Opioid Antagonists, Partial Agonists, and Agonists/Antagonists: The Role of Office-Based Detoxification

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Background: The opioid receptor antagonists naloxone and naltrexone are competitive antagonists at the mu, kappa, and sigma receptors with a higher affinity for the mu receptor and lacking any mu receptor efficacy. Buprenorphine is classified as a partial agonist. It has a high affinity, but low efficacy at the mu receptor where it yields a partial effect upon binding. It also, however, possesses kappa receptor antagonist activity making it useful not only as an analgesic, but also in opioid abuse deterrence, detoxification, and maintenance therapies. Naloxone is added to sublingual buprenorphine (Suboxone®) to prevent the intravenous abuse of buprenorphine. The same product (sublingual buprenorphine) when used alone (i.e. without naloxone) is marketed as Subutex®.

Objective: To evaluate and update the available evidence regarding the use of agonist/antagonists to provide office-based opioid treatment for addiction.

Methods: A review using databases of EMBASE and MEDLINE (1992 to December 2007). These included systematic reviews, narrative reviews, prospective and retrospective studies, as well as cross-references from other articles.

Outcome Measures: The primary outcome measure was treatment retention. Other outcome measures included opioid-free urine drug testing, opioid craving, intensity of withdrawal, pain reduction, adverse effects, addiction severity index, and HIV risk behavior.

Results: The results found 17 studies, 1 systematic review, 12 RCTs, and 4 observational series, which document the efficacy and safety of buprenorphine alone and in combination with naloxone in detoxifying and maintaining abstinence from illicit drugs in patients with opioid addiction.

Conclusion: Based on the present evaluation, it appears that opioid antagonists, partial agonists, and antagonists are useful in office-based opioid treatment for addiction.

Key words: Opioid, antagonist, partial agonist, tolerance, dependence, detoxification, withdrawal, hyperalgesia, buprenorphine, naloxone, naltrexone, methylnaltrexone, butorphanol, nalbuphine, pentazocine

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Compounds can have intrinsic affinity and efficacy at receptors, with affinity being a measure of the "strength of interaction" between a compound binding to its receptor and efficacy being a measure of the strength of activity or effect from this binding at the receptor. An agonist has both affinity and efficacy; an antagonist has affinity but no efficacy; a partial agonist/antagonist has affinity, but only partial efficacy. Regarding the opioids, the relevant receptors are the mu, kappa, and delta receptors. Compounds can have differing degrees of affinity and efficacy at these various receptors.

The opioid receptor antagonists naloxone and naltrexone are competitive antagonists at the mu, kappa, and sigma receptors with a higher affinity for the mu receptor and 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 adequate duration of effect coverage for opioid maintenance or deterrent therapy. Naltrexone is orally effective with a long duration of action making it useful in abuse deterrent, 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. Naloxone and naltrexone can be combined with mu agonists or partial agonists. Ultra-low dose naltrexone combined with oxycodone (Oxytrex®) is currently under study to see if the naltrexone will suppress opioid tolerance. Nalmefene is available for use in the United States for the reversal of opioid drug effects (1). Methylnaltrexone and alvimopan are peripherally acting mu receptor antagonists currently under investigation for use in treating postoperative ileus and opioid-induced bowel dysfunction.

Buprenorphine is classified as a partial agonist. It has a high affinity, but low efficacy at the mu receptor where it yields a partial effect upon binding. It also, however, possesses kappa receptor antagonist activity making it useful not only as an analgesic, but also in opioid abuse deterrence, detoxification, and maintenance therapies. Buprenorphine (Buprenex®) has been approved for use in the United States since December 1981. A 72-hour transdermal product designed to continuously release buprenorphine at 35, 52.5, or 70 mcg/hr is available in Europe (but not in the United States) for the treatment of persistent pain. Naloxone is added to sublingual buprenorphine (Suboxone®) to prevent the intravenous abuse of buprenorphine. The same product (sublingual buprenorphine) when used alone (i.e., without naloxone) is marketed as Subutex®.

Buprenorphine has a poor bioavailability with extensive first pass effect by the liver. Conversely, because of high lipid solubility, it has an excellent sublingual bioavailability. The typical daily dose for opioid addiction ranges from 4 to 32 mg daily. The naloxone component exhibits almost no sublingual absorption and very little oral absorption. The intent of its addition is to reverse the effects of an IV or IM administered buprenorphine. 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 metabolized 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.

