REVIEW ARTICLE

Coadministration of an Opioid Agonist and Antagonist for Pain Control

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Abstract: The increased use of opioids in the treatment of chronic pain encourages the search for drugs with low abuse and tolerance potential but with potent analgesic activity. Opioid agonist-antagonists and partial agonists have less abuse potential than do mu opioid receptor agonists such as morphine, and have been used for many years for their analgesic affects. Recently they have been approved for treatment of opioid addiction. As a guard against abuse, an opioid antagonist, such as naloxone, is added to some opioid formulations. Doctors are often hesitant to prescribe agonist-antagonists and partial agonists to opioid-tolerant patients, fearing that these drugs may precipitate withdrawal. Can drugs being used safely for addiction treatment also safely replace opioid agonists to provide analgesia in chronic pain patients who are opioid-tolerant?

Key Words: agonist-antagonist, pentazocine, buprenorphine, chronic pain, opioid, addiction, mu receptor, kappa receptor, opioid withdrawal, naloxone

PREMISE

It is common for partial agonists and mixed agonists-antagonists to be discussed as a group. The agonist-antagonist and partial agonist opioid analgesics are a heterogeneous group of drugs with moderate to strong analgesic activity but with a limited effective dose range. The group includes drugs that act as agonists or partial agonists at one receptor and as antagonists at another.1 There are three major classes of opioid receptor sites involved in analgesia: mu, delta, and kappa. Most clinically useful opioid analgesics bind to mu-opioid receptor sites and are the mainstay for controlling acute and cancer pain. Examples include morphine, codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, oxycodone, and propoxyphene.2 Pentazocine and butorphanol are partial mu-agonists and kappa-agonists. Nalbuphine is a mu-antagonist and kappa-agonist. Buprenorphine is a partial mu-agonist and kappa-agonist.3,4 It is recommended that mu receptor partial agonists and antagonists be avoided (or used with caution) in patients receiving mu-opioid opioids, as they can reverse opioid effects and precipitate withdrawal syndrome.

Drugs in the mixed agonists-antagonists—partial antagonist group of interest for sustained treatment of chronic pain are those available for oral including sublingual, use. Formulations that include pentazocine and buprenorphine fit this criterion. