New directions in the treatment of opioid withdrawal

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The treatment of opioid withdrawal is an important area of clinical concern when treating patients with chronic, non-cancer pain, patients with active opioid use disorder, and patients receiving medication for opioid use disorder. Current standards of care for medically supervised withdrawal include treatment with μ-opioid receptor agonists, (eg, methadone), partial agonists (eg, buprenorphine), and α2-adrenergic receptor agonists (eg, clonidine and lofexidine). Newer agents likewise exploit these pharmacological mechanisms, including tramadol (μ-opioid receptor agonism) and tizanidine (α2 agonism). Areas for future research include managing withdrawal in the context of stabilising patients with opioid use disorder to extended-release naltrexone, transitioning patients with opioid use disorder from methadone to buprenorphine, and tapering opioids in patients with chronic, non-cancer pain.

Introduction

> The treatment of morphine withdrawal in all cases requires the full and constant attention of the doctor.
>
> *Emil Kraepelin, Morphinism (1899)*[1]

Opioid withdrawal is an important clinical syndrome that can cause considerable discomfort, perpetuate drug-seeking behaviour, and preclude engagement in appropriate treatment in patients with opioid use disorder and chronic, non-cancer pain (CNCP).[2] Although conventionally considered non-life threatening, the clinical manifestations of opioid withdrawal can lead to severe fluid loss and electrolyte abnormalities that result in haemodynamic instability and death; necessitating, per Kraepelin's dictum, astute clinical management.[3] For patients with CNCP taking long-term prescription opioids, opioid withdrawal is a major obstacle to successfully decreasing opioid dose or discontinuing opioid therapy altogether.[4] Further, managing opioid withdrawal is also relevant for the treatment of opioid use disorder.[3] Standards of care include medications for opioid use disorder (MOUD)—either partial (buprenorphine) or full (methadone) μ-opioid receptor agonists, or antagonist treatment, namely, monthly, injectable extended-release naltrexone.[5,6] Withdrawal treatment is usually the first step in stabilising patients with opioid use disorder onto MOUD.[2] Additionally, when patients transition from methadone to buprenorphine, a taper is usually necessary, and emergent withdrawal symptoms often complicate this transition.[7] Regarding extended-release naltrexone, practice guidelines dictate that the patient must be abstinent for 7–10 days before receiving the medication, which is administered intramuscularly, and studies have shown that this time gap is a strong driver of both failure to initiate treatment and relapse, largely because of the withdrawal discomfort patients can experience.[5,8,9] Although stabilisation on MOUD is ideal, access to long-term care can be problematic, patients are often not interested in MOUD, and many treatment centres do not accept, or have the capabilities to prescribe, MOUD.[10–13] In these situations, the treatment of opioid withdrawal can itself serve as an end in terms of a pharmacotherapeutic intervention. In this Therapeutics paper, we will assess the current state of treatment for opioid withdrawal, examine innovations and new approaches, and discuss how future research could best be directed towards managing opioid withdrawal, firstly in the context of opioid dose reduction and discontinuation in patients with CNCP and subsequently in the context of MOUD initiation and stabilisation.

Search strategy and selection criteria

We searched PubMed, MEDLINE, Cochrane Library, and references from relevant articles for publications dating from June 1, 2014, to April 1, 2020. We searched for the Medical Subject Headings terms "Opioid-Related Disorders" or "Analgesics, Opioid" and "Substance Withdrawal Syndrome". We only viewed articles that were available in English. We tried to select articles from the past 5 years as indicated by our search dates but also included relevant, older, highly cited articles (from references) and articles of historical importance.

Opioid withdrawal: clinical syndrome and pathophysiology

Withdrawal from a substance is characterised in the Diagnostic and Statistical Manual for Mental Disorders, 5th edition (DSM-5), as "the substance-specific problematic behavioral change, with physiologic and cognitive components, that is due to the cessation of, or reduction in, heavy and prolonged substance use"[14] and in the International Classification of Diseases, 10th edition, as "a group of symptoms of variable clustering and severity occurring on absolute or relative withdrawal of a psychoactive substance after persistent use of that substance".[15] The opioid withdrawal syndrome is a collection of characteristic clinical signs, which include hypertension, tachycardia, mydriasis, piloerection (ie, goose bumps), lacrimation, rhinorrhoea, yawning, insomnia, nausea, vomiting, and diarrhoea.[2,16,17] The time course of opioid withdrawal is dependent principally on the half-life of the opioid used. For example, opioids with short half-lives (eg, heroin at 3–5 h) are associated with withdrawal onset within 12 h of last use, whereas cessation of opioids with longer half-lives (eg, methadone at up to 96 h), could result in withdrawal symptoms occurring 1–3 days after

last use.[2,18–20] Similarly, the duration of the syndrome typically correlates with the half-life of the opioid. For example, heroin withdrawal lasts 4–5 days and methadone withdrawal lasts 7–14 days but can be even more protracted, in some cases lasting several weeks.[2,18–20]

Pharmacotherapeutic agents aimed at treating opioid withdrawal target the underlying, pathophysiological mechanisms of the syndrome. The euphoric effect of opioids is principally mediated through the binding of the drug to the μ-opioid receptor.[21] However, the opioid withdrawal syndrome does not appear to result from direct changes in μ-opioid receptor expression.[22] When an opioid agonist binds to the μ-opioid receptor on noradrenergic neurons in the locus coeruleus, release of norepinephrine is suppressed, resulting in sedation, hypotension, and a decreased respiration rate—recognisable signs of opioid intoxication.[2,23,24] This process is mediated through inhibition of the downstream cyclic AMP (cAMP) pathway, in which opioid binding to the μ-opioid receptor results in decreased cAMP and cAMP-dependent protein phosphorylation, ultimately leading to decreased norepinephrine release from the locus coeruleus.[24] With chronic opioid use, this pathway recovers, as evidenced by the induction of adenylyl cyclase (which converts ATP to cAMP) and protein kinase A. During withdrawal states, cAMP and protein kinase A signalling again increases, leading to increased norepinephrine release from the locus coeruleus, which underlies some of the characteristic symptoms of opioid withdrawal (eg, lacrimation, diaphoresis, tachycardia, and mydriasis). The pathophysiology of withdrawal, specifically relating to the interactions between opioid and noradrenergic systems, forms the basis for pharmacotherapy for opioid withdrawal (figure 1).[24] Indeed, direct μ-opioid receptor agonists and partial agonists (eg, methadone and buprenorphine), and α2 agonists (eg, clonidine and lofexidine) are the agents principally used for the treatment of opioid withdrawal.[2]

Evidence-based treatments for opioid withdrawal

Buprenorphine

Buprenorphine is a μ-opioid receptor partial agonist that, both alone and in combination with the μ-opioid receptor antagonist naloxone, is approved for the treatment of opioid use disorder in both the USA and Europe.[5,6,25] Additionally, buprenorphine has considerable utility in the treatment of medically supervised withdrawal.[5,6] In a 2017 Cochrane review, Gowing and colleagues[26] investigated the utility of buprenorphine in the treatment of opioid withdrawal, reviewing 27 studies involving 3048 individuals that compared buprenorphine with either clonidine or lofexidine (14 studies), buprenorphine with methadone (six studies), or differing rates of buprenorphine dose reduction (seven studies). Compared with the α2 agonists clonidine and lofexidine, buprenorphine was associated with a lower withdrawal score (n=902, seven studies, standardised mean difference [SMD] –0·43, 95% CI –0·58 to –0·28), longer retention in treatment (n=558, five studies, SMD 0·92, 0·57 to 1·27), and increased likelihood of withdrawal treatment completion (n=1264, 12 studies, risk ratio [RR] 1·59, 95% CI 1·23 to 2·06). Notably, the scales used to assess withdrawal severity differed between studies, precluding a direct comparison. Nevertheless, in each study, a higher withdrawal score indicated a more severe withdrawal syndrome.

Compared with methadone, buprenorphine was no different in terms of treatment duration (n=82, two studies, mean difference 1·30 days, 95% CI –8·11 to 10·72) or treatment completion rate (n=457, five studies, RR 1·04, 95% CI 0·91 to 1·20). Different buprenorphine dose reduction rates had no effect on treatment completion for either inpatient (n=60, two studies, RR 1·00, 95% CI 0·84 to 1·18) or outpatient (n=647, four studies, RR 0·86, 95% CI 0·44 to 1·70) studies. However, the authors note that low data quality and high heterogeneity (I^2=80) in the outpatient studies restrict interpretation of the results. Collectively, these results suggest that, compared with patients who undergo medically supervised withdrawal with either clonidine or lofexidine, patients treated with buprenorphine experience less severe withdrawal and improved treatment retention and completion. Buprenorphine and methadone are likely to be similar but whether the taper duration influences completion rate is equivocal.[26]

In terms of dosing, waiting for withdrawal symptoms to emerge is essential; buprenorphine is a highly potent μ-opioid receptor partial agonist and can precipitate withdrawal if given too soon after ingestion of a full μ-opioid receptor agonist.[2,19] After the emergence

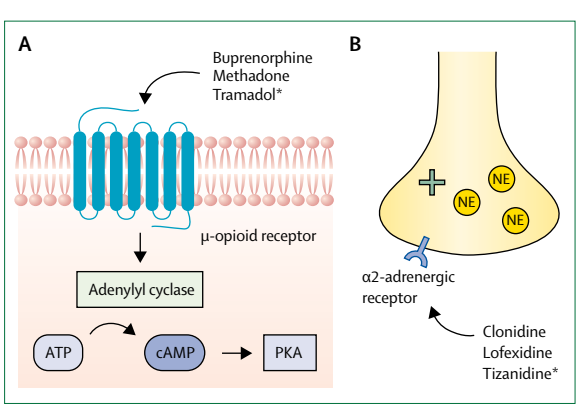

Figure 1: **Pharmacological mechanisms of agents used in the treatment of opioid withdrawal**

Acute opioid binding to the μ-opioid receptor inhibits the downstream cAMP (A), which recovers with chronic opioid use and further increases in withdrawal, leading to excess NE discharge from the noradrenergic neurons in the locus coeruleus (B). Therefore, treatment of withdrawal involves either attenuating the cAMP pathway through μ-opioid receptor agonism (A) or inhibiting excess NE discharge from locus coeruleus neurons through presynaptic α2-receptor agonism. ATP=adenosine triphosphate. cAMP=cyclic adenosine monophosphate. PKA=protein kinase A. NE=norepinephrine. *Not approved by the US Food and Drug Administration yet.

of mild-to-moderate withdrawal symptoms, 2–4 mg of buprenorphine should be administered and, if symptoms persist after 1–2 h, an additional 2–4 mg should be administered, for a total dose of 8–12 mg on the first day and up to 16 mg on the second day. Some patients might experience residual withdrawal symptoms that can be treated with clonidine and ancillary medications including sedative hypnotics for anxiety (benzodiazepines) and sleep (zolpidem) that act on the γ-aminobutyric-acid receptor system, non-steroidal anti-inflammatory drugs for muscle cramps, bismuth subsalicylate for diarrhoea, and prochlorperazine or ondansetron for nausea and vomiting.[2,19,27] If a benzodiazepine is given, prudence should be exercised given the potential for diversion and oversedation.[2,19,27] These ancillary medications have never been investigated in randomised controlled trials specifically for the treatment of residual, opioid withdrawal symptoms in terms of optimal dosing, efficacy, and tolerability; instead, during studies, they are often given as needed when symptoms emerge.[27] Once withdrawal symptoms are controlled, buprenorphine can then be tapered over the course of five days.[2,19,27]

α2-adrenergic receptor agonists

Clonidine is an α2-adrenergic receptor agonist approved by the US Food and Drug Administration for the treatment of hypertension and attention-deficit hyperactivity disorder.[28] Clonidine treats opioid withdrawal symptoms through its anti-adrenergic actions, specifically targeting noradrenergic hyperactivity in locus coeruleus neurons that cause opioid withdrawal symptoms.[2,19,24] In a 2016 Cochrane review, Gowing and colleagues[29] investigated the use of α2 agonists (mostly clonidine but also lofexidine, tizanidine, and guanfacine) in the treatment of medically supervised opioid withdrawal. Treatment with an α2 agonist (five studies with clonidine, one with lofexidine) was more effective than placebo in ameliorating withdrawal (RR 0·32, 95% CI 0·18 to 0·57) and more likely to result in the completion of treatment (RR 1·95, 1·34 to 2·84). When α2 agonists were compared with methadone dose reduction (12 studies), withdrawal signs and symptoms occurred and resolved earlier, and treatment duration was shorter with α2 agonist treatment than with methadone dose reduction (SMD –1·07; 95% CI –1·31 to –0·83), but there was no significant difference in treatment completion or withdrawal severity between the two treatments. Although measures of withdrawal severity differed between studies, two studies reported data on peak withdrawal severity, five reported on severe withdrawal defined as intolerable withdrawal leading to treatment dropout or a score of more than 5 on the Objective Opiate Withdrawal Scale, and three studies reported data on overall withdrawal severity. Nevertheless, methadone appeared to be better tolerated than α2 agonists; hypotension and sedation were more likely to occur with α2-agonist treatment than with methadone treatment (RR 1·92, 1·19 to 3·10). These results suggest that, compared with methadone, α2 agonists might be similar in terms of alleviating withdrawal discomfort, have a shorter withdrawal treatment duration, and cause more discomfort in terms of side-effects, particularly hypotension and sedation.[29]

A common clinical observation is that clonidine relieves some, but not all, withdrawal symptoms.[2,19,27] To empirically assess the specific withdrawal symptoms that clonidine treats, Jasinski and colleagues[30] characterised withdrawal symptoms in patients on methadone maintenance tapered with oral morphine, clonidine, or placebo. They found that clonidine selectively attenuated, more so than morphine, the noradrenergic-mediated symptoms of opioid withdrawal, including yawning, diaphoresis, mydriasis, and rectal temperature, but did not suppress subjective discomfort or improve sleep behaviour. As such, clinical practice standards generally dictate symptomatic treatment with ancillary medications.[2,19,27]

Lofexidine, an α2-receptor agonist that is a structural analogue of clonidine with a milder side-effect profile, was approved for the treatment of opioid withdrawal in the UK in 1992 and in the USA in 2018.[31] Its approval in the USA was based on two clinical trials.[31–33] In the first study,[32] 264 patients with DSM-4 diagnoses of opioid dependence were randomly assigned to receive either lofexidine 2·88 mg (in four divided doses) or placebo for 5 days. Primary endpoints were withdrawal symptom severity, as measured by the Short Opiate Withdrawal Scale-Gossop (SOWS-Gossop) on the third day, and the time to dropout. Compared with patients randomly assigned to placebo, those assigned to lofexidine had significantly greater reductions in withdrawal symptom severity (mean SOWS-Gossop 6·32 *vs* 8·67, p=0·02) and greater treatment retention (assessed as early termination, 59 [44·0%] of 134 *vs* 80 [65·5%] of 130, p=0·0034). Incidentally, patients assigned to lofexidine had clinically significant hypotension (mean systolic blood pressure decrease of 15 mm Hg and mean diastolic blood pressure decrease of 9 mm Hg, p<0·01) and sedation (p<0·01) compared with the placebo group.[32]

In a follow-up inpatient study done by Fishman and colleagues,[33] 603 patients diagnosed with opioid use disorder were randomly assigned to receive either placebo (n=151), low-dose lofexidine (n=230, 2·16 mg daily), or high-dose lofexidine (n=222, 2·88 mg daily). Patients assigned to either lofexidine dose had milder withdrawal symptoms (SOWS-Gossop log-transformed least squares mean 0·21, 95% CI –0·37 to 0·04, p=0·02) and showed greater treatment retention and completion than patients assigned to the placebo (completion was 41·5% for lofexidine 2·16 mg *vs* 27·8% for placebo, odds ratio [OR] 1·85, p=0·007; 39·6% for lofexidine 2·88 mg, OR 1·71, p<0·02;). No difference was found between the treatment outcomes of the two lofexidine doses. Compared with placebo, patients assigned to lofexidine did have, albeit at a relatively low frequency, clinically

significant dizziness (3·0% *vs* 0·7%), hypotension (2% *vs* 0%), orthostasis (2·0% *vs* 0·7%), and bradycardia (2% *vs* 0%) leading to discontinuation (2% *vs* 0%), although the most common reason for early discontinuation was the absence of sufficient control of withdrawal symptoms. In both studies, ancillary medications were given. These results suggest that, although lofexidine shows efficacy versus placebo in terms of treatment retention and reduction in withdrawal symptoms with a tolerable side-effect profile, the inability of lofexidine to completely suppress withdrawal symptoms might contribute to poor treatment retention.