Partial agonist-antagonists, such as nalorphine, pentazocine, nalbuphine, and butorphanol, have high mu affinity but have poor mu efficacy and also have kappa agonist activity. These agents can be used as analgesics, but have partial or a ceiling to their 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 dysesthesia, as with Talwin®.

A unique analgesic, Tramadol, is an atypical opioid, a 4-phenyl-piperidine analogue of codeine, with partial mu agonist activity in addition to central GABA, catecholamine and serotonergic activities. Tramadol is used primarily as an analgesic, but has demonstrated usefulness in treating opioid withdrawal (2).

Office-Based Opioid Treatment (OBOT)

The most important use currently for this class of medications is office-based opioid detoxification/treatment. With the current trends in prescription opioid abuse and the overlap of pain and addiction, it behooves the pain specialist to be aware of the current treatments for opioid addiction.

Historically, opioid dependence has been a problem for most of the twentieth century. Before the

Harrison Narcotic Act of 1914 was enacted, physicians could prescribe opioids for any condition, including opioid dependence. In 1919, the US Supreme Court ruled that the Harrison Act disallowed prescription of opioids for maintenance purposes, which effectively ended OBOT for addiction.

After World War I, many cities established maintenance clinics for opioid addiction to respond to a huge wave of heroin addicts. In New York City, pioneering efforts were engaged in the treatment of more than 8,000 addicts through the city's health department. Unfortunately, these clinics were shut down by the federal government. From the 1920s forward, physicians were discouraged from treating opioid addiction, and it was reconceptualized as a criminal rather than a medical problem (1).

It was not until the 1970s when opioid addiction was addressed at the federal level with methadone regulations (21 CFR Part 291) in 1972 and the Narcotic Addict Treatment Act of 1974 which created federal and state licensed methadone clinics. A physician who wished (until very recently) to treat opioid addiction with methadone had to obtain additional registration from the DEA and DHHS with additional approval from state authorities, thus involving an intimidating beaurocratic gauntlet that few physicians have been willing to negotiate.

In October 2002, the US FDA approved Schedule III sublingual buprenorphine tablets for the use in treatment of opioid addiction. The Drug Addiction Treatment Act (DATA) of 2000, an amendment to the Controlled Substances Act, allowed certified physicians to prescribe and dispense Schedule III, IV, and V narcotic drugs that have been approved by the Food and Drug Administration for use in addiction treatment (i.e., maintenance or medical withdrawal/detoxification). Physicians who wish to prescribe buprenorphine for the treatment of opioid dependence must meet 1 or more of the following requirements:

♦ Board certified in Addiction Psychiatry
♦ Certified in Addiction Medicine by American Society of Addiction Medicine (ASAM)
♦ Certified in Addiction Medicine by American Osteopathic Association (AOA)
♦ Investigator in buprenorphine clinical trials
♦ Has completed 8 hours of CME provided by American Psychiatric Association, American Academy of Addiction Psychiatry, ASAM, American Medical Association, AOA (or other organizations designated by Health and Human Services)
♦ Training/experience as determined by State licensing board
♦ Other criteria established by Health and Human Services

Qualified physicians must submit notification to Center for Substance Abuse Treatment (CSAT) and a unique identification is then issued from the DEA in the form of an "X" number, thus giving these physicians 2 different DEA numbers. Initially, a provider was limited to treating no more than 30 patients, but in 2007 this was increased to 100 with secondary notification to CSAT.

Buprenorphine is commercially available for pain control in an injectable form known as Buprenex®. It should be noted that the only legally approved form of buprenorphine for the treatment of opioid dependence is the sublingual form (Subutex®, Suboxone®).

Prior to its use in the United States, buprenorphine in its sublingual form (Subutex®) was used very successfully in Europe for the treatment of opioid addiction. Over 10 years of clinical research has supported the use of buprenorphine and its combination with naloxone (Suboxone®) as an alternative to methadone.

Literature Review

A literature review was undertaken to determine the evidence-based support for the uses of opioid antagonists and partial agonists/antagonists 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. All English language randomized controlled trials, observational trials, systematic reviews, and meta-analysis with more than 6 human subjects involving medications/therapies approved for use in the United States published between 1992 and 2007 were included. Studies describing treatment of opioid-induced constipation were excluded because this therapy was not approved for use in the United States at the time of this writing. Interested readers are referred to the systematic review on this subject by Becker et al (3), and the review of opioid complications in this issue. Studies describing treatment of opioid withdrawal other than with agonist/antagonists or antagonists were also excluded as being beyond the focus of this review.

