Diphenhydramine or hydroxyzine is helpful for anxiety. If necessary, benzodiazepines can be used with caution, and those with less abuse potential (eg, clonazepam, oxazepam) are preferred. Sigmon et al. provide dosing recommendations for supportive medications.<sup>38</sup>

### CONCLUSIONS

ODU and opioid physical dependence, a precursor to OUD, affect millions of Americans resulting in morbidity and an increasing number of opioid-overdose fatalities.<sup>3,4</sup> 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 favorable for OAT or when OAT is inadequate alone.  $\alpha$ -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 combination with lofexidine and with consideration for optimal matching of medication combinations with specific patients based on biomarkers such as genetic polymorphisms.

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### Declaration of Interest

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