Opioid Detoxification and Naltrexone Induction Strategies: Recommendations for Clinical Practice

Stacey C. Sigmon, Ph.D.[1], **Adam Bisaga, M.D.**[2], **Edward V. Nunes, M.D.**[2], **Patrick G. O'Connor, M.D., M.P.H.**[3], **Thomas Kosten, M.D.**[4], and **George Woody, M.D.**[5]

[1]Department of Psychiatry, University of Vermont College of Medicine, Burlington, VT, USA

[2]Department of Psychiatry, New York State Psychiatric Institute and Columbia University, New York, NY, USA

[3]Yale University School of Medicine, New Haven, CT, USA

[4]Baylor College of Medicine, Houston, TX, USA

[5]Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Abstract

Background—Opioid dependence is a significant public health problem associated with high risk for relapse if treatment is not ongoing. While maintenance on opioid agonists (i.e., methadone, buprenorphine) often produces favorable outcomes, detoxification followed by treatment with the μ-opioid receptor antagonist naltrexone may offer a potentially useful alternative to agonist maintenance for some patients.

Method—Treatment approaches for making this transition are described here based on a literature review and solicitation of opinions from several expert clinicians and scientists regarding patient selection, level of care, and detoxification strategies.

Conclusion—Among the current detoxification regimens, the available clinical and scientific data suggest that the best approach may be using an initial 2–4 mg dose of buprenorphine combined with clonidine, other ancillary medications, and progressively increasing doses of oral naltrexone over 3–5 days up to the target dose of naltrexone. However, more research is needed to empirically validate the best approach for making this transition.

Keywords

opioid dependence; detoxification; taper; naltrexone; naloxone; buprenorphine; methadone

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Address correspondence to Stacey C. Sigmon, Department of Psychiatry, University of Vermont College of Medicine, UHC-SATC Room 1415, 1 South Prospect Street, Burlington, VT 05401, USA. stacey.sigmon@uvm.edu.

Introduction

Opioid dependence is a serious public health problem associated with substantial morbidity, mortality, and psychosocial problems (1,2). Detoxification is an alternative to agonist maintenance for patients who do not want or cannot access maintenance treatment or for those who are on methadone or buprenorphine maintenance but no longer want to be physically dependent on opioid agonists. Detoxification alone, however, is typically associated with very high rates of relapse (3–5). Naltrexone and its active metabolite 6-β-naltrexol are competitive antagonists at μ- and κ-opioid receptors and, to a lesser extent, at δ-opioid receptors (6). When taken regularly in sufficient doses, naltrexone blocks the reinforcing effects of opioids, is not associated with tolerance, withdrawal, or abuse potential, and decreases the likelihood of relapse to opioid use (7–9). Additionally, because it is not a controlled substance, it can be prescribed flexibly in a wide range of treatment settings (10–15). Despite these strengths, the effectiveness of oral naltrexone as a treatment for opioid dependence has been limited by (1) poor tolerability of naltrexone induction, making the transition from opioids to naltrexone difficult as it precipitates opioid withdrawal if given too early in detoxification and (2) poor adherence following induction, with retention rates generally less than 20% except in special populations (e.g., recovering health professionals) or when combined with intensive behavioral treatments (9,16–19).

Over the past decade, the problem of poor adherence to oral naltrexone has begun to be addressed through the development of both injectable (20) and surgically implantable (21,22) sustained-release formulations that circumvent the need for daily oral doses. In October 2010, the FDA approved extended-release naltrexone, previously approved for alcohol dependence (23,24), for prevention of relapse to opioid dependence following detoxification. A placebo-controlled trial, conducted in Russia with chronic heroin-dependent patients, found treatment with extended-release naltrexone to be associated with significantly greater confirmed opioid-abstinent weeks (90% vs. 35%; $p = 0.0002$), more patients retained for the 6-month treatment duration (53.2% vs. 37.9%; $p = 0.0171$), and a more marked reduction in opioid craving ($p < 0.0001$) compared with placebo (25). While the efficacy and retention rates in that 6-month trial were promising, data on longer-term retention associated with extended-release naltrexone formulations are not yet available. Also worth noting is that, in Russia, agonist treatment is prohibited by law and inpatient detoxification and rehabilitation treatment are routine, making it relatively easy to start patients on naltrexone. For this reason, Russian naltrexone studies have typically randomized patients after they have been hospitalized, detoxified, and were opioid free for a week or more (22,25–27).

For extended-release formulations to reach their potential in the United States, detoxification will need to be initiated in a wider range of settings, including outpatient and brief hospital or residential settings. Indeed, for physicians to be in a position to treat patients with naltrexone in any form, a safe, reliable, and time-sensitive method for transitioning a patient from agonist use to antagonist therapy must be available. We therefore undertook this review to summarize the scientific and clinical knowledge available regarding opioid detoxification and naltrexone induction, with a focus on the treatment options and considerations that could facilitate safe and effective naltrexone induction. For procedures

that are directly supported by the scientific literature, we have included the relevant published studies. For the many individual elements in detoxification and naltrexone induction that have not been empirically evaluated, we sought opinions from several expert clinicians and scientists (primarily the authors of this report) and summarized them into recommendations for conducting opioid detoxification and naltrexone induction.

Opioid Withdrawal

Abrupt cessation of opioids in persons who are physiologically dependent results in an overactivity of the noradrenergic system (locus ceruleus, periaqueductal gray region) and possible decreased dopamine activity in the ventral tegmental area resulting in symptoms that are almost a mirror opposite of agonist effects (28,29). These include pupillary dilation, sweating, restlessness, lacrimation, rhinorrhea, hot flashes/chills, anxiety, insomnia, hyperalgesia (e.g., aches and pains), and GI distress (e.g., nausea, vomiting, diarrhea) along with an anxious, irritable emotional state. Although opioid withdrawal by itself is not typically life threatening unless in the presence of serious medical problems (e.g., advanced cardiovascular disease), it is often extremely unpleasant and, in the absence of treatment, patients typically experience strong cravings to use opioids to terminate the discomfort. Acute symptoms typically peak in 24–48 h and diminish over 3–5 days when withdrawing from short-acting opioids (e.g., heroin or most short-acting narcotic analgesics like oxycodone) or up to 10 or more days when withdrawing from methadone or other longer-acting opioid formulations. These acute symptoms may be followed by subacute withdrawal (e.g., anhedonia, fatigue, insomnia, anorexia) that persists for weeks to months (30,31).

Antagonist-Precipitated Withdrawal

Administration of an opioid antagonist (e.g., naloxone, naltrexone) while receptors are still occupied by an agonist displaces opioids from their receptors and results in the sudden onset of withdrawal. If these symptoms are precipitated by naloxone, for example, when treating an opioid overdose, they typically resolve within 45 minutes because naloxone is short acting. Withdrawal precipitated by naltrexone, a longer-acting antagonist, can take a day or more to resolve. For this reason, prescribing information for extended-release naltrexone, such as the recently approved injectable formulation, specifies that the patient "must be opioid free for a minimum of 7–10 days before starting treatment" (32). However, initiating oral naltrexone within a shorter period of time can help prevent relapse in the early days following detoxification and is possible if certain precautions are taken. It is also important to keep in mind that opioid withdrawal, particularly antagonist-precipitated withdrawal, may exacerbate underlying psychiatric or medical disorders such as anxiety or depression, glycemic control in diabetes, or blood pressure control in hypertension (33,34) and may feature altered sensorium, disorientation, hypomania, and psychosis (34,35). If a patient has just initiated naltrexone therapy and becomes disoriented, alcohol or sedative withdrawal or other neurological or medical causes of altered sensorium should also be considered.

