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Focused Review

Office-Based Opioid Dependence Treatment

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Background: Opioid misuse and abuse occurring in association with the treatment of chronic non-cancer pain are not new phenomena, but their increasing prevalence in recent years is unprecedented. Advancements in pharmaceutical technologies have provided opioid-related drugs, which lack the pure mu agonist activity characteristic of the typical opioid congeners. This absent or altered mu receptor activity imparts an opioid receptor antagonistic or partial agonistic pharmacologic action, which serves to modulate the development of opioid-induced tolerance and physical dependence and facilitate detoxification and withdrawal from opioids. Opioid antagonists and partial agonists are being used in abuse deterrent strategy regimens to prevent opioid tolerance and the development of dependence, as well as in the management of opioid detoxification and treatment of withdrawal. The specific opioid antagonists and partial agonists used in these various therapeutic modalities will be the focus of this review.

Objectives: Evaluate the comparative therapeutic utility of opioid antagonists and partial agonists in preventing the development of opioid tolerance and treating opioid dependence, detoxification, and withdrawal. A primary focus is the use of opioid antagonists and partial agonists within an office-based practice.

Methods: A narrative review of the current literature involving the therapeutic use of opioid antagonists and partial agonists in the management of opioid tolerance, dependence, detoxification, and withdrawal.

A computerized literature search in the PubMed, EMBASE, BioMed, and Cochrane Library review databases from 2008 through 2010 was performed. This search included systematic and narrative reviews, prospective and retrospective studies, as well as cross-references from bibliographies of notable primary and review articles and abstracts from scientific meetings. US Food and Drug Administration records and pharmaceutical manufacturers' product literature were also used in the search.

Conclusion: Opioid dependency, whether it results from the misuse or abuse of prescription or street drugs, continues to be a significant public health issue. Passage of DATA 2000 and US Food and Drug Administration approval of buprenorphine and buprenorphine/ naloxone has revolutionized opioid dependence therapy. The traditional addiction medicine therapy regimen of methadone maintenance, with its inherent legal limitations and restrictions, has been challenged by an office-based dependence practice with buprenorphine serving as a prominent therapeutic tool.

Key words: opioid antagonist, opioid partial agonist, tolerance, dependence, detoxification, withdrawal, hyperalgesia, buprenorphine, suboxone, naloxone, naltrexone, methylnaltrexone, nalmefene, tramadol, butorphanol, nalbupine, pentazocine.

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Opioid dependence and addiction have plagued mankind for centuries; they continue to be a major societal problem in the United States. The nature of this problem has changed over the last one to 2 decades, with a decrease in heroin use and an increase in misuse of prescription drugs (1-8). Opioid detoxification entails both dependence and addiction maintenance, as well as opioid deterrence therapy. Regardless of the type of opioid addiction, the most effective treatment for the last 30 years, and the "gold standard" by which addiction treatment is judged, is methadone (2,9). Methadone maintenance for opioid addiction treatment was established in the 1970s with the Federal methadone regulation (21CFR Part 291) in 1972 {this should be a citation in your references list} and the Narcotic Addict Treatment Act of 1974 {this too} Please be sure to renumber all subsequent references. This legislation limits methadone treatment to a highly regulated environment and to patients with documented chronic addiction. These restrictions limited the number of patients with opioid dependence who would or could seek treatment (10).

In response to the problem of patients needing detoxification, but who would not or could not seek methadone treatment, the Drug Addiction Treatment Act of 2000 (DATA 2000) amended the Controlled Substances Act to allow "qualified" physicians to prescribe FDA-authorized Schedule III, IV or V medications. Since methadone is a Schedule II drug, its use was excluded under DATA 2000. DATA 2000 provided a means by which opioid dependence could be treated in an office-based setting by "qualified" physicians. The FDA approved buprenorphine in October 2002 for the treatment of opioid dependence. Buprenorphine remains the only medication which meets DATA 2000 requirements for office-based opioid treatment. Aside from the methadone "gold standard" for opioid maintenance, opioid detoxification and deterrence is primarily managed with opioid antagonists and partial agonists.

Opioid Antagonists and Partial Agonists

Compounds can be characterized by their affinity, intrinsic activity, and efficacy at receptors. Affinity is a measure of the strength of interaction between a compound binding to its receptor; intrinsic activity is the binding and production of a second messenger, such as G-proteins; and efficacy is a measure of the strength of activity or effect from this binding at the receptor (11). An agonist has both affinity and efficacy; an antagonist has affinity but no efficacy; a partial agonist has affinity, but only partial efficacy. A compound can be a full agonist for one endpoint, such as analgesia, and a partial agonist for another endpoint, such as respiratory depression. In this review, the term "partial agonist" will be used; "agonist/antagonist" is often used by others and has an identical meaning. Regarding opioids, the relevant receptors are the mu, kappa and delta receptors. Opioid compounds can have differing degrees of affinity and efficacy at these various receptors.