Methadone

Initiation of methadone treatment usually begins with 10–30 mg as the first dose, and the appropriate amount is calculated using the patient's history of opioid use and the severity of opioid withdrawal. For example, in a patient with low or unknown tolerance, 10 mg might be appropriate, whereas 20–30 mg might be appropriate for patients with a higher tolerance or whose symptoms do not attenuate after 10–20 mg in the first hour, or both.[2,19] The maximum daily dose on the first day of methadone treatment should not exceed 40 mg.[19] This recommendation is made because of the variability in methadone's bioavailability, half-life, and time to peak plasma concentration, all of which can contribute to an excess accumulation of methadone if the initial dose is too high, putting the patient at risk for sedation, respiratory depression, and death.[20] Following the initial dose, methadone can be tapered over the next 7 days in one of two ways: (1) by 10 mg daily for 3 days and then by 2 mg per day for 4 days, or (2) by 5 mg per day (panel 1). Monitoring the patient for objective signs of withdrawal before initiating treatment is considered best practice.[2,19] However, given that methadone is a full μ-opioid receptor agonist with no risk of precipitating withdrawal, waiting for withdrawal signs or symptoms is not absolutely necessary to initiate treatment, although care should be taken to monitor vital signs and respiratory status.[2,19]

Tramadol

Tramadol is a weak μ-opioid receptor agonist that is approximately 6000 times less potent than morphine,[34] and is classified by the US Drug Enforcement Administration as a Schedule IV substance because of its "low potential for abuse and low risk of dependence".[35,36] In the UK, tramadol is classified as a Schedule 3 controlled substance.[37] In one randomised controlled trial investigating the use of tramadol for opioid withdrawal in residential settings, 103 individuals with opioid use disorder received a taper with either a tramadol extended-release taper (n=36), clonidine (n=36), or buprenorphine (n=31) over a 7-day withdrawal period.[38] This taper period was followed by a 7-day post-taper period, during which all individuals received placebo tablets. During the taper period, patients assigned to clonidine had more severe withdrawal symptoms (as measured by the area under the curve of SOWS total scores) than those assigned to extended-release tramadol (p=0·02), and those assigned to buprenorphine (p<0·001), with no difference between tramadol and buprenorphine. Regarding treatment retention, individuals assigned to buprenorphine were more likely to complete treatment through the taper period than individuals assigned to clonidine (90·3% *vs* 61·1%, p=0·01), and 72·2% of individuals assigned to extended-release tramadol completed treatment, which was not significantly different from either of the other two groups. Further, individuals who were assigned to either tramadol or clonidine had significant reductions in withdrawal symptoms in the 7-day post-taper phase, whereas individuals assigned to buprenorphine did not (p=0·03 for tramadol, p<0·001 for clonidine). Thus, because of its similarity to buprenorphine in treatment

Panel 1: **Medically supervised withdrawal protocols for buprenorphine, clonidine, lofexidine, and methadone, along with recommendations for ancillary medications for symptoms**

Buprenorphine (begin when withdrawal symptoms emerge)[2,19,27]
- Day 1: 2–4 mg every hour for 4 h (total dose 8–12 mg)
- Day 2: 16 mg in divided doses (eg, 8 mg twice daily)
- Day 3–9: decrease by 2–4 mg per day as tolerated; add clonidine 0·1 mg every 4–6 h for breakthrough symptoms

Clonidine[2,19,27]
- Day 1: 0·1–0·2 mg every 4–6 h with a maximum dose of 1·2 mg
- Day 2 onward: taper by 0·1–0·2 mg per day

Lofexidine[32,33]
- Day 1: 0·54–0·72 mg every 6 h (total daily dose 2·16–2·88 mg)
- Day 2 onward: decrease each dose by 0·18 mg every 1–2 days

Methadone[2,19]
- Day 1: begin with 10 mg, increase by 10 mg every 6–8 h for maximum dose of 40 mg

Option 1:
- Days 2–4: decrease by 10 mg each day
- Days 5–8: decrease by 2 mg each day

Option 2:
- Days 2–8: decrease by 5 mg each day

Ancillary medications[27]

Anxiety
- Clonazepam 0·5–2·0 mg every 4–8 h (maximum 6 mg daily)

Muscle cramps
- Ibuprofen 400 mg every 4–6 h (maximum 2400 mg daily)

Nausea, vomiting, or diarrhoea
- Bismuth subsalicylate 2 tablets every hour (maximum 10 tablets daily)
- Ondansetron 8–16 mg every 8–12 h
- Prochlorperazine 5–10 mg every 3–4 h (maximum 40 mg daily)

Sleep
- Trazodone 50–150 mg at bedtime
- Zolpidem 10 mg at bedtime

retention and withdrawal symptom suppression, tramadol might be useful when treating withdrawal in patients with CNCP who are discontinuing opioids, or when buprenorphine and induction onto MOUD are not available. However, given that tramadol is a scheduled medication in both the USA and the UK and has not specifically been approved for the treatment of opioid use disorder or opioid withdrawal, its use in withdrawal settings in these countries is, to date, illegal.[36]

Treating opioid withdrawal in the context of opioid dose changes in CNCP

Opioid dose changes during treatment of CNCP is another situation in which the treatment of opioid withdrawal is relevant. In the USA, according to guidelines from the Centers for Disease Control and Prevention, and the Departments of Health and Human Services, Veteran Affairs, and Defense, in most instances, opioid analgesic treatment is most appropriate for acute, rather than chronic, pain.[39–41] In CNCP, chronic opioid treatment can result in physiological dependence and opioid-induced hyperalgesia, if not always opioid use disorder.[42,43] In addition, the risk of fractures, delirium, dementia, and other medical complications becomes concerning, necessitating opioid dose reduction or discontinuation.[39,42,44] When physiological dependence does occur, dose reduction or discontinuation can be extremely difficult, largely because of the potential for withdrawal.[2,42] Guidelines suggest tapering regularly taken opioids but this approach often fails, and existing protocols are not backed up with evidence for their efficacy or safety.[39–41,45] Therefore, alternative methods for managing withdrawal in patients with CNCP who are undergoing opioid dose reduction or discontinuation is a necessary area of investigation. Specific guidance on deciding between dose reduction and discontinuing opioid analgesic medications in patients with CNCP is beyond the scope of this Therapeutics paper but recommendations can be accessed in the guidelines cited here.[39–41] For patients with both CNCP and opioid use disorder, maintenance treatment with either methadone or buprenorphine is indicated to manage both conditions.[39–41]

An ongoing clinical trial is investigating the safety and effectiveness of lofexidine in treating withdrawal symptoms in patients with CNCP undergoing an opioid taper (NCT04070157) and another is comparing a buprenorphine taper both with gabapentin and placebo for the treatment of withdrawal symptoms in patients with CNCP who discontinue opioids (NCT02737826). In an additional ongoing study, patients with CNCP are being tapered off their standing opioid regimens over 6 months, and those who require a dose increase will be administered a 1-month buprenorphine maintenance treatment followed by a 5-month buprenorphine taper (NCT03156907). Notably, the medications involved in these trials—buprenorphine and lofexidine—have shown efficacy for opioid withdrawal and act through the two principal receptor systems that underlie opioid withdrawal symptoms: the μ-opioid receptor in the case of buprenorphine and α2-adrenergic receptors in the case of lofexidine. Indeed, the appropriate agent can be selected by the desired outcome: α2 agonists might be more appropriate for managing withdrawal when the goal of treatment is opioid dose reduction, whereas μ-opioid receptor agonists (full or partial) might be more appropriate when the goal of treatment is opioid discontinuation. However, prospective studies designed with these specific outcomes are needed to determine optimal practice.