Regimens For Detoxification and Naltrexone Induction

Two main strategies have been developed for opioid detoxification and naltrexone induction: (1) gradual opioid taper and (2) more rapid discontinuation with use of adjunctive

nonopioid medications. Since withdrawal results from the absence of agonist effects on opioid receptors, substitution of a long-acting agonist (e.g., methadone) or a high-affinity partial agonist (e.g., buprenorphine), followed by a gradual taper, can facilitate a "soft landing" while allowing underlying neuroadaptations to revert gradually to their normal state. More rapid opioid withdrawal methods use little or no opioid agonists and rely on nonopioid medications to alleviate withdrawal (Table 1). The most commonly used of these medications is clonidine, an antihypertensive that is an agonist at α-2 adrenergic autoreceptors and acts to reduce central and peripheral sympathetic activity associated with opioid withdrawal (36–39). Another α-2 agonist, lofexidine, has been used in the United Kingdom since 1992 in the treatment of opioid withdrawal; however, it is not available at present in the United States. Lofexidine is structurally related to clonidine but may have a greater selectivity for the subtype of α-2 receptors. Specifically, while lofexidine retains potent noradrenergic antagonist activity, which is useful in the alleviation of withdrawal, it has limited effect on the blood pressure (1,2,40,41). However, lofexidine can adversely affect cardiac conduction, particularly when given in combination with methadone; therefore close ECG monitoring is warranted. The effectiveness of lofexidine appears to be comparable to that of clonidine, and lofexidine may be particularly useful in outpatient treatment settings where the risk of significant hypotension with higher clonidine doses may not be acceptable. Both clonidine and lofexidine reduce the peripheral (e.g., sympathetic arousal) but not the central (e.g., dysphoria, aches) effects of opioid withdrawal.

Detoxification with Methadone or Buprenorphine

Recent Cochrane Reviews have evaluated detoxification with methadone or buprenorphine, often comparing them to taper strategies using other opioids (e.g., levomethadyl acetate (LAAM), propoxyphene), adrenergic agents (e.g., clonidine), anxiolytics (e.g., chlordiazepoxide, buspirone), or other approaches such as abrupt discontinuation with placebo (41–43). Methadone and buprenorphine tapers are generally comparable and both are superior to placebo, clonidine, and other medications in terms of treatment retention and opioid abstinence (14,41,49). However, the emergence of persistent and/or delayed withdrawal after completing detoxification using agonist or nonagonist medication is a common problem; thus, continued watchfulness and clinical management in the days following detoxification is important to help prevent relapse.

In terms of clinical practice, buprenorphine generally should not be started until a patient is experiencing withdrawal so as to avoid precipitated withdrawal due to the combination of tight receptor binding and partial agonist effects of buprenorphine. One approach is to begin with 2–4 mg buprenorphine when withdrawal symptoms emerge, usually 12–18 h after the last dose of a short-acting opioid, titrate up to 4–16 mg per day until withdrawal symptoms are suppressed, and then taper to 0 mg over the next 7–14 days. Because of buprenorphine's high affinity for opioid receptors, it "self-tapers" and hence more rapid taper schedules (5 days or less) have some evidence of success (47–50). If relapse occurs before the taper is completed, the dose can be increased and tapered again or buprenorphine may be continued as a maintenance treatment with the option of trying detoxification again at some future time.

In several community-based evaluations conducted by the National Institute on Drug Abuse (NIDA) Clinical Trials Network, a buprenorphine taper was well accepted by patients and clinicians and was superior to clonidine-assisted detoxification in terms of discomfort and rates of completing detoxification (46,51,52). A number of studies have examined varying durations of opioid taper, particularly with buprenorphine (see (53) for review). More gradual tapers were generally associated with greater opioid abstinence during the taper than rapid tapers, though there was no significant association between taper duration and severity of withdrawal or retention at the end of detoxification. The studies conducted thus far on the question of taper duration have employed such a wide range of designs and outcome measures that comparisons across them are difficult (53,54). In particular, the interpretation of results is complicated by the fact that variability in taper duration is inherently intertwined with assessment time point. Overall, however, risk for relapse to illicit opioid use after buprenorphine or methadone discontinuation is very high, regardless of variations in taper regimen or population (55).

Detoxification With Clonidine and Other Nonopioid Medications

As noted above, clonidine has modest efficacy in suppressing opioid withdrawal though it can also produce excessive sedation or hypotension (37,38,41) and generally results in less-favorable outcomes than detoxification using methadone or buprenorphine (41,46,51,52). Advantages of clonidine include that it is not a controlled substance, has little risk of diversion or abuse, and can reduce the delay between stopping opioids and starting naltrexone. A clonidine-only taper may be particularly appropriate for highly motivated patients with relatively low-dependence severity, a capacity to tolerate withdrawal discomfort, and a supportive environment.

Other medications that have been used to alleviate withdrawal severity are listed in Table 1 and include benzodiazepines for anxiety and restlessness, preferably agents with slower onset and less abuse potential (e.g., oxazepam); low doses of sedating antidepressants (e.g., doxepin, trazodone) or zolpidem for insomnia; antiemetics for GI distress (e.g., prochlorperazine, ondansetron); and nonsteroidal anti-inflammatories for withdrawal-related aches. Oral hydration (e.g., sports drinks) is also important to prevent dehydration in cases of withdrawal-related nausea, anorexia, vomiting, and diarrhea.

While there is general agreement among experienced clinicians that these adjunctive medications are useful for target symptoms (e.g., anxiety, insomnia), randomized controlled trials that specifically evaluate their optimal dosing, efficacy, and tolerability in managing opioid withdrawal are lacking. Rather, they have been used as part of regimens that combine several medications (e.g., buprenorphine + naltrexone + clonidine) (see below) or administered on an as-needed basis when symptoms emerge (14,56). Administering clonidine and other adjunctive medications proactively, before withdrawal symptoms emerge, may improve symptom control; however, such procedures have not been empirically evaluated.

Detoxification with Buprenorphine + Clonidine

Another strategy involves administration of a small dose of buprenorphine (i.e., 4–8 mg) approximately 16–24 h after the patient ceases opioid use and when withdrawal symptoms begin to occur, followed by administration of clonidine and other adjunctive medications (e.g., benzodiazepines, antiemetics, NSAIDS, sleep medications) (31,57). This approach is based on the rationale that buprenorphine will reduce withdrawal severity while making a transition from a full to a partial agonist. Initiation of naltrexone can then be tried within several days with any naltrexone-precipitated withdrawal managed with clonidine and other ancillary medications. Several variations in this approach have now been reported (14,31,33,58–61) and include one study demonstrating that it permitted administration of extended-release naltrexone within 6–7 days (20).

Rapid Detoxification and Naltrexone Induction

Another procedure involves abrupt discontinuation of opioids followed by initiation of oral naltrexone on day 1 in combination with nonopioid medications (e.g., clonidine, adjunctive medication) to reduce any resulting naltrexone-precipitated withdrawal, then followed by administration of extended-release naltrexone later that day or on the following day if the patient tolerated the initial oral dose. While this approach may permit induction onto naltrexone more quickly than gradual agonist tapers (36,58), data from several studies suggest that it may produce severe withdrawal symptoms that require close medical monitoring and that could be life threatening (e.g., vomiting, diarrhea, hypotension, occasionally delirium) (41,43) and is best used in patients with a low level of physiological dependence.

Ultrarapid Detoxification and Naltrexone Induction

Various regimens have been developed using heavy sedation or general anesthesia with opioid antagonist administration in an effort to initiate naltrexone immediately after ceasing opioids. One ultrarapid detoxification strategy, for example, has been reported in which patients undergo several hours of naloxone-induced withdrawal under general anesthesia with intubation and mechanical ventilation (62). A related approach utilizes intravenous sedation and has a similar 1-day time course of treatment (63,64). Generally these approaches also employ α-2 antagonists (e.g., clonidine) and other adjunctive medications (e.g., antiemetics). While they may increase the likelihood of successful naltrexone induction compared with gradual opioid agonist or clonidine taper, there is no consistent evidence that they produce better outcomes than the more gradual approaches outlined above (33,65–67). Furthermore, ultrarapid induction procedures have produced life-threatening adverse events including aspiration pneumonia, pulmonary edema, diabetic ketoacidosis, and sudden death (33). Patients may also still experience weeks of withdrawal symptoms and the acute stress response is very high, as indicated by markedly elevated plasma adrenocorticotropic hormone, cortisol, and epinephrine levels (68,69). Thus, ultrarapid detoxification cannot be recommended, as it has no clear advantage over more gradual methods and may be medically dangerous (33,67,69–71).

Practice Recommendations

Patient Selection

Motivation is an important factor in selecting patients for naltrexone treatment. Motivation to initiate naltrexone therapy may be found in those not interested in agonist maintenance therapy or long-term residential treatment, who are treated in settings or under circumstances where these treatments are not available, or who are currently receiving agonist maintenance but wish to no longer be dependent on opioid agonists. Worth noting is that patients who have been stable and abstinent on agonists should be encouraged to remain on the effective treatment, particularly if they have a history of failure of other treatment approaches. However, for patients who strongly desire to be detoxified off the agonist, a transition onto antagonists may be a preferred strategy over the one that does not involve pharmacological support.

Prospective, controlled studies that identify differential predictors of response to naltrexone maintenance versus other therapies for opioid dependence have not been conducted but clinical observations (72) suggest that the patient characteristics that are associated with favorable outcomes in other treatment approaches also apply to naltrexone. Examples are patients who are older, employed, and have stable family relationships with minimal antisocial behavior and psychopathology. Furthermore, clinical experience suggests that patients with a lower level of physiological dependence, briefer history of opioid dependence, failure of other treatment methods, and extended opioid-free periods between episodes of use may be better candidates. Patients who have been abstinent for several days, such as those who completed hospital-based detoxification and entered residential treatment program, those who are leaving a controlled environment, or those who were able to discontinue use at home and remain abstinent, are also good candidates as are those who have tried antagonist-based treatment previously with some success. Relative contraindications to naltrexone treatment include inability to tolerate at least some temporary discomfort and presence of chronic pain or other medical issues that require ongoing treatment with opioid agonists, as well as a history of overdose, particularly following detoxification or during prior treatment with naltrexone. Finally, it should be noted that many opioid-dependent patients, particularly those with lengthy histories and/or high levels of opioid dependence, will have better outcomes with long-term maintenance on buprenorphine or methadone.

While not developed for opioid-dependent patients per se, the Patient Placement Criteria (PPC) of the American Society of Addiction Medicine may provide a useful framework for evaluating opioid-dependent patients and making decisions about appropriate treatment options (73,74). For example, the PPC call for systematic assessment of the patient across six dimensions: (1) withdrawal severity potential; (2) biomedical conditions and complications; (3) psychiatric conditions and complications; (4) readiness for change; (5) relapse/continued use potential; and (6) environmental conditions. Research is not yet available that addresses how levels of severity in one or more of the six PPC dimensions may predict a more favorable outcome using agonist maintenance, long-term residential treatment, or detoxification and transition to antagonist maintenance. It also should be noted

that whatever patient outcome predictors may be identified in controlled studies, limited access to agonist maintenance or long-term residential therapies may frequently influence the choice of therapy.

Summary of Naltrexone Induction Methods

The available scientific and clinical evidence suggest that there is no single best detoxification method but rather a set of pharmacologic approaches and treatment settings that can be customized to individual patient needs. Preference and the amount of experience that the treatment team have with a particular method are important factors for treatment success. Additionally, the ability of the treatment team to expect and respond to emerging complications, their enthusiasm and confidence in the method, and the general attitudes and expectations of both patients and clinician can influence outcomes (75,76). A treatment algorithm based on the setting and anticipated level of withdrawal severity is presented in Table 2. The most effective method will likely balance the degree of discomfort that the patient tolerates with the best available management strategies and shortest duration of treatment that will minimize the likelihood of relapse before starting naltrexone.

For all patients, in addition to a thorough substance use-focused history and physical examination, a urine test for natural and synthetic opiates (e.g., oxycodone, methadone, buprenorphine) should be done to confirm abstinence prior to starting naltrexone, particularly in outpatient settings. It is important to note the different types of prescription opioids being used and to ensure that the test can detect all that the patient may have used. Patients should be fully and carefully informed of the potential risks associated with opioid detoxification and naltrexone induction prior to initiating treatment. It is especially important that patients understand the risk of precipitated withdrawal and the importance of having a clear and accurate assessment of recent substance use. If any significant doubt remains about a patient's opioid status, a naloxone challenge (0.8–1.6 mg IM/IV) or a low dose of oral naltrexone (e.g., 6 mg to one-eighth of a 50 mg tablet) that minimizes the risk of severe withdrawal should be used to confirm the absence of physiologic dependence. A variety of brief standardized assessments are available that can be used to provide an objective measure of opioid withdrawal generally, but particularly in the period following antagonist challenge. For example, the Clinical Institute Narcotic Assessment (77) is an 11-item instrument that is commonly used in clinical settings and combines self-report items with observer-rated signs of withdrawal. The Clinical Opiate Withdrawal Scale (78) is an 11-item instrument that assesses many of the same symptoms as well as two physiological measures (i.e., blood pressure, pupil diameter). Once it is determined that the antagonist challenge produced no discernible withdrawal, administration of a therapeutic dose of naltrexone may proceed.

Patients with a *mild level* of opioid dependence (1–2 bags per day of heroin or less than 50 mg of oxycodone or the equivalent dose of other opioids) may likely be able to initiate naltrexone in an outpatient or partial hospital setting using clonidine and ancillary medications, though some may benefit from a single transitional dose of buprenorphine 4 mg on day 1 following discontinuation of their opioid agonist. As above, naloxone or low-dose naltrexone challenge should always be used if there is concern about the veracity of

patient self-report. Patients with a *moderate level* of opioid dependence (3–6 bags per day of heroin, 50–100 mg of oxycodone, or the equivalent amount of other opioids, and those completing a methadone or buprenorphine taper) are best managed in a partial hospital setting with hospitalization available as a backup. A taper regimen for patients whose anticipated level of withdrawal is moderate includes 3–4 days of treatment with clonidine and adjunctive medication and buprenorphine (4–8 mg/day) on the first 1–2 days to attenuate withdrawal severity. Aggressive oral hydration to avoid dehydration and vital signs taken standing and sitting 1.5–2 h after each clonidine dose will monitor for postural hypotension and the need to adjust the clonidine dose. Two days after discontinuing buprenorphine, typically on days 3–4, oral naltrexone induction can be initiated. The algorithm is similar for patients whose level of withdrawal is anticipated to be *severe* (>6 bags per day of heroin, >100 mg oxycodone, or the equivalent), except that it requires an inpatient setting to permit closer monitoring, since higher doses of clonidine and sedative/ hypnotics have greater potential for hypotension and other side effects, and to minimize the chances for relapse prior to starting naltrexone. It may be necessary to extend the interval between the last dose of buprenorphine and the initiation of naltrexone by 1–3 days for patients with more severe withdrawal to minimize the risk of precipitated withdrawal. In all the cases of high levels of physiologic dependence, a naloxone challenge prior to receiving naltrexone will minimize the chance of precipitated withdrawal. If the test is negative, a low dose of oral naltrexone (6 mg) followed by a second higher dose in 3–4 h (12–25 mg) and a full therapeutic dose on the next day will further minimize the chances for precipitated withdrawal. If a discernible amount of withdrawal is precipitated with the first naltrexone dose, the second dose should be postponed until the next day and preceded by a urine test and repeat naloxone challenge. Pretreatment with adjunctive medications (e.g., clonidine, sedatives, antiemetic) approximately 1–2 h before the first dose of naltrexone and a clear-liquid diet on the first day of naltrexone induction will further minimize the chances for withdrawal-associated distress.