Partial agonists can be used as analgesics, but have a ceiling to their analgesic effect, so that escalating the dosage beyond a certain level will only yield greater opioid side effects. The stimulation of kappa receptors can provide undesired dysesthesias, as with pentazocine. Partial agonists with high affinity but low efficacy for the mu receptor can precipitate withdrawal in opioid-dependent individuals by displacing agonists with lower affinity from the mu receptor.

Partial Mu Agonists and Kappa Antagonists: Buprenorphine

Buprenorphine is a partial agonist. It has a high affinity, but low intrinsic activity and efficacy, at the mu receptor where it yields a partial effect upon binding, yet possesses kappa receptor antagonist activity, making it useful not only as an analgesic, but also in opioid abuse deterrence, detoxification, and maintenance therapies. Buprenorphine is also a nociceptin receptor agonist (norbuprenorphine) and partial agonist (buprenorphine). The kappa and nociceptin activities are not significant regarding opioid detoxification.

Buprenorphine has poor bioavailability with an extensive first pass effect by the liver. Conversely, because of high lipid solubility, it has an excellent sublingual and transdermal bioavailability. After sublingual administration, there is a rapid onset of effect (30-60 minutes) with a peak effect at about 90-100 minutes. It has a prolonged, if highly variable, half-life, of about 37 hours, and a range of 20-73 hours.

Buprenorphine is the only Schedule III, IV or V drug approved by the US Food and Drug Administration (FDA) for the treatment of opioid dependence; as such, it is the only medication which meets the DATA 2000 requirements for office-based opioid dependence. The typical daily dose for opioid addiction ranges from 4 to 24 mg daily. The naloxone component exhibits almost no sublingual absorption and very little oral absorption. After sublingual administration, there is a rapid onset of effect (30-60 minutes) with a peak effect at about 90-

100 minutes. It is used on a once-a-day dose for maintenance therapy. Buprenorphine is primarily metabolised by P450 3A4. There are extensive drug-drug interactions which can exist based on the induction or inhibition of the 3A4 system. Buprenorphine's usual adverse effects may include sedation, nausea and/or vomiting, dizziness, headache, and respiratory depression.

Buprenorphine has been approved for use in the US since December 1981. A 72-hour transdermal product designed to continuously release buprenorphine at 35, 52.5, or 70 µg/hr is available in Europe (but not in the US) for the treatment of persistent pain. Recently, a transdermal buprenorphine preparation, delivering 5, 10 or 20 µg/hr, was approved by the FDA for use in the US (12).

There is recent evidence from Europe that, when used transdermally for pain, buprenorphine is a full agonist for analgesia but a partial agonist for respiratory depression. Note, however, that buprenorphine's mechanism of action differs from the prototype full agonists, such as morphine, particularly with regard to supraspinal activity, suggesting both a lower potential for abuse with buprenorphine while providing a pharmacological rationale for its efficacy in the office-based treatment of opioid addiction (11).

Buprenorphine: Office-based Treatment of Opioid Addiction

Buprenorphine has been widely studied for its use in the office-based treatment of opioid addiction (10,13-17); its use is promoted by the Substance Abuse and Mental Health Services Administration of the US Department of Health and Human Services (2). Buprenorphine is as effective as high dose methadone therapy in maintaining abstinence (18). One year retention rates as high as 75% have been reported (19). Combination treatment, with counseling in addition to medication, leads to a higher percentage of opioid-free urine drug screens than does buprenorphine without counseling (20). Buprenorphine occupies between 85-92% of the brain's mu receptors at 16 mg/d dosing; at 32 mg/d, it occupies between 94-98% of the brain's mu receptors (21). Based upon these findings, 4 mg to 16 mg/d are the doses which are typically effective for most patients; 16-24 mg/d is the upper limit of recommended dosing.

Despite its efficacy and its ability to open up treatment of opioid dependency to those who might otherwise avoid it, there is concern about the potential abuse of buprenorphine. Fortunately, buprenorphine alone is rarely the drug of choice for drug abusers (22,23). Despite this, Cicero (22) also found that misuse was very high in the 2005-2007 period. The major source of the drug was physicians, and there is a suggestion that some practices are operating as "pill mills." There is concern that buprenorphine is being used for maintenance during the week, with "binge" illicit drug use during the weekend. Accordingly, opioid prescription precautions, including urine drug screens, pill counts, and use of prescription monitoring programs, are as necessary when prescribing buprenorphine/naloxone as when prescribing other medications. Ling et al (24) showed in 2005 that the combination of buprenorphine and naloxone in a 2:1 ratio was more effective than clonidine in successfully detoxifying opioid addicts over a 13-day period. Ziedonis et al (25) found that during medically supervised withdrawal, buprenorphine/naloxone provided a greater reduction in withdrawal severity and better treatment outcomes for opioid detoxification than clonidine, regardless of the treatment setting. Marsch et al (26) studied opioid-dependent adolescents and found that buprenorphine, coupled with behavioral therapy, was more effective in completing withdrawal over a 28-day period than was clonidine coupled with behavioral therapy. Raistrick et al (27) showed that, in first-time detoxification from heroin, buprenorphine was at least as effective as lofexidine in successfully detoxifying patients over 5-7 days. Schottenfeld et al (28) showed that buprenorphine provided greater reduction in heroin relapse, longer periods of abstinence, and greater effectiveness in preventing risk behaviors than either naltrexone or placebo. Sullivan et al (29) compared characteristics of patients receiving buprenorphine treatment in a primary care clinic (new versus previously treated), and those enrolled in a methadone maintenance program. They showed that patients enrolled in office-based buprenorphine treatment were more likely to be men, employed, have fewer years of opioid dependence, lower rates of intravenous drug abuse, no history of methadone treatment, and lower rates of hepatitis C. This study demonstrated that office-based buprenorphine can expand access to treatment for patients who may not enroll in methadone clinics and facilitate earlier access to treatment for patients who have more recently initiated opioid use, providing an opportunity to prevent hepatitis C and HIV.