Managing withdrawal in the context of MOUD treatment initiation

The standard of care for opioid use disorder includes treatment with MOUD—either buprenorphine, methadone, or extended-release naltrexone. Regarding buprenorphine, the patient should be stabilised on a maintenance dose, as tapering and discontinuation of buprenorphine after withdrawal symptoms abate frequently results in relapse.[46–48] The efficacy of methadone for the treatment of

***Panel 2*: Outstanding research questions and potential solutions in the treatment of opioid withdrawal**

Managing withdrawal in patients with chronic, non-cancer pain (CNCP) undergoing opioid dose reduction or discontinuation[39–41]

- Lofexidine is being investigated as a treatment for withdrawal in patients with CNCP undergoing an opioid taper (NCT04070157)
- Trials investigating buprenorphine tapers for patients with CNCP who discontinue opioids are also underway (NCT02737826, NCT03156907)
- α2 agonists and ancillary medications might be most appropriate for patients with CNCP undergoing dose reduction (but not discontinuation)
- Buprenorphine might be most appropriate for patients with CNCP who discontinue opioids
- Tramadol might also be useful for the treatment of withdrawal during discontinuation but requires further study

Standardising the transition from methadone to buprenorphine[2,19,50]

- Buprenorphine microdosing has promise but requires evaluation in randomised controlled trials[51]

Improving induction rates onto extended-release naltrexone[8,9,56]

- Managing withdrawal symptoms with α2 agonists and other ancillary medications seems to be the most important factor, rather than reducing time to induction[56]
- Tizanidine with ancillary medications might hold promise[57]
- Lofexidine is being examined in outpatient transition to extended-release naltrexone (NCT04056182)
- Extended (21-day) buprenorphine taper followed by 2-day washout with ancillary medications and three oral naltrexone up-titrations before extended-release naltrexone administration is underway (NCT03711318)

Defining the optimal strategy to manage opioid withdrawal in patients who refuse medications for opioid use disorder or in situations in which medication is not available[10–13]

- Tramadol is an ideal medication given its low potency and relatively low abuse potential[38]

opioid use disorder is established and the patient does not need to be in a withdrawal state to initiate treatment (as opposed to buprenorphine); however, limitations on access and the burden of daily clinic visits could be problematic for some patients.[2,19] Additionally, patients might want to transition from methadone to buprenorphine either because of intolerable side-effects from methadone or because of a desire to discontinue MOUD entirely.[49] For the transition from methadone to buprenorphine, management of withdrawal is relevant, as methadone must eventually be stopped before fully transitioning to buprenorphine.[7] Although no clear consensus on the method of transition from methadone to buprenorphine exists, a taper is often necessary and management of the withdrawal symptoms is prudent for successful transitioning and avoiding relapse.[7] Further, at methadone doses of 50 mg or more, an inpatient setting might be necessary for a successful transition.[50] To facilitate this transition, a buprenorphine microdosing protocol, in which doses of buprenorphine starting at 0·5 mg are gradually up-titrated with concurrent administration and eventual cessation of methadone, has shown promising results. With this method, in a case series of three patients in an inpatient setting on 40 mg (n=2) and 100 mg (n=1), patients were successfully withdrawn from methadone and stabilised on 12–16 mg buprenorphine daily with manageable withdrawal symptoms.[51] Rigorous clinical trials are required to validate this method before being implemented on a broader scale.

Alternatively, extended-release naltrexone is a viable treatment for opioid use disorder and could be especially useful for patients who struggle with adherence and are prone to agonist diversion or misuse, as treatment consists of a monthly injection and the drug has no reinforcing properties.[5] Injectable and implantable forms of buprenorphine are available, although they are not as widely available as extended-release naltrexone and thus access could be an issue.[52–55] A major barrier to successful treatment of opioid use disorder with extended-release naltrexone is induction failure, as patients are often unable to abstain from opioids for the requisite 7–10 days.[8,9,56] A principal reason for opioid use during this period is the emergence of withdrawal symptoms, particularly in outpatient settings. Improving induction success rates, particularly in relation to the management of withdrawal before extended-release naltrexone administration, remains an active area of investigation.

An outpatient randomised controlled trial in patients with opioid use disorder (n=378) was done by Bisaga and colleagues[56] to evaluate a naltrexone–buprenorphine protocol, consisting of concurrent naltrexone up-titration and buprenorphine tapering over a 7-day period with subsequent administration of extended-release naltrexone. The comparison groups were given either naltrexone and buprenorphine, naltrexone and buprenorphine placebo, or buprenorphine placebo and naltrexone placebo. All three groups had similar rates of successful extended-release naltrexone induction (46·0% for buprenorphine and naltrexone, 40·5% for naltrexone and buprenorphine placebo, and 46·0% for naltrexone placebo and buprenorphine placebo). Subjective withdrawal symptoms following extended-release naltrexone administration were significantly lower in the buprenorphine and naltrexone group than the other two groups, though there were no differences in objective symptom ratings. In addition to extensive outpatient support, ancillary medications (clonazepam and clonidine) were provided, suggesting that these medications, rather than the aforementioned protocols, have an essential role in the treatment of withdrawal during the transition to extended-release naltrexone, provided that external structure and support is sufficient. Further, patients who used opioids during this