The expected level of medical monitoring will guide the choice of treatment setting and intervention needed to assure safe and successful naltrexone induction. In addition to the anticipated level of physiologic dependence, clinical experience suggests that factors such as medical and psychiatric comorbidity and lack of a supportive home environment for sustaining abstinence during detoxification may also suggest the need for a higher level of treatment setting even in the presence of milder dependence severity.

Use of Ancillary Medications during Detoxification and Naltrexone Induction

Careful monitoring and use of ancillary medications can impact the tolerability of detoxification and eventual success of naltrexone induction (Table 1). Clonidine can be helpful but may require using the high range of doses (0.2–0.3 mg, QID), thus increasing the risk for clinically significant hypotension. While severe hypotension is rarely a problem when adequate premedication with clonidine and buprenorphine and aggressive oral hydration are used, intravenous fluids should be available as a backup. Other essential adjunctive medications include a low abuse liability benzodiazepine for anxiety and muscle tension (e.g., clonazepam, oxazepam, chlordiazepoxide), an NSAID or acetaminophen for aches and pain, and a medication for sleep disturbance. A medication for nausea, such as

prochlorperazine, may also be added as needed. Many of the descriptions in the literature recommend adding in these medications "PRN" – that is, administering them reactively once withdrawal symptoms set in. Clinical experience suggests that it may be better to start these medications *before* the onset of withdrawal symptoms as regular standing doses rather than PRN, in order to "stay ahead" of emerging symptoms. Serious withdrawal symptoms can begin fairly quickly and, if the patient has not been premedicated, it can be difficult to get symptoms under control once they emerge. Adjunctive medications may also be used during the first few weeks of stabilization on naltrexone to suppress residual signs and symptoms of withdrawal, particularly in patients who transitioned rapidly from heroin onto naltrexone. Most commonly seen are insomnia, anergy, anxiety, irritability, and anhedonia (79). Proactive treatment of insomnia using nonbenzodiazepine hypnotics, sedating antidepressants, or sedating atypical neuroleptics improves treatment engagement. Other symptoms of protracted withdrawal may respond to clonidine. Most of these symptoms, and the need for adjunctive medication, resolve within 2–4 weeks of naltrexone initiation.

Safety Concerns – Testing the Blockade, Relapse Management, and Risk of Overdose

Some patients will "test the blockade" (i.e., use opioids while on naltrexone), because of craving, contact with other drug abusers, or curiosity. It most commonly happens in the first few days after naltrexone initiation, on — one to three occasions, using low doses of the opioid, after which the patient is reassured that the blockade "works" and will not attempt it again (80). A minority of patients will use large amounts in attempts to surmount the blockade, which can occur if the patient has access to large amounts of opioids (25,81). Interestingly some of these patients are interested in continuing naltrexone and can remain on it with close monitoring and the expectation that this behavior will promptly stop. A transition to agonist treatment or longer-term residential treatment should be initiated in patients who are unwilling to maintain compliance with naltrexone. Long-acting preparations of naltrexone are likely better in retaining patients who test the blockade; however, clinical experience shows that some patients receiving a long-acting preparation of naltrexone can begin to experience opioid-like effects of heroin 2–3 weeks after the injection and may become re-dependent, possibly due to individual differences in metabolism. More frequent extended-release naltrexone dosing (every 3 weeks) or supplementation with oral naltrexone should be considered in these patients.

Most commonly, relapse and physiological redependence occurs when the patient stops coming for appointments and taking the medication. The blockade wears off after 1–2 days from the last dose of the oral formulation and 5–6 weeks after the last dose of extended-release naltrexone (82). It is important to quickly respond to signs that a patient is losing motivation for treatment (e.g., missing doses or appointments) with attempts to reengage the patient (83). Pairing naltrexone therapy with additional psychosocial support can also improve adherence (9,16,84–86). For example, involving the patient's significant other or close peers has been found useful in improving adherence to oral naltrexone (17,19,27,87,88), and this might be expected to generalize to injectable naltrexone. If there are signs that a patient is at risk for relapse or has relapsed, inpatient stabilization and/or detoxification followed by another attempt at naltrexone treatment, referral to residential treatment or a sober house, or an agonist treatment should be initiated.

Opioid overdose is always a serious concern when dealing with opioid-dependent patients. Particularly risky times include when patients are unfavorably discharged or drop out of agonist maintenance treatment (89) as well as when tolerance is lost following completion of opioid detoxification or following release from a controlled environment where they have been detoxified, such as prison (90–93). The risk of opioid overdose is also increased when naltrexone is discontinued, at which time patients' level of tolerance to opioids is much lower than it was prior to treatment. All patients should be educated about the risk of overdose, and treatment providers should consider this risk and educate the patient and the patient's family when developing an appropriate treatment plan. It should be assumed that most patients dropping out of treatment do so to resume opioid use. Some evidence suggests that overdose risk may be lower when patients are maintained on sustained-release rather than oral naltrexone (94), particularly as the blocking effects abate more gradually with a long-acting preparation of naltrexone and there is a longer period of time in which therapeutic interventions can be implemented. Nonetheless, a contingency plan for such an event is essential; it should be *prearranged* with the patient and others in their support network. Patient and family education, with a detailed description of the relapse process and associated risks, is of paramount importance. A detailed, written consent form may also be useful at treatment initiation and periodically afterwards to help ensure the patient understands and agrees to the relapse contingency plan. Other elements of the plan should include (1) active follow-up by the clinical team and supportive other(s) as appropriate; (2) reassessment of the patient's needs and revised preferences; and (3) discussion of what treatment to use in the event of relapse. In most cases, relapse occurs in the first 1–3 months of treatment after which the risk of relapse is significantly lower.

Duration of Treatment

If successful stabilization on naltrexone is achieved, a plan is still needed to facilitate continued medication adherence and recovery. There are no controlled data assessing the optimal duration of treatment with naltrexone but clinical experience suggests the longer the period of treatment, the greater the chance of a lifelong recovery (72). It is not known if a long enough period of treatment may allow for stopping the naltrexone without the increased risk of relapse. Ongoing efforts to work with the patient's support network are important, particularly in the early stages of treatment, as they will help facilitate continued naltrexone adherence. Ongoing supportive or cognitive therapy, voucher-based incentives for adherence, and family counseling may still be needed for promoting continued adherence (9,16,17,19).

Future Directions for Research

More research is needed to improve the available methods for inducting opioid-dependent patients onto antagonist therapy. Particularly important questions include the following: (1) Should the initial dose of buprenorphine be limited to the minimum needed to attenuate initial spontaneous withdrawal or will a higher initial dose help attenuate subsequent precipitated withdrawal when naltrexone is introduced? (2) Once a low dose of oral naltrexone (e.g., 6–12.5 mg) has been tolerated, can extended-release, injectable naltrexone be administered right away or is it important to build up to a 25 or 50 mg daily oral

naltrexone dose before naltrexone injection is given? Novel alternatives to the rapid induction schedule may also have promise, including outpatient stabilization on buprenorphine and a slow cross-taper of buprenorphine to naltrexone over a 30-day period (95) or an outpatient procedure when naltrexone is introduced first at much lower doses such as 1 mg. Additional questions to be answered by longer-term studies include the optimal duration of treatment (53) and the degree to which patients will continue on extended-release formulations of naltrexone versus their preference to use oral preparations on a daily or as-needed basis.

A limitation of the buprenorphine–clonidine– naltrexone procedure, even if further optimized, is that spontaneous and precipitated withdrawal will always be a concern and must be anticipated and actively managed. Such management frequently requires partial hospital or inpatient settings and/or medication, which are expensive and require a trained and experienced clinical staff and also some discomfort on the part of patients, which may lead to patient attrition. As a result, more research is needed on new medications or schedules that might substantially reduce the severity of withdrawal and make the induction shorter, less symptomatic, and easier to manage (61). The list of ancillary medications currently employed (Table 1) has also changed little in the last 20 years. Recent clinical experience suggests that methylphenidate (20-60 mg/day) may attenuate withdrawal severity during naltrexone induction, perhaps by countering the hypotensive effects of clonidine and allowing more aggressive clonidine dosing and by providing some dopaminergic stimulation to counter the dysphoria of opioid withdrawal (89). One study suggested that adding a daily dose of buprenorphine once patients achieve a therapeutic dose of naltrexone might suppress cocaine use via its antagonist effects on the κ-opioid receptor and agonist effects at the nociceptin-opioid receptor (96). Other pharmacological strategies, including NMDA receptor antagonists, serotonin reuptake inhibitors, α-2 adrenergic, opioid, and γ-aminobutyric acid agonist medications, are also being explored (61,97).