Partial Mu and Kappa Agonists

Opioids which have partial mu and kappa agonist properties include nalorphine, pentazocine, nalbu-

phine, and butorphanol; they share high mu affinity but have no mu efficacy and also have kappa agonist activity. These agents can be used as analgesics, but have a ceiling or partial analgesic effect, such that escalating the dosage beyond a certain level will only yield greater opioid side effects. The stimulation of kappa receptors can provide undesired dysesthesias. These agonist-antagonists are potent analgesics with a ceiling effect, and therefore a potentially decreased abuse potential. It must be remembered that their antagonist properties may precipitate withdrawal.

Pure antagonists

The 2 most commonly used opioid (mu receptor) antagonists are naloxone and naltrexone. They are competitive antagonists at the mu, kappa, and sigma receptors, with a high affinity for the mu receptor but lacking any mu receptor efficacy. Naloxone and naltrexone act centrally and peripherally, but have differing pharmacokinetic profiles favoring different therapeutic uses.

Naloxone has low oral bioavailability, but a fast onset of action following parenteral administration, for rapid reversal of acute adverse opioid effects. Its short duration of action risks the potential for "re-narcotization," thus not providing an adequate duration of effect coverage for long-acting opioid maintenance or deterrent therapy. Naltrexone is orally effective with a long duration of action, making it useful in abuse deterrence, detoxification, and maintenance treatment modalities. Nalmefene, a mu-opioid receptor antagonist, is a water-soluble naltrexone derivative with a longer duration of action than naloxone, and is available for use in the US for the reversal of opioid drug effects.

Naloxone and naltrexone can be combined with mu agonists or partial agonists. Naloxone is used with sublingual buprenorphine to prevent the divergence and intravenous abuse of buprenorphine. Sublingual buprenorphine is also available by itself. Ultra-low dose naltrexone combined with oxycodone is currently under study to see if the naltrexone will suppress opioid tolerance. Methylnaltrexone and alvimopan are peripherally acting mu receptor antagonists currently under investigation for use in opioid-induced bowel dysfunction. In the context of the treatment of opioid abuse, naltrexone is useful in the post-opioid detoxification stage, as it does not respond to the issue of craving. It will prevent the activity of any supplemental opioids taken while it is present. Because of difficulty with compliance when using the short-acting preparation, it has had limited use in a depot formulation (30-32). Recently, the FDA approved a depot form of naltrexone to treat and prevent relapse of patients with opioid dependence who have undergone detoxification treatment (33). It was previously approved in 2006 for the treatment of alcohol dependence.

An alternative approach to improve compliance and outcomes in the post-opioid detoxification stage of treatment has been to add low-dose naltrexone (34,35). Both of these approaches are in the early stages of investigation. Their ultimate role in the treatment of opioid addiction is unclear.

Naltrexone is also used in anesthesia-assisted detoxification, in which naloxone is administered under general anesthesia to precipitate withdrawal. This technique is also known as ultra-rapid or rapid detoxification, or opioid antagonist detoxification under sedation or anesthesia. Advocates argue that this technique allows the patient to have only minimal withdrawal symptoms, with minimal risk (36). However, there are reports of significant withdrawal symptoms and complications after the procedure. Controlled studies have not demonstrated any benefit of anesthesia-assisted detoxification in terms of improved outcomes or continued abstinence over other techniques (37-40).

Naloxone is a mu receptor antagonist which has a significant first pass effect. It is most commonly used intravenously. Its most prevalent use in opioid dependence treatment is its admixture with buprenorphine to prevent the intravenous abuse of buprenorphine.

Conclusions

Opioid dependency, whether from prescription drugs or heroin, continues to be a significant public health problem. With the passage of DATA 2000 and the FDA approval of buprenorphine/naloxone and buprenorphine for the office-based treatment of opioid dependency, treatment of this problem has moved beyond traditional addiction medicine and has become available to all physicians who elect to become qualified to use buprenorphine for addiction. For physicians providing opioid management of pain, the use of buprenorphine/naloxone is an important tool to respond to the opioid dependency issues which arise in treating chronic pain.

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