	Advantages	Disadvantages	Ideal situation for use
Buprenorphine	Better symptom control and treatment completion than α2 agonists; more accessible and safer than methadone	μ-opioid receptor agonist properties; potential for misuse; appears to not be helpful with extended-release naltrexone induction	Patients with OUD who will be stabilised on buprenorphine for OUD maintenance treatment; patients with OUD who will not be stabilised on MOUD (by choice or because of availability); patients with CNCP who undergo opioid discontinuation
Clonidine	Accessible, not scheduled; no substantial misuse potential	Substantial side-effect profile; hypotension and sedation; worse withdrawal symptom control compared with buprenorphine; only treats autonomic symptoms	Patients with OUD who will not be stabilised on MOUD (by choice or because of availability); transition to extended-release naltrexone (with substantial support and ancillary medications); patients with CNCP who undergo an opioid dose reduction
Lofexidine	Not scheduled; no substantial misuse potential; lower side-effect burden than clonidine	Side-effect burden still substantial; probably does not treat all withdrawal symptoms (just autonomic symptoms)	Patients with OUD who will not be stabilised on MOUD (by choice or because of availability); transition to extended-release naltrexone (with substantial support and ancillary medications); patients with CNCP who undergo an opioid dose reduction
Methadone	Better side-effect profile than clonidine	Needs to be dispensed at a licensed clinic; risk of misuse, diversion, and overdose; possibly requires a longer taper than with either α2 agonists or buprenorphine	Patients who will be stabilised on methadone for OUD maintenance treatment

CNCP=chronic, non-cancer pain. MOUD=medications for opioid use disorder. OUD=opioid use disorder.

Table: **Evaluation of withdrawal treatment by drug with indications for most appropriate use**

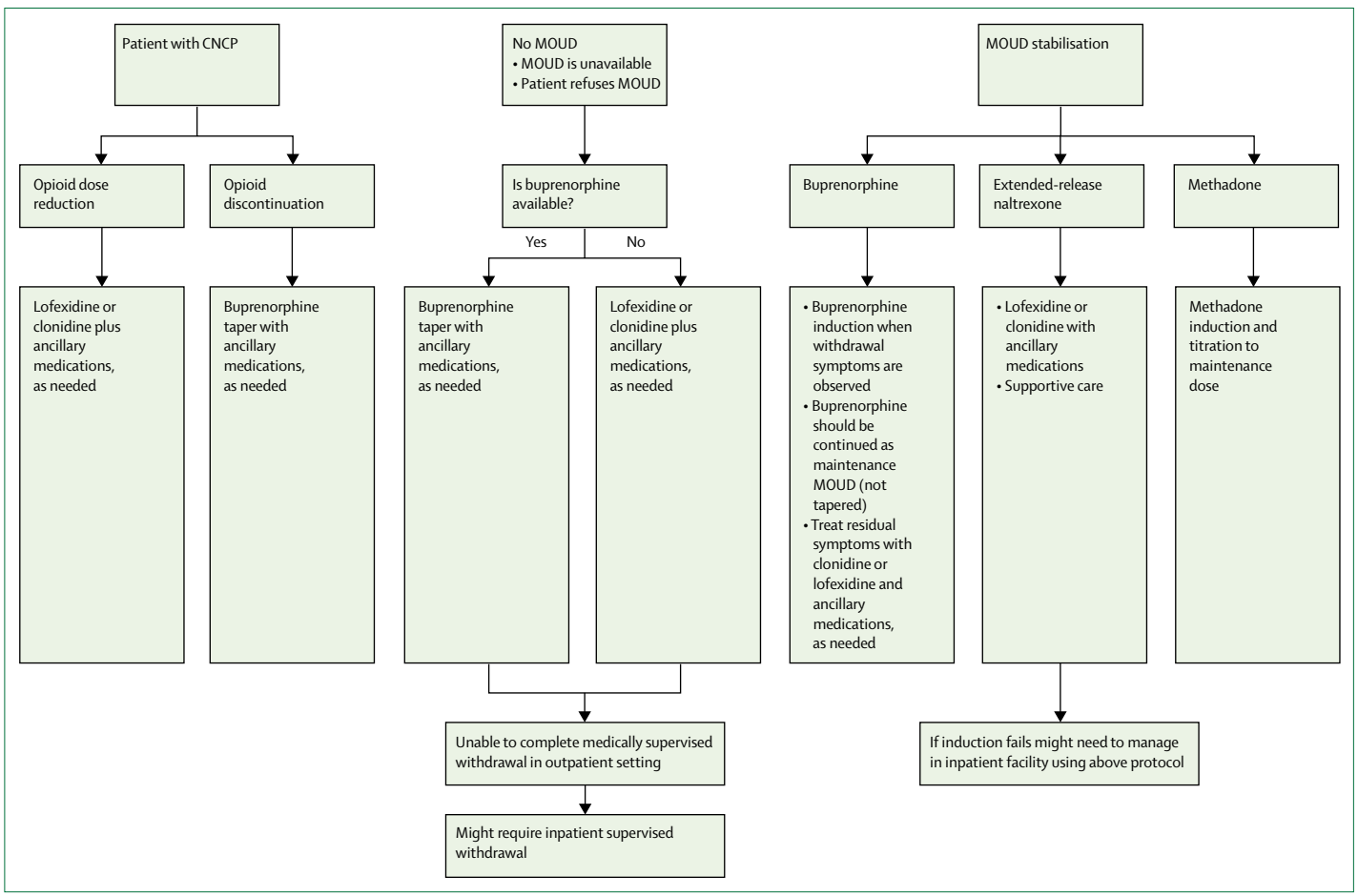

Figure 2: **Algorithm for the treatment of medically supervised opioid withdrawal**
CNCP=chronic, non-cancer pain. MOUD=medications for opioid use disorder.

period (and so would normally be unable to receive extended-release naltrexone) were still successfully inducted onto extended-release naltrexone. These findings suggest that, although a delay is required before administering extended-release naltrexone, this time period should be used to treat opioid withdrawal with supportive care and non-opioid medications (eg, α2 agonists and other ancillary medications). Structure and support, including treatment such as with the α2 agonist clonidine (rather than naltrexone titration or a concurrent buprenorphine taper) for emergent withdrawal symptoms, is essential for transitioning patients to extended-release naltrexone in outpatient settings.

An important consideration when interpreting results is the difference in rates of induction success for different types of opioids used, namely for heroin versus prescription opioids. Prescription opioid users had higher rates of induction onto extended-release naltrexone than did heroin users (56·3% *vs* 37·2%, p<0·001).[56] However, in a randomised clinical trial comparing buprenorphine with extended-release naltrexone for opioid use disorder, Lee and colleagues[9] observed a more than 70% extended-release naltrexone induction rate for heroin-dependent patients in an inpatient setting. These results suggest that an outpatient protocol with structure, support, and treatment of emergent withdrawal symptoms might be useful for individuals who use prescription opioids, whereas heroin users might require medically supervised withdrawal in an inpatient setting.

Nevertheless, fewer than 50% of patients were able to complete any of the protocols in Bisaga and colleagues' trial.[56] Improving induction success rates for extended-release naltrexone therefore remains an active area of investigation, with a focus on α2 agonism to mitigate withdrawal symptoms. For example, a retrospective chart review examined a 4-day protocol of scheduled α2 agonist tizanidine (32 mg per day), gabapentin (1500 mg per day), and hydroxyzine (600 mg per day) in 84 opioid-dependent individuals admitted to an inpatient facility for medically supervised withdrawal. 42 (50%) of the patients reported using only heroin, 32 (38%) reported using only oxycodone, seven (8%) reported using both heroin and oxycodone, and three (4%) reported using methadone. 79 (94%) patients successfully completed

Panel 3: Approaches that do not show promise or for which evidence is minimal

μ-opioid receptor antagonist treatment[8,61]

When a μ-opioid receptor antagonist (ie, naloxone or naltrexone) is administered before the onset of opioid withdrawal, although initially the severity of withdrawal is increased, the duration is shortened by several days. In a 2017 Cochrane review, Gowing and colleagues reviewed nine studies (five outpatient, four inpatient) comparing α2-adrenergic agonist (clonidine or lofexidine) therapy combined with a μ-opioid receptor antagonist (naloxone or naltrexone) for opioid withdrawal. Peak withdrawal severity appeared to be greater in the combination groups taking a μ-opioid receptor antagonist and an α2 agonist but average withdrawal severity was generally lower in these groups than in the groups taking only α2 agonists. Differences in treatment retention were inconsistent, although delirium was reported in two studies after the first dose of naltrexone. Ultimately, the authors concluded that although μ-opioid receptor antagonist treatment protocols are feasible, whether they reduce withdrawal duration, improve treatment retention, or lead to greater success of oral naltrexone stabilisation, when compared with α2-adrenergic agonist protocols, is unclear. Further, a higher degree of care might be required due to the initial, precipitated withdrawal symptoms, which can include severe nausea, vomiting, and diarrhoea.

Calcium channel blockers: gabapentin and pregabalin[62–68]

Gabapentin is a γ-aminobutyric-acid (GABA) analogue that acts pharmacologically as an n-type calcium channel blocker. Early evidence showed that adjunctive gabapentin was associated with reductions in post-surgical morphine, and data from clinical trials showed that gabapentin could reduce withdrawal symptoms and, when compared with placebo, was associated with reductions in opioid use. A more recent study compared gabapentin (1600 mg daily) with pregabalin (450 mg daily), another GABA analogue and voltage-gated calcium channel blocker, and placebo as adjunctive treatment to a buprenorphine taper over 4 weeks in 50 patients with opioid use disorder undergoing medically supervised withdrawal in an outpatient setting. Neither gabapentin nor pregabalin was superior to placebo for withdrawal symptom severity (as measured by Short Opiate Withdrawal Scale scores).

Ibogaine[69–74]

Ibogaine is a psychedelic alkaloid with a varied pharmacological profile, including serotonin reuptake inhibition and weak activity at the μ-opioid, κ-opioid, and N-methyl-D-aspartate receptors. The literature suggests that the primary reason for which ibogaine is used is for treatment of withdrawal, although the mechanism of action in treating opioid withdrawal remains unclear, as ibogaine does not have typical μ-opioid receptor agonist effects (and does not have downstream effects consistent with μ-opioid receptor agonism), nor does it have affinity for α-adrenergic receptors. Given that ibogaine is illegal in the USA and many other countries, it has not been studied in high-quality, randomised clinical trials; thus current evidence is restricted to open-label and retrospective studies. In one retrospective chart review of patients undergoing medically supervised withdrawal with ibogaine in an inpatient setting and two prospective open-label studies, withdrawal symptoms decreased substantially. Alhough adverse effects were not reported in the prospective studies, clinically significant cardiovascular and neuropsychiatric side-effects of ibogaine are well documented and would probably caution against its implementation.

Kratom[75–80]

Kratom (*Mitragyna speciosa*) is a plant indigenous to southeast Asia that contains several indole alkaloids, principally mitragynine and 7-hydroxymitragynine, with variable pharmacological properties including agonism at the μ-opioid, δ-opioid, and κ-opioid receptors. Kratom is currently regulated in the USA as a dietary supplement and is banned in the UK. Emerging evidence indicates that kratom, like other opioids, can lead to tolerance and withdrawal on cessation and is subject to misuse; kratom withdrawal has been managed successfully with clonidine and buprenorphine, and kratom overdose has been successfully reversed with naloxone. Recently, in the USA, it has been used in non-medical settings for reducing, or abstaining from, heroin use, managing chronic pain, and managing opioid withdrawal. However, it has not been evaluated for safety and efficacy in randomised controlled trials and is not available as a pharmaceutical grade product.

medically supervised withdrawal and 24 (89%) of 27 patients who chose to receive extended-release naltrexone were successfully inducted.[57] Notably, the medically supervised withdrawal protocol was successful for heroin users (39 [93%] of 42), mixed heroin and oxycodone users (six [86%] of seven), and oxycodone users (24 [75%] of 32).[57] Thus, tizanidine might be another useful agent that warrants further study, especially given that its sedative and hypotensive side-effects are of shorter duration than those of clonidine.[58]

Regarding ongoing studies in outpatient settings, an open-label trial investigating lofexidine in the treatment of opioid withdrawal before extended-release naltrexone induction is ongoing (NCT04056182). As an alternative approach, another trial (NCT03711318) is investigating an extended 21-day buprenorphine taper followed by a 2-day washout and a 3-day up-titration of oral naltrexone to improve induction rates of extended-release naltrexone. During the washout period, clonidine and ancillary medications will be provided to manage withdrawal symptoms. Thus, developing induction protocols for extended-release naltrexone that focus on novel methods for mitigating withdrawal symptoms and retaining patients in treatment, particularly in the outpatient setting, rather than on treating opioid withdrawal itself as an end, is an essential next step in translational research, and α2 agonism is a key mechanism to exploit. The outstanding research questions and potential

solutions in the treatment of opioid withdrawal are outlined in panel 2.

Future directions and conclusion

Although α2 agonists and full or partial μ-opioid receptor agonists have shown efficacy in alleviating withdrawal symptoms, future research should be directed towards managing withdrawal in the context of the desired outcome. The table summarises the advantages and disadvantages of different pharmacological agents, and the appropriate situations in which to use them. For example, in patients with CNCP, when the goal is opioid analgesic dose reduction, α2 agonists and other non-opioid, ancillary medications could be treatments of choice to treat residual withdrawal symptoms, as buprenorphine can precipitate withdrawal when added to a full μ-opioid receptor agonist. For discontinuation, buprenorphine might be the ideal treatment given its superiority in terms of symptom control and withdrawal treatment completion when compared with α2 agonists—although if buprenorphine alone does not control withdrawal symptoms, α2 agonists can be used along with other, ancillary medications. Given that buprenorphine might not yet be available in all settings, promising alternatives that have μ-opioid receptor agonist properties yet low misuse potential, such as tramadol, could have considerable utility and should likewise be investigated. However, randomised controlled trials are needed to definitively establish which medications might be best suited for managing withdrawal symptoms during either opioid dose reduction or discontinuation in patients with CNCP.

Tramadol could also be a viable option (along with buprenorphine) in the treatment of withdrawal for patients with opioid use disorder who refuse MOUD or for whom these medications are unavailable. For patients with opioid use disorder for whom MOUD stabilisation is the primary goal, the agents selected for medically supervised withdrawal depend on the MOUD chosen. Factors influencing appropriate selection of a MOUD agent include patient access issues, pregnancy status, previous experiences (successes or failures) with a given treatment, and system-level issues.[5] If the patient is to be stabilised on buprenorphine, then buprenorphine is naturally the most appropriate agent for managing withdrawal, although the physician should wait for withdrawal symptoms to emerge before administering the drug.[2,19] When transitioning from methadone to buprenorphine for MOUD, a taper is often necessary and, at high doses (eg, 50 mg or more), transitioning should occur in an inpatient setting.[7,50] Buprenorphine microdosing might help alleviate withdrawal symptoms when transitioning from high doses, although more research is needed regarding the standardisation of doses and establishment of a protocol.[51] As buprenorphine becomes more widely available and methadone falls increasingly out of favour, this clinical scenario could become more common and is a useful direction for future research.

If extended-release naltrexone is desired, close supervision and treatment with α2 agonists and other adjunctive medications are required to ensure the patient is inducted successfully, particularly in outpatient settings. Although induction rates for extended-release naltrexone, particularly for heroin users, are generally higher in inpatient settings, access is often an issue, thus necessitating outpatient treatment.[59] However, outpatient treatment offers less structure and support than inpatient treatment, increasing the likelihood of relapse during the withdrawal period, an observation noted by Gold and colleagues over 40 years ago.[60] Future developments should focus on improving treatment retention and induction rates, chiefly through improved management of withdrawal symptoms during the required period of abstinence from last opioid use to administration of extended-release naltrexone. An algorithm for the treatment of medically supervised opioid withdrawal is outlined in figure 2.

Historically, studies investigating the treatment of opioid withdrawal have largely focused on the control of symptoms as an end in itself, usually in inpatient settings. This fundamental research has focused largely on α2 agonists and μ-opioid receptor agonists for the treatment of opioid withdrawal, and newer medications currently being investigated affect those same mechanisms. Other medications, by contrast, either have not shown promise (eg, gabapentin and pregabalin) or are associated with clinically significant adverse effects (eg, ibogaine; panel 3).[62,69] Therefore, future research will be most useful when directed towards the development of better medications that exploit known mechanisms (ie, μ-opioid receptor agonists with low abuse potential, α2 agonists with minimal side-effects), medications operating through novel mechanisms with low side-effect burdens, and tailored treatment of withdrawal to each of the clinical scenarios we have described in this Therapeutics paper.

Contributors

ABS did the initial literature search and drafted the manuscript. FRL and JJM provided guidance and intellectual contribution to the content, and edited each revision of the manuscript.

Declaration of interests

ABS has received personal fees from the Dana Foundation. FRL receives grant support from the US National Institute on Drug Abuse, Substance Abuse and Mental Health Services Administration, and US WorldMeds, was an unpaid member of a Scientific Advisory Board for Alkermes and US WorldMeds but did not personally receive any compensation in the form of cash payments (honoraria or consulting fees), food and beverages (FRL declined food and beverages in both circumstances), or travel reimbursement. FRL receives medication at no charge for an ongoing study from US WorldMeds. JJM declares no competing interests.

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