Conclusion

Opioid dependence is a significant public health problem associated with high risk for relapse in outpatient settings if medication maintenance therapy is not ongoing. When an opioid-dependent patient presents for treatment, an evaluation of clinical characteristics and environmental conditions is important for pairing the patient with the most appropriate treatment approach, which typically ranges from agonist maintenance to detoxification followed by residential treatment and/or medication-assisted therapy using naltrexone. For patients determined to be appropriate for opioid detoxification and subsequent naltrexone maintenance, we recommend that naltrexone be introduced early during the detoxification to minimize the possibility of dropout before treatment can be implemented. To minimize the severity of withdrawal resulting from abrupt agonist cessation, 1-2 doses of buprenorphine can be given followed by progressive doses of oral naltrexone over 3-5 days, at which point a target dose of oral naltrexone or injection naltrexone may be administered. Additional considerations (e.g., timing of the agonist-to-antagonist transition, the choice of adjunctive medications for managing withdrawal, arranging treatment alternatives, and long-term plans) can also influence the probability of patient success. Here we have provided an overview of what is currently known about how to best transition patients from

physiological opioid dependence to naltrexone. Overall, more research is needed on how to identify patients who are best suited for antagonist therapy, the most effective ways to transition them from physiological opioid dependence to naltrexone, how long naltrexone treatment should be continued, and how best to facilitate it. The development of sustained-duration naltrexone formulations has the potential to change the image of naltrexone from a medication with very limited impact to one with more substantial promise for treating opioid dependence. Here we have summarized the existing knowledge on how to get patients started on naltrexone, but much more information is needed on this and many other areas so as to take full advantage of this new and potentially valuable addition to the existing treatment options.

Acknowledgments

References

1. Hser YI, Hoffman V, Grella CE, Anglin MD. A 33-year follow-up of narcotic addicts. Arch Gen Psychiatry. 2001; 58(5):503–508. [PubMed: 11343531]

2. Robertson JR, Ronald PJ, Raab GM, Ross AJ, Parpia T. Deaths HIV infection, abstinence, and other outcomes in a cohort of injecting drug users followed up for 10 years. BMJ. 1994; 309(6951):369–372. [PubMed: 8081134]

3. Tai, B.; Blaine, J. [Last accessed on March 4, 2011] Naltrexone: An antagonist therapy for heroin addiction; NIDA Meeting Summary. Nov. 1997 p. 12-13.Available at http://www.archives.drugabuse.gov/meetings/naltrexone.html

4. Mayet S, Farrell M, Ferri MMF, Amato L, Davoli M. Psychosocial treatment for opiate abuse and dependence. Cochrane Database Syst Rev. 2004; 4:CD004330. [PubMed: 24737603]

5. Amato L, Minozzi S, Davoli M, Vecchi S, Ferri MM, Mayet S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. Cochrane Database Syst Rev. 2008; 4:CD005031. [PubMed: 18843675]

6. Wang D, Sun X, Sadee W. Different effects of opioid antagonists on mu-, delta-, and kappa-opioid receptors with and without agonist pretreatment. J Pharmacol Exp Ther. 2007; 321:544–552. [PubMed: 17267582]

7. Gonzalez JP, Brogden RN. Naltrexone: A review of the pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. Drugs. 1988; 35:192–213. [PubMed: 2836152]

8. Martin WR, Jasinski DR, Mansky PA. Naltrexone, an antagonist for the treatment of heroin dependence. Effects in man Arch Gen Psychiatry. 1973; 28(6):784–791.

9. Preston KL, Silverman K, Umbricht A, DeJesus A, Montoya ID, Schuster CR. Improvement in naltrexone treatment compliance with contingency management. Drug Alcohol Depend. 1999; 54:127–135. [PubMed: 10217552]

10. Kleber HD, Kosten TR, Gaspari J, Topazian M. Nontolerance to the opioid antagonism of naltrexone. Biol Psychiatry. 1985; 20:66–72. [PubMed: 2981129]

11. Jaffe, JH.; Martin, WR. Opioid analgesics and antagonists. In: Goodman Gilman, A.; Rall, TW.; Nies, AS.; Taylor, P., editors. Goodman and Gilman's the Pharmacological Basis of Therapeutics. New York, NY: Pergamon Press; 1990. p. 485-521.

12. Kosten TR, Morgan C, Kleber HD. Treatment of heroin addicts using buprenorphine. Am J Drug Alc Abuse. 1991; 17(2):119–128.

13. Rounsaville, BJ. Can psychotherapy rescue naltrexone treatment of opioid addiction?. In: Onken, LS.; Blaine, JD., editors. Potentiating the Efficacy of Medications NIDA Research Monograph. Vol. 105. Rockville, MD: National Institute on Drug Abuse; 1995. p. 37-52.

14. O'Connor PG, Carroll KM, Shi JM, Schottenfeld RS, Kosten TR, Rounsaville BJ. Three methods of opioid detoxification in a primary care setting: A randomized trial. Ann Intern Med. 1997; 127:526–530. [PubMed: 9313020]

15. Stine, SM.; Kosten, TR. Pharmacologic interventions for opioid dependence. In: Ries, RK.; Fiellin, DA.; Miller, SC.; Saitz, R., editors. Principles of Addiction Medicine. 4th. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.

16. Carroll KM, Sinha R, Nich C, Babuscio T, Rounsaville BJ. Contingency management to enhance naltrexone treatment of opioid dependence: A randomized clinical trial of reinforcement magnitude. Exp Clin Psychopharmacol. 2002; 10:54–63. [PubMed: 11866252]

17. Fals-Stewart W, O'Farrell TJ. Behavioral family counseling and naltrexone for male opioid-dependent patients. J Consult Clin Psychol. 2003; 71:432–442. [PubMed: 12795568]

18. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev. 2006; 2:CD001333.

19. Nunes EV, Rothenberg JL, Sullivan MA, Carpenter KM, Kleber HD. Behavioral therapy to augment oral naltrexone for opioid dependence: A ceiling on effectiveness? Am J Drug Alcohol Abuse. 2006; 32:503–517. [PubMed: 17127538]

20. Comer SD, Sullivan MA, Yu E, Rothenberg JL, Kleber HD, Kampman K, Dackis C, O'Brien CP. Injectable, sustained-release naltrexone for the treatment of opioid dependence: A randomized, placebo-controlled trial. Arch Gen Psychiatry. 2006; 63(2):210–218. [PubMed: 16461865]

21. Hulse GK, Morris N, Arnold-Reed D, Tait RJ. Improving clinical outcomes in treating heroin dependence: Randomized, controlled trial of oral or implant naltrexone. Arch Gen Psychiatry. 2009; 66(10):1108–1115. [PubMed: 19805701]

22. Krupitsky EM, Blokhina EA. Long-acting depot formulations of naltrexone for heroin dependence: A review. Curr Opin Psychiatry. 2010; 23(3):210–214. [PubMed: 20224403]

23. Garbutt JC, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BL, Loewy JW, Ehrich EW. Vivitrex Study Group Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: A randomized controlled trial. JAMA. 2005; 293(13):1617–1625. [PubMed: 15811981]

24. O'Malley SS, Garbutt JC, Gastfriend DR, Dong Q, Kranzler HR. Efficacy of extended-release naltrexone in alcohol-dependent patients who are abstinent before treatment. J Clin Psychopharmacol. 2007; 27:507–512. [PubMed: 17873686]

25. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: A double-blind, placebo-controlled, multicentre randomised trial. Lancet. 2011; 377:1506–1513. [PubMed: 21529928]

26. Krupitsky E, Zvartau E, Woody G. Use of naltrexone to treat opioid addiction in a country in which methadone and buprenorphine are not available. Curr Psychiatry Rep. 2010; 12(5):448–453. [PubMed: 20640538]

27. Krupitsky EM, Zvartau EE, Masalov DV, Tsoi MV, Burakov AM, Egorova VY, Didenko TY, Romanova TN, Ivanova EB, Bespalov AY, Verbitskaya EV, Neznanov NG, Grinenko AY, O'Brian CP, Woody GE. Naltrexone for heroin dependence treatment in St. Petersburg, Russia. J Subst Abuse Treat. 2004; 26(4):285–294. [PubMed: 15182893]

28. Christie MJ. Cellular neuroadaptations to chronic opioids: Tolerance, withdrawal and addiction. Br J Pharmacol. 2008; 154:384–396. [PubMed: 18414400]

29. Nestler EJ. Historical review: Molecular and cellular mechanisms of opiate and cocaine addiction. Trends Pharmacol Sci. 2004; 25:210–218. [PubMed: 15063085]

30. Chang, G.; Kosten, TR. Detoxification, section VI, chapter 35 In Substance Abuse: A Comprehensive Textbook. 4th. Lowinson, JH.; Ruiz, P.; Millman, RB.; Langrod, JG., editors. Philadelphia, PA: Lippincott Williams & Wilkins; 2005. p. 579-587.

31. Kosten TR, O'Connor PG. Current concepts-management of drug withdrawal. N Engl J Med. 2003; 348:1786–1795. [PubMed: 12724485]

32. Vivitrol® US prescribing information. [Last accessed on March 4, 2011] Available at http://www.vivitrol.com/hcp/Vivitrol_Info/default.aspx

33. Collins ED, Kleber HD, Whittington RA, Heitler NE. Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: A randomized trial. JAMA. 2005; 294:903. [PubMed: 16118380]

34. Department of Health–Mental Health and Drug and Alcohol Office. Rapid Detoxification from Opioids-Guidelines. North Sydney, NSW: Department of Health NSW; 2005. Available at www.health.nsw.gov.au [Accessed on December 15, 2011]

35. Sullivan MA, Nunes EV. New-onset mania and psychosis following heroin detoxification and naltrexone maintenance. Am J Addict. 2005; 14:486–487. [PubMed: 16257886]

36. Kleber HD, Gold MS, Riordan CE. The use of clonidine in detoxification from opiates. Bull Narc. 1980; 32:1–10. [PubMed: 6907020]

37. Gold MS, Pottash AC, Sweeney DR, Kleber HD. Opiate withdrawal using clonidine A safe, effective, and rapid nonopiate treatment. JAMA. 1980; 243(4):343–346. [PubMed: 7351747]

38. Gold MS, Pottash AL, Sweeney DR, Kleber HD. Efficacy of clonidine in opiate withdrawal: A study of thirty patients. Drug Alcohol Depend. 1980; 6(4):201–208. [PubMed: 7023893]

39. Taylor JR, Elsworth JD, Garcia EJ, Grant SJ, Roth RH, Redmond DE. Clonidine infusions into the locus coeruleus attenuate behavioral and neurochemical changes associated with naloxone-precipitated withdrawal. Psychopharmacology. 1988; 96(1):121–134. [PubMed: 3147472]

40. Yu E, Miotto K, Akerele E, Montgomery A, Elkashef A, Walsh R, Montoya I, Fischman MW, Collins J, McSherry F, Boardman K, Davies DK, O'Brien CP, Ling W, Kleber H, Herman BH. A Phase 3 placebo-controlled, double-blind, multi-site trial of the alpha-2-adrenergic agonist, lofexidine, for opioid withdrawal. Drug Alcohol Depend. 2008; 97(1–2):158–168. [PubMed: 18508207]

41. Gowing L, Farrell M, Ali R, White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Database Syst Rev. 2009:CD002024. [PubMed: 19370574]

42. Amato L, Davoli M, Minozzi S, Ali R, Ferri M. Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database Syst Rev. 2005; 3:CD003409. [PubMed: 16034898]

43. Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. Cochrane Database Syst Rev. 2009; (3):CD002025.10.1002/14651858.CD002025.pub4 [PubMed: 19588330]

44. Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE. A clinical trial of buprenorphine: Comparison with methadone in the detoxification of heroin addicts. Clin Pharmacol Ther. 1988; 43(1):72–78. [PubMed: 3275523]

45. Cameron D, Allen D, Galway K. A pilot study of the effectiveness of buprenorphine and methadone as detoxification agents when choice is given to the consumer. J Sub Use. 2001; 6:101–109.

46. Ling W, Amass L, Shoptaw S, Annon JJ, Hillhouse M, Babcock D, Brigham G, Harrer J, Reid M, Muir J, Buchan B, Orr D, Woody G, Krejci J, Ziedonis D. Buprenorphine Study Protocol Group. A multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid detoxification: Findings from the National Institute on Drug Abuse Clinical Trials Network. Addiction. 2005; 100:1090–1100. [PubMed: 16042639]

47. Lintzeris N. Buprenorphine dosing regime in the management of out-patient heroin withdrawal. Drug Alcohol Rev. 2002; 21:39–45. [PubMed: 12189003]

48. Lintzeris N, Bell J, Bammer G, Jolley DJ, Rushworth L. A randomized controlled trial of buprenorphine in the management of short-term ambulatory heroin withdrawal. Addiction. 2002; 97(11):1395–1404. [PubMed: 12410780]

49. Rounsaville BJ, Kosten T, Kleber H. Success and failure at outpatient opioid detoxification: Evaluating the process of clonidine- and methadone-assisted withdrawal. J Nerv Ment Dis. 1985; 173:103–110. [PubMed: 3881558]

50. Woody GE, Kane V, Lewis K, Thompson R. Premature deaths following discharge from methadone maintenance: A replication. J Addict Med. 2007; 1(4):180–185. [PubMed: 21768955]

51. Ziedonis DM, Amass L, Steinberg M, Woody G, Krejci J, Annon JJ, Cohen AJ, Waite-O'Brien N, Stine SM, McCarty D, Reid MS, Brown LS Jr, Maslansky R, Winhusen T, Babcock D, Brigham G, Muir J, Orr D, Buchan BJ, Horton T, Ling W. Predictors of outcome for short-term medically supervised opioid withdrawal during a randomized, multicenter trial of buprenorphine-naloxone and clonidine in the NIDA clinical trials network drug and alcohol dependence. Drug Alcohol Depend. 2009; 99:28–36. [PubMed: 18805656]

52. Amass L, Ling W, Freese TE, Reiber C, Annon JJ, Cohen AJ, McCarty D, Reid MS, Brown LS, Clark C, Ziedonis DM, Krejci J, Stine S, Winhusen T, Brigham G, Babcock D, Muir JA, Buchan BJ, Horton T. Bringing buprenorphine–naloxone detoxification to community treatment providers: The NIDA Clinical Trials Network field Experience. Am J Addict. 2004; 13:S42–S66. [PubMed: 15204675]

53. Dunn KE, Sigmon SC, Strain EC, Heil SH, Higgins ST. The association between outpatient buprenorphine detoxification duration and clinical treatment outcomes: A review. Drug Alcohol Depend. 201110.1016/j.drugalcdep.2011.05.033

54. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2008; 2:CD002207. [PubMed: 18425880]

55. Weiss RD, Potter JS, Provost SE, Huang Z, Jacobs P, Hasson A, Lindblad R, Connery HS, Prather K, Ling W. A multi-site, two-phase, Prescription Opioid Addiction Treatment Study (POATS): Rationale, design, and methodology. Contemp Clin Trials. 2010; 31(2):189–199. [PubMed: 20116457]

56. Stine SM, Kosten TR. Use of drug combinations in treatment of opioid withdrawal. J Clin Psychopharmacol. 1992; 12:203–209. [PubMed: 1629388]

57. Rothenberg JL, Sullivan MA, Church SH, Seracini A, Collins E, Kleber HD, Nunes EV. Behavioral naltrexone therapy: An integrated treatment for opiate dependence. J Subst Abuse Treat. 2002; 23(4):351–360. [PubMed: 12495797]

58. Vining E, Kosten TR, Kleber HD. Clinical utility of rapid clonidine-naltrexone detoxification for opioid abusers. Br J Addict. 1988; 83(5):567–575. [PubMed: 3382815]

59. O'Connor PG, Waugh ME, Carroll KM, Rounsaville BJ, Diagkogiannis IA, Schottenfeld RS. Primary care-based ambulatory opioid detoxification: The results of a clinical trial. J Gen Intern Med. 1995; 10:255–260. [PubMed: 7616334]

60. Umbricht A, Montoya ID, Hoover DR, Demuth KL, Chiang CT, Preston KL. Naltrexone shortened opioid detoxification with buprenorphine. Drug Alcohol Depend. 1999; 56(3):181–190. [PubMed: 10529020]

61. Bisaga A, Sullivan MA, Cheng W, Carpenter KM, Mariani JM, Levin FR, Raby WN, Nunes EV. A placebo controlled trial of memantine as an adjunct to oral naltrexone for opioid dependence. Drug Alcohol Depend. 2011 Jun 28. Epub ahead of print.

62. O'Connor PG, Kosten TR. Rapid and ultrarapid opioid detoxification techniques. JAMA. 1998; 279:229. [PubMed: 9438745]

63. Brewer C, Rezac H, Bailey C. Opioid withdrawal and naltrexone induction in 48–72 hours with minimal dropout, using a modification of the naltrexone-clonidine technique. Br J Psychiatry. 1988; 153:340–343. [PubMed: 3250670]

64. Brewer C. Ultra-rapid antagonist-precipitated opiate detoxification under general anaesthesia or sedation. Addict Biol. 1997; 2:291–302.

65. Rabinowitz J, Cohen H, Tarrasch R, Kotler M. Compliance to naltrexone treatment after ultra-rapid opiate detoxification: An open label naturalistic study. Drug Alcohol Depend. 1997; 47:77–86. [PubMed: 9298329]

66. Cucchia AT, Monnat M, Spagnoli J, Ferrero F, Bertschy G. Ultra-rapid opiate detoxification using deep sedation with oral midazolam: Short and long-term results. Drug Alcohol Depend. 1998; 52:243–250. [PubMed: 9839150]

67. Gowing L, Ali R, White JM. Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. Cochrane Database Syst Rev. 2010 Jan.20(1):CD002022. [PubMed: 20091529]

68. Kienbaum P, Thuraf N, Michel MC, Scherbaum N, Gastpar M, Peters J. Profound increase in epinephrine concentration in plasma and cardiovascular stimulation after mu-opioid receptor

blockade in opioid- addicted patients during barbiturate-induced anesthesia for acute detoxification. Anesthesiology. 1998; 88:1154–1161. [PubMed: 9605673]

69. Elman I, D'Ambra MN, Krause S, Breiter H, Kane M, Morris R, Tuffy L, Gastfriend DR. Ultrarapid opioid detoxification: Effects on cardiopulmonary physiology, stress hormones and clinical outcomes. Drug Alcohol Depend. 2001; 61(2):163–172. [PubMed: 11137281]

70. Pfab R, Hirtl C, Zilker T. Opiate detoxification under anesthesia: No apparent benefit but suppression of thyroid hormones and risk of pulmonary and renal failure. J Toxicol Clin Toxicol. 1999; 37:43–50. [PubMed: 10078159]

71. Hamilton RJ, Olmedo RE, Shah S, et al. Complications of ultrarapid opioid detoxification with subcutaneous naltrexone pellets. Acad Emerg Med. 2002; 9(1):63–68. [PubMed: 11772672]

72. Resnick RB, Washton AM, Thomas MA, Kestenbaum RS. Naltrexone in the treatment of opiate dependence. NIDA Res Monogr. 1978; 19:321–332. [PubMed: 218108]

73. O'Brien CP, Koob GF, Mee-Lee D, Rosenthal RN. New developments in addiction treatment. J Clin Psychiatry. 2006; 67:1801–1812. [PubMed: 17196062]

74. Chuang E, Wells R, Alexander JA, Friedmann PD, Lee IH. Factors associated with use of ASAM criteria and service provision in a national sample of outpatient substance abuse treatment units. J Addict Med. 2009; 3:39–150.

75. Gossop M, Johns A, Green L. Opiate withdrawal: Inpatient versus outpatient programmes and preferred versus random assignment to treatment. Br Med J (Clin Res Ed). 1986; 293:103–104.

76. Phillips GT, Gossop M, Bradley B. The influence of psychological factors on the opiate withdrawal syndrome. Br J Psych. 1986; 149:235–238. l.

77. Peachy JE, Lei H. Assessment of opioid dependence with naloxone. Br J Addiction. 1988; 83(2):193–201.

78. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs. 2003; 35(2):253–259. [PubMed: 12924748]

79. Mariani, JJ.; Sullivan, M.; Bisaga, A.; Carpenter, K.; Murray, KA.; Levin, FR.; Nunes, EV. Naltrexone-induced protracted opioid withdrawal. Poster presented at CPDD 71st Annual Meeting; Reno, Nevada. 2009.

80. Kunøe N, Lobmaier P, Vederhus JK, Hjerkinn B, Gossop M, Hegstad S, Kristensen Ø, Waal H. Challenges to antagonist blockade during sustained-release naltrexone treatment. Addiction. 2010; 105(9):1633–1639. [PubMed: 20707781]

81. Fishman M. Precipitated withdrawal during maintenance opioid blockade with extended release naltrexone. Addiction. 2008; 103(8):1399–1401. [PubMed: 18855831]

82. Comer SD, Sullivan MA, Hulse GK. Sustained-release naltrexone: Novel treatment for opioid dependence. Expert Opin Investig Drugs. 2007; 16(8):1285–1294.

83. Sullivan MA, Garawi F, Bisaga A, Comer SD, Carpenter K, Raby WN, Anen SJ, Brooks AC, Jiang H, Akerele E, Nunes EV. Management of relapse in naltrexone maintenance for heroin dependence. Drug Alcohol Depend. 2007; 91(2–3):289–292. [PubMed: 17681716]

84. Everly JJ, DeFulio A, Koffarnus MN, Leoutsakos JM, Donlin WD, Aklin WM, Umbricht A, Fingerhood M, Bigelow GE, Silverman K. Employment-based reinforcement of adherence to depot naltrexone in unemployed opioid-dependent adults: A randomized controlled trial. Addiction. 2011; 106(7):1309–1318. [PubMed: 21320227]

85. Grabowski J, O'Brien CP, Greenstein R, Ternes J, Long M, Steinberg-Donato S. Effects of contingent payment on compliance with a naltrexone regimen. Am J Drug Alcohol Abuse. 1979; 6(3):355–365. [PubMed: 539577]

86. Kosten TR, Kleber HD. Strategies to improve compliance with narcotic antagonists. Am J Drug Alcohol Abuse. 1984; 10(2):249–266. [PubMed: 6475891]

87. Galanter M, Brook D. Network therapy for addiction: Bringing family and peer support into office practice. Int J Group Psychother. 2001; 51(1):101–122. [PubMed: 11191590]

88. Krupitsky EM, Zvartau EE, Masalov DV, Tsoy MV, Burakov AM, Egorova VY, Didenko TY, Romanova TN, Ivanova EB, Bespalov AY, Verbitskaya EV, Neznanov NG, Grinenko AY, O'Brien CP, Woody GE. Naltrexone with or without fluoxetine for preventing relapse to heroin addiction in St. Petersburg, Russia J Subst Abuse Treat. 2006; 31(4):319–328.

89. Ockert DM, Volpicelli JR, Baier AR, Coons EE, Fingesten A. A nonopioid procedure for outpatient opioid detoxification. J Addiction Med. 2011; 5(2):110–114.

90. Darke S, Ross J, Zador D, Sunjic S. Heroin-related deaths in New South Wales, Australia, 1992-1996. Drug Alcohol Depend. 2000; 60:141–150. [PubMed: 10940541]

91. Seal KL, Kral AH, Gee L, Moore LD, Bluthenthal RN, Lorvick J, Edlin BR. Predictors and prevention of nonfatal overdose among street-recruited injection heroin users in the San Francisco Bay area, 1998–1999. Am J Pub Health. 2001; 91:1842–1846. [PubMed: 11684613]

92. Binswanger IA, Stern MF, Deyo RA, Heagerty PJ, Cheadle A, Elmore JG, Koepsell TD. Release from prison: A high risk of death for former inmates. New Engl J Med. 2007; 356:157–165. [PubMed: 17215533]

93. Kinlock TW, Gordon MS, Schwartz RP, Fitzgerald TT, O'Grady K. A randomized clinical trial of methadone maintenance for prisoners: Results at twelve-months post-release. J Subst Abuse Treat. 2009; 37:277–285. [PubMed: 19339140]

94. Hulse GK, Tait RJ, Comer SD, Sullivan MA, Jacobs IG, Arnold-Reed D. Reducing hospital presentations for opioid overdose in patients treated with sustained-release naltrexone implants. Drug Alcohol Depend. 2005; 79(3):351–357. [PubMed: 15899557]

95. Sigmon SC, Dunn KE, Badger GF, Heil SH, Higgins ST. Brief buprenorphine detoxification for the treatment of prescription opioid dependence: A pilot study. Addict Behav. 2009; 34:304–311. [PubMed: 19081679]

96. Gerra G, Fantoma A, Zaimovic A. Naltrexone and buprenorphine combination in the treatment of opioid dependence. J Psychopharmacol. 2006; 20(6):806–814. [PubMed: 16401652]

97. Mannelli P, Peindl KS, Wu LT. Pharmacological enhancement of naltrexone treatment for opioid dependence: A review. Subst Abuse Rehabil. 2011; 2:113–123. [PubMed: 21731898]

Table 1

Adjunctive, nonopioid medications used to treat opioid withdrawal symptoms.

Withdrawal symptoms	Drug class	Medication (dosage)	Comments and precautions
Autonomic (sympathetic) arousal	α-2 adrenergic agonists	• Clonidine (0.1–0.3 mg PO q 6–8 h to max of 1.2 mg/d) • Lofexidine (0.6–2 mg/d in 2–3 divided doses)	• Hypotension common with clonidine, particularly with nausea/vomiting/diarrhea leading to dehydration; monitor vital signs, encourage fluids (see below)
Anxiety/restlessness	Benzodiazepines	• Clonazepam (0.5–2 mg PO q 4–8 h, max 6 mg/d) • Oxazepam (15–30 mg PO q 4–6 h, max of 180 mg/d) • Lorazepam if parenteral (IM, IV) administration needed	• Others (e.g., diazepam, alprazolam) less preferred due to rapid absorption and greater abuse potential
	Antihistamines	• Diphenhydramine (50–100 mg PO q 4–6 h, max 300 mg/d) • Hydroxyzine (100–150 mg PO q 6 h, max 600 mg/d)	
Insomnia	Sedating antidepressants	• Trazodone (50–150 mg PO at hs) • Doxepin (50–100 mg at hs)	
	Nonbenzodiazepine hypnotics	• Zolpidem (10 mg PO at hs) • Eszopiclone (3 mg PO at hs)	
	Sedating atypical neuroleptics	• Quetiapine (50–200 mg PO at hs)	
Musculoskeletal pain	NSAIDs	• Ibuprofen (400 mg PO q 4–6 h, max 2400 mg/d) • Aspirin (650 mg PO q 4—6 h, max 4 g/d) • Ketorolac (30 mg IM q 6 h, max 120 mg/d for a total of 5 days)	• Gastric irritation - consider prophylaxis with H2 antagonist (e.g., ranitidine) or proton pump inhibitor (e.g., omeprazole)

Withdrawal symptoms	Drug class	Medication (dosage)	Comments and precautions
	Aniline analgesics	• Acetaminophen (650–1000 mg PO q 4–6 h, max 1 g/d)	• Use with caution if liver damage or active hepatitis
	Antispasmodics	• Cyclobenzaprine (5–10 mg PO q 4–6 h, max 30 mg/d); others include baclofen, tizanide, methocarbamol	
GI distress (nausea, vomiting, diarrhea)	Oral hydration	• Sports drinks (contain electrolytes), diluted fruit juice, bouillon • IV fluids as backup if needed	• Dehydration is common given nausea, and possible fluid losses (vomiting, diarrhea) - actively encourage fluid intake; monitor vital sign for postural hypotension
	Neuroleptic antiemetics	• Prochlorperazine (5–10 mg PO or IM q 3–1 h, max 40 mg/d) • Promethazine (25 mg PO or IM q 4–6 h, max 50 mg/d)	
	5-HT$_3$ antagonist	• Ondansetron (8–16 mg PO or IM q 8–12 h)	
	Miscellaneous	• Bismuth subsalicylate (2 tablets PO q 1 h, max 10 tablets/d) • Loperamide (2 mg PO after each loose stool, max 16 mg/d)	

Note: PO, oral; IM, intramuscular; IV, intravenous; q, every; hs, hours of sleep; d, day; max, maximum dose.

Table 2

Rapid opioid detoxification and naltrexone induction: suggested treatment algorithm based on level of dependence and anticipated withdrawal severity.

	Severity (Physiological dependence/anticipated withdrawal)			
	None	**Mild**	**Moderate**	**Severe**
	Already abstinent (e.g., completed agonist taper and has sustained abstinence of several days, exiting controlled environment)	1–2 bags/day; low-level prescription opioid use (<50 mg/day)	3–6 bags/day; moderate prescription opioid use (50–100 mg/day); finishing short-term methadone or buprenorphine taper	>6 bags/day; illicit methadone; severe prescription opioid use (>100 mg/day); significant medical problems
Setting	Outpatient	Outpatient or partial hospital	Partial hospital with inpatient backup	Inpatient or partial hospital with inpatient backup
Buprenorphine dose	None	None or 4 mg, day 1	4–8 mg, day 1 or 2	8 mg, day 1 or 2, or >8 mg as needed
Clonidine	None	0.1–0.2 mg TID to QID	0.2 mg TID to QID	0.2–0.3 mg QID
Clonazepam	None	0.5 mg BID	0.5–1.0 mg TID to QID	1.0–2.0 mg QID
Ancillary medications	None	Sleep, pain (e.g., NSAID)	Sleep, pain (e.g., NSAID), GI distress	Sleep, pain (e.g., NSAID), GI distress
Hydration	Routine	Aggressive oral hydration (e.g., sports drinks)	Aggressive oral hydration (e.g., sports drinks)	Aggressive oral hydration (e.g., sports drinks)
Naltrexone induction				
Time to first oral dose	Day 1	Day 3	Days 3–4	Days 4–5 (later if needed)
Initial oral dose	25–50 mg QD	12.5 mg QD	6 mg BID	3–6 mg BID
Extended-release naltrexone				
Time to first injection	Days 1–2	Day 4; or days 5–6 after titrating oral naltrexone to 25–50 mg QD	Days 4–5; or days 5–7 after titrating oral naltrexone to 25–50 mg QD	Days 5–6; or days 6–7 after titrating oral naltrexone to 25–50 mg QD

Note: QD, each day; BID, twice each day; TID, three times each day; QID, four times each day; NSAID, nonsteroidal anti-inflammatory drugs; GI, gastrointestinal.