Table 1. *Summary of studies meeting inclusion criteria.*

STUDY	PARTICIPANTS	INTERVENTION	OUTCOMES	RESULTS	CONCLUSION
Gowing et al (18) systematic review	9 studies (5 randomized control trials) N= 775 participants were primarily opioid dependent	Experimental interventions: opioid antagonists in combination with minimal sedation to mange withdrawal, comparison interventions: other approaches or different opioid antagonist regime	Intensity of withdrawal, Duration of treatment/ treatment retention, Adverse effects, Treatment completion Engagement in further treatment	Withdrawal induced by opioid antagonists in combination with adrenergic agonists is more intense than withdrawal managed with clonidine or lofexidine alone. Antagonist induced withdrawal may be more severe with methadone rather than a short acting opioid e.g. heroin. No significant difference in rates of treatment completion for withdrawal induced by opioid antagonists + adrenergic agonist, compared with adrenergic agonist alone.	Use of opioid antagonists combined with adrenergic agonists is a feasible approach to manage opioid withdrawal. It is unclear if this approach reduced duration of withdrawal or facilitates transfer to naltrexone treatment to a greater extent than withdrawal managed primarily with adrenergic agonist.
Sullivan et al (19) prospective, cross sectional & longitudinal analysis	Patients in 2 settings: PCC: (N = 96) Buprenorphine trial in primary care clinic OTP: (N = 94) methadone maintenance in local opioid treatment Program	Compare PCC subjects with OTP subjects. Compare PCC patients with no history of methadone treatment (new-to-treatment) to those with prior methadone treatment	Clinical characteristics of PCC vs. OTP subjects. Characteristics and treatment outcomes of new-to-treatment PCC vs. with prior methadone treatment PCC subjects	PCC subjects were more likely to be male, full time employed, no history of methadone treatment, fewer years of opioid dependence, lower rates of injection drug use (IDU). New-to-treatment PCC subjects were younger, more likely to be white, fewer years of opioid dependence, less likely to have IDU history and lower rates of hepatitis C. Abstinence and treatment retention were comparable in both groups.	Office based treatment of opioid dependence is associated with new types of patients entering into the treatment. Treatment outcomes with buprenorphine in a PCC do not vary based on history of prior methadone treatment.
Kakko et al (14) randomized, placebo controlled trial	40 heroin dependent adults, meeting DSM-IV criteria for opioid dependence for at least 1 year, but did not fulfill Swedish criteria for methadone maintenance treatment	2 groups of 20: Daily fixed dose SL buprenorphine 16 mg for 12 months. Tapered 6 day buprenorphine, followed by placebo. Individual counseling weekly and cognitive behavioral group therapy to both groups	1 year retention in treatment. Addiction severity index (ASI). 3/week supervised urine samples	1-year retention in treatment was 75% (15/20) and 0% in the buprenorphine and placebo groups, respectively (p=0.0001; risk ratio 58.7 [95% CI 7.4-476.4]). Urine screens were about 75% negative for illicit opiates, central stimulants, cannabinoids, and benzodiazepines in patients remaining in treatment.	Combination of buprenorphine and intensive psychosocial treatment is safe and highly effective for heroin dependent patients.
Comer et al (5) randomized, double-blind, placebo controlled trial	60 heroin-dependent adults, stratified by sex and years of heroin use	Received injections of either placebo or 192 mg or 384 mg of depot naltrexone	Retention in treatment and % of opioid negative urine samples	Retention was dose-related; 39%, 60%, and 68% in the placebo, 192 mg and 384 mg naltrexone groups, respectively, being retained in treatment; no significant difference in % opioid negative urine samples between the placebo and treatment groups.	Depot naltrexone is safe and effective in retaining heroin-dependent patients in treatment.

Table 1.cont.

STUDY	PARTICIPANTS	INTERVENTION	OUTCOMES	RESULTS	CONCLUSION
Johnson et al (9) randomized control trial	220 patients with opioid dependence according to DSM-IV criteria	4 treatment groups: *Methadone 20 mg daily (control) *Levomethadyl 75-115mg 3 times/week *Buprenorphine 16-32 mg 3 times/ week *Methadone 60-100 mg daily	Retention in the study; continued opioid usage; degree of continuous abstinence from opioid use; and, patient's global ratings of severity of their drug problem	Greater retention with high-dose methadone, buprenorphine and levomethadyl than control group. Levomethadyl, buprenorphine, and high-dose methadone groups had fewer opioid-positive urine specimens than the control group. Control group gave the highest severity rating to their drug problem	Levomethadyl, buprenorphine, and high-dose methadone are more effective than low-dose methadone in reducing illicit opioid use.
Marsch et al (16) randomized, double-blind, controlled trial	36 self-referred adolescents (ages 13-18 years) meeting DMS-IV criteria for opioid dependence randomized into a 28 day outpatient medication-assisted withdrawal treatment	2 detoxification groups: *Buprenorphine- flexible dosing based on weight and self-reported opioid use *Clonidine-0.1 and 0.2 mg patches Behavioral counseling and incentive contingencies for both groups	Treatment retention; opioid abstinence; HIV risk behavior	72% of patients receiving buprenorphine retained in treatment compared to 39% receiving clonidine; 64% opioid negative urine tests in the buprenorphine group compared to 32% in the clonidine group. HIV risk behavior significantly decreased in both groups.	Combining behavioral interventions with buprenorphine is significantly more efficacious in treating opioid-dependent adolescents than with clonidine.
Ling et al (8) randomized, double-blind controlled trial	736 patients meeting DSM-iV criteria for opioid dependence enrolled at 12 clinic sites, for a 16-week maintenance treatment period	Randomized to 4 dosage groups and treated double blind: 1, 4, 8, and 16-mg/day buprenorphine Weekly counseling sessions for all groups	4 efficacy domains: Treatment retention; illicit opioid use; opioid craving; global ratings of drug problem severity by patients and staff	51% of the patients completed the 16-week study. 1 mg buprenorphine group had significantly worse retention (40%) compared to the 8 mg group (52%). 1 mg group had a significantly lower number of opioid negative urines than the other dosage groups. Significantly higher heroin graving scale scores were noted in the 1 mg group. Significantly better global rating scores were obtained in the 8 mg group compared to the 1 mg group.	8-mg/day buprenorphine was safe, effective, and superior to 1 mg/ day dose in each of the 4 efficacy domains studied.
Johnson et al (7) randomized, double-blind controlled trial	162 volunteer patients seeking treatment for opioid dependence	Randomized into 3 treatment groups: *Buprenorphine 8mg/ day; *Methadone 60mg/day; *Methadone 20mg/day 17 week maintenance phase followed by a 8 week detoxification phase	Retention in treatment; opioid-negative urine samples; and failure to maintain abstinence	Retention rates were significantly greater for buprenorphine (30%), methadone 60mg/day (20%) than for methadone 20mg/day (6%) for the entire 25 weeks. Buprenorphine had significantly more opioid-negative urine samples (59%) than either methadone 60mg/day (43%) or methadone 20mg/day (39%). Failure to maintain abstinence was significantly greater for methadone 20mg/ day than buprenorphine.	Buprenorphine was as effective as methadone 60mg/day and both were superior to methadone 20mg/day in treating opioid dependence.

Table 1.cont.

STUDY	PARTICIPANTS	INTERVENTION	OUTCOMES	RESULTS	CONCLUSION
Fudala et al (12) randomized, placebo-controlled trial	Patients meeting DSM-IV criteria for opioid dependence, seeking opiate-substitution pharmacotherapy. 2 study parts: 326 patients in 4-week double-blind efficacy trial; 461 patients in 48-week open-label safety assessment study	Double-blind trial, subjects randomized to: • Buprenorphine 16 mg/day + naloxone 4mg/day • Buprenorphine 16mg/day • Placebo Open-label study, daily doses up to: buprenorphine 24mg + naloxone 6mg	Measures of treatment efficacy: % of opioid-negative urine samples; self-reported craving for opiates. Secondary measures: subject/staff ratings of overall status; urine samples negative for other drugs of abuse; retention; rates of adverse medical events	Double-blind trial: Opioid-negative urine samples were higher in the buprenorphine + naloxone (17.8%) and buprenorphine (20.7%) groups compared with placebo (5.8%). Buprenorphine + naloxone and buprenorphine alone groups reported significantly less opiate craving than placebo. Rates of adverse events were similar between active-treatment and placebo groups.	Double-blind trial was terminated early because buprenorphine and naloxone in combination and buprenorphine alone were found to have greater efficacy than placebo. Open-label study showed the buprenorphine and naloxone combine treatment was safe and well tolerated.
Gerra et al (21) prospective observational study	60 naltrexone treatment-seeking heroin-dependent patients, meeting DSM-IV criteria were enrolled in a 12 week clinical evaluation	Non-randomized into 2 treatment groups: Naltrexone 50mg; Buprenorphine 4mg + naltrexone 50mg	Retention in treatment; negative urinalysis; changes in psychological symptoms; and craving scores	Retention rate was significantly higher (73.3%) in the buprenorphine + naltrexone group compared with the naltrexone alone (40%). Buprenorphine + naltrexone group showed a significantly lower rate of positive urinalysis for opiates and cocaine. Psychological symptoms and craving scores decreased significantly in the buprenorphine + naltrexone group, as compared with naltrexone alone.	Combination of buprenorphine and naltrexone significantly improved the treatment outcome of opioid dependence over the use of opioid antagonists alone.
Chindalore et al (4) randomized, double-blind, placebo-controlled trial	360 patients with moderate to severe chronic osteoarthritis pain involving hip and knees were enrolled in a 3-week, Phase II trial assessing the safety and efficacy of Oxytrex	Randomized into 4 treatment groups: • Placebo QID • Oxycodone QID • Oxytrex QID • Oxytrex BID Active-treatment doses of oxycodone escalated as the same total daily dose from 10mg/day to 40mg/day. Oxytrex was formulated to contain 0.001mg naltrexone per dose.	Daily numerical pain rating; weekly evaluations of the quality of analgesia; duration and extent of pain control; global assessment of the study drug; SF-12 Health Survey; and WOMAC Osteoarthritis Index	32.2% of the patients did not complete the study. Oxytrex bid produced a 39% reduction in pain intensity, significantly greater than placebo or the other 3 treatment groups. Oxytrex bid was superior to placebo and the other active treatment groups in the quality of analgesia, duration of pain control, global assessment, and WOMAC total score. Incidence of side effects was comparable between active-treatment groups.	Oxytrex bid provided greater efficacy in pain control and quality of analgesia at a lesser dosing frequency.
Tamaskar et al (2) Retrospective observational study	Charts from 64 patients with mild to moderate heroin addiction, who underwent opioid detoxification were reviewed	Patients were categorized into 2 treatment groups: *Oral tramadol *SQ buprenorphine Clonidine as needed for breakthrough withdrawal	Severity of opioid withdrawal-average Clinical Institute Narcotic Assessment (CINA); length of stay; amount of clonidine needed for withdrawal control.	Average CINA maximum for tramadol was 9 vs. 11.2 for buprenorphine. Length of stay was 3.7 days with tramadol vs. 4.1 days with buprenorphine. Use of clonidine pills per patient was 1.6 with tramadol vs. 0.1 with buprenorphine. Leaving against medical advice was higher for the buprenorphine group.	Tramadol compared favorably to buprenorphine in the management of acute withdrawal from less than 10 bags per day of heroin.

Table 1.cont.

STUDY	PARTICIPANTS	INTERVENTION	OUTCOMES	RESULTS	CONCLUSION
Mitchell et al (6) Prospective observational, crossover study	18 methadone maintenance patients	Subjects were transitioned from oral methadone to a once-daily slow-release oral morphine (SROM) product for a 6-week period; then methadone maintenance was recommended.	Opioid withdrawal severity during transition; 4 weeks after transition, outcome assessments made for treatment preference, efficacy, acceptability, health, depression and sleep.	Withdrawal severity was significantly greater during transition to SROM than during resumption of methadone maintenance. 78% preferred SROM over methadone 22%. SROM was associated with significantly better outcomes over methadone in treatment efficacy, acceptability, fewer side effects and social functioning.	SROM could serve as an effective maintenance pharmacotherapy for opioid dependence.
Correia et al (20) Prospective observational study	8 patients with active opioid dependence according to DSM-IV criteria	Each subject maintained on 3 different double-blind doses of buprenorphine/naloxone (B/N): 8/2, 16/4 and 32/8mg; order of administration was randomized. Challenge doses of IM hydromorphone 0, 6 and 12mg, given double-blind, at 2, 26, 50, 74 and 98 hours after last dose of B/N.	Efficacy of opioid blockade and spontaneous withdrawal assessed using: physiologic parameters; subject VAS scores and subject/observer adjective-rating questionnaires; psychomotor/cognitive performance measures.	As the time period increased since the last B/N dose, hydromorphone challenge doses produced decreased reports of opioid agonist effects and increases in mild withdrawal symptoms. Substantial but incomplete blockade against opioid effect was provided by B/N for 98 hours.	B/N doses greater than 8/2mg provide minimal benefit in terms of opioid blockade and withdrawal suppression and intermittent B/N dosing may be effective for up to 98 hours.
Ahmadi et al (11) Randomized controlled trial	204 IV buprenorphine-dependent patients, for at least 6 mos., seeking treatment, meeting DMS-IV criteria for opioid dependence	Randomized into 3 treatment groups: 1. Oral methadone 50mg 2. SL buprenorphine 5mg 3. Oral naltrexone 50 mg	Treatment retention	Overall, 54.4% completed the 24-week study. 83.8% in methadone group 58.8% in buprenorphine group 20.6% in naltrexone group	Methadone and buprenorphine are effective for maintenance treatment of buprenorphine-dependent patients.
Lintzeris et al (10) Prospective randomized controlled trial	114 heroin-dependent patients, meeting DSM-IV criteria, seeking ambulatory withdrawal treatment, 8-day program with 4-week follow-up	Randomized into 2 treatment groups: Control group receiving clonidine and other symptomatic medications; Experimental group SL buprenorphine regimen Open-label study	Self-reported heroin use during withdrawal; retention in withdrawal treatment; participation in post withdrawal treatment; severity of withdrawal; adverse effects.	Significantly more experimental participants reported no heroin use during withdrawal. 86% experimental participants compared to 57% of controls completed the withdrawal program. 62% of experimental participants compared to 39% of controls were retained in some form of treatment post withdrawal. Experimental group reported significantly less withdrawal severity.	Buprenorphine is more effective than clonidine and symptomatic medications in treating short-term ambulatory heroin withdrawal, with greater retention, less heroin use, less withdrawal severity and increased post withdrawal treatment retention.
Ling et al (15) randomized controlled trial	344 participants—113 in-patient and 231 out-patient, meeting DSM-IV criteria for opioid dependence, seeking treatment for opioid withdrawal, in a 13-day detoxification study	In-patients and out-patients were randomized into 2 treatment groups on a 2:1 ratio buprenorphine-naloxone (bup-nx): clonidine groups	Treatment retention, negative urine samples, withdrawal severity, opioid craving	Both inpatient and outpatient bup-nx groups had significantly better retention, fewer withdrawal symptoms, and significantly lower craving rating than the clonidine groups.	Buprenorphine-naloxone is clinically more effective than clonidine in treating opioid detoxification.

Table 1.cont.

STUDY	PARTICIPANTS	INTERVENTION	OUTCOMES	RESULTS	CONCLUSION
Mattick et al (13) randomized double-blind controlled trial	405 opioid-dependent patients, meeting DSM-IV criteria, seeking treatment, over a 13-week treatment period	Randomized into 2 treatment groups: SL buprenorphine; oral methadone flexible dosing regimen, double-blind	Efficacy assessments: Retention in treatment; opioid negative urine samples; Opiate Treatment Index (OTI) and Symptom Checklist-90-R (SCL-90-R) measures of heroin, illicit drug use, HIV-risk behavior, social functioning, physical and mental status	Overall, 54.8% of patients completed the 13-week trial. 59% of methadone compared to 50% of buprenorphine patients completed the trial. No significant differences in opioid negative urine samples between the 2 groups. Significant improvements, but no differences between groups in self-reported OTI and SCL-90-R measures.	Both methadone and buprenorphine are comparably effective in treating opioid dependence.
Raistrick et al (17) randomized controlled trial	481 heroin users seeking detoxification meeting DSM-IV criteria for opioid-dependence, first-time detoxifications	210 participants randomized into 2 treatment regimens: 1. 5-day lofexidine 2. 7-day buprenorphine 271 participants opted to choose one of the 2 Open-label	Outcome measures: completion of detoxification regimen; abstinence at 1-month follow-up; severity of withdrawal; treatment acceptability	65% of participants on buprenorphine compared to 46% of those on lofexidine completed detoxification. 45.9% of the buprenorphine group and 35.7% of the lofexidine group reported abstinence at 1-month. Significant improvements, but no statistically significant differences between groups in measures of social functioning mental status. Severity of withdrawal was rated less with buprenorphine.	Buprenorphine is at least as effective as lofexidine detoxification.

RESULTS

Table 1 summarizes the studies considered for this review. All of the studies found, with the exception of Chindalore et al (4), Comer et al (5) and Mitchell et al (6) , dealt with the use of buprenorphine for the treatment of opioid addiction. The Chindalore et al (4) study involved the addition of naltrexone to oxycodone to prevent tolerance and hyperalgesia. Since the formulation (Oxytrex®) is not currently available in the United States, it is not further discussed. In like manner, Comer et al (5) documented the efficacy of depot naltrexone for the treatment of opioid addiction. As this treatment is not currently available in the United States, it is not further discussed. Mitchell et al (6) showed that sustained release oral morphine could be substituted for methadone for opioid maintenance therapy.

A total of 17 articles were found evaluating the use of buprenorphine for the treatment of opioid addiction. Of these, 1 was a systematic review, 12 were randomized controlled trials (RCTs), and 4 were observational studies.

Several studies have reported on buprenorphine versus methadone maintenance. Johnson et al (7) in 1992 compared the efficacy of buprenorphine to methadone for short-term maintenance and opioid detoxification. In a randomized, double blind, parallel group study buprenorphine 8 mg/day was compared with methadone 60 mg/day and methadone 20mg/day. There was a 17-week maintenance phase followed by an 8-week detoxification phase. Retention rates and percentage urine samples negative for opioids was significantly greater for buprenorphine and

methadone 60mg/d than for methadone 20mg/day during the maintenance phase. There was no difference between groups with respect to negative urine samples for opioids during the detoxification phase. Buprenorphine was considered to be as effective as high dose methadone in reducing illicit opioid use and in maintaining patients in treatment for 25 weeks.

A multicenter randomized, double blind clinical trial by Ling et al (8) evaluated safety and efficacy of different doses of buprenorphine in heroin addicts. Patients received 1, 4, 8 or 16mg/day of buprenorphine. Outcomes in the 8 mg group were significantly better than in the 1 mg group in all 4 efficacy domains: treatment retention, illicit opioid use, opioid craving, and global ratings by patient and staff; no deaths occurred in either group and the 8 mg group did not show an increase in the frequency of adverse events. The 16 mg group did better than the 8 mg group but the differences did not reach statistical significance. The median percentage of clinics attended by the 375 patients who remained in treatment was 89% and 18% (63/375) attended clinics less than 70% of the time. Missed urine samples was only 18% among completers. Sixty-eight patients completed 16 weeks of treatment without producing a single urine negative for opioids.

Johnson et al (9) studied the use of illicit opioids in 220 opioid dependent patients randomized to receive either levomethadyl, buprenorphine, high-dose methadone, or low dose methadone. The percentage of patients with 12 or more consecutive opioid-negative urine specimens was 36% in levomethadyl group, 26% in buprenorphine group, 28% in high does methadone group, and 8% in low dose methadone group. As compared with low dose methadone, participants taking levomethadyl acetate had a higher rate of continuous abstinence from opioids, and those taking buprenorphine and high dose methadone had a trend towards higher rate of continuous abstinence.

Lintzeris et al (10) showed that buprenorphine was more effective than clonidine in treating opioid withdrawal. Ahmadi et al (11) looked at patients who were dependent upon IV buprenorphine and found that oral methadone 20 mg and sublingual buprenorphine 5 mg, but not oral naltrexone, provided effective maintenance therapy over 24 weeks. Fudala et al (12) conducted a 4-week, multicenter randomized, placebo controlled trial on 326 opiate dependent patients and compared efficacy of buprenorphine 16 mg alone, buprenorphine 16 mg with naloxone 4 mg, and placebo. The trial was stopped early because of the

greater efficacy of the buprenorphine treatments. The active treatment groups reported less opiate craving. Safety of buprenorphine and naloxone was assessed from data obtained on 461 opiate addicts in an open label study and showed that the combined treatment was safe and well tolerated.

Mattick et al (13), in 2003, confirmed that both buprenorphine and methadone were effective in treating opioid dependence. Kakko et al (14), in a randomized placebo-controlled trial from Sweden, evaluated the long-term effectiveness of buprenorphine in heroin dependent individuals. One year efficacy of buprenorphine in combination with intensive psychosocial therapy for treatment of heroin dependence was assessed by taking 40 heroin dependent individuals and randomly allocating them either to sublingual buprenorphine 12 mg/day for 12 months or to a tapered 6-day regimen of buprenorphine, followed by placebo. Thrice weekly supervised urine samples were obtained to detect illicit drug use. One year retention in treatment was 75% in the buprenorphine group and 0% in the placebo group (p = 0.0001; risk ratio 58.7 [95% CI7.4-467.4]). Urine screens were about 75% negative for illicit drugs in patients remaining in the treatment.

Ling et al (15) 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. Marsch et al (16) in 2005, 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 (17) showed that in first-time detoxification from heroin, buprenorphine was at least as effective as lofexidine in successfully detoxifying patients over 5 – 7 days.

Gowing et al (18), in 2006, performed a Cochrane Review of the use of opioid antagonists for the treatment of opioid withdrawal, looking at 9 studies, including 5 randomized controlled trials. Gowing et al concluded that the use of opioid antagonists combined with alpha2 adrenergic agonists is a feasible approach to the management of opioid withdrawal.

Four observational studies document the efficacy of buprenorphine. A cross-sectional and longitudinal analysis by Sullivan et al (19) showed that patients in office-based buprenorphine treatments in a primary care clinic (PCC) are different from those enrolled in a local opioid treatment program (OTP) in a methadone

clinic. PCC subjects compared with OTP subjects were more likely to be male (77% versus 55%), full-time employed (46% versus 15%, $p < 0.001$), have no history of prior methadone treatment (46% versus 61%), have fewer years of opioid dependence (10 versus 15, $p < 0.001$), and lower rates of injection drug use (IDU) (46% versus 61%). Furthermore, within the PCC group, the new-to-treatment subjects were younger, more likely to be white, had fewer years of opioid dependence, less likely to have a history of IDU, and lower rates of hepatitis C than subjects with prior methadone treatment. These results suggest office-based buprenorphine treatment expands 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.

Correia et al (20) showed that there was no minimal benefit in increasing the buprenorphine/naloxone dose above 8 mg/2mg day in terms of response to a hydromorphone challenge, and that an intermittent dose of buprenorphine might last as long as 98 hours. Tamaskar et al (2), in a retrospective study, found that the severity of withdrawal from less than 10 bags of heroin was slightly less with tramadol than with buprenorphine. Gerra et al (21), in a prospective study published in 2005, showed that over a 12-week period, the combination of buprenorphine and naltrexone was significantly more effective in retaining treatment than was naltrexone alone.

DISCUSSION

Various studies have evaluated efficacy and safety for opioid agonists, partial agonist, and antagonists in treating opioid dependence. The measure used to determine treatment efficacy are treatment retention, illicit opioid use, opioid craving, and global ratings by patient and staff. However, treat-

ment retention does not tell the whole story. For example, in the study by Ling et al (15), 18% attended clinics less than 70% of the time. Missed clinic visits translate into missing urine samples, which was 18% among completers. Sixty-eight patients completed 16 weeks of treatment without producing a single urine negative for opioids. Clinic attendance without reduction in opioid use cannot be considered as unqualified therapeutic success for buprenorphine. Acceptance of efficacy of buprenorphine as a maintenance treatment has to be tempered by the reality that drug use status of many patients will not be altered by buprenorphine (15).

Detoxification means assisting street heroin addicts to become abstinent or discontinuing patients from opioid maintenance. An effective medication for detoxification should suppress withdrawal symptoms sufficiently to allow an opiate dependent person to become opiate free. Few studies have examined this aspect of treatment.

CONCLUSION

Seventeen studies, 1 systematic review, 12 RCTs, and 4 observational series, which document the efficacy and safety of buprenorphine alone and in combination with naloxone in detoxifying and maintaining abstinence from illicit drugs in patients with opioid addiction, were reviewed.

Additional new uses for antagonists, including their use to prevent tolerance with chronic opioid use, may soon be available.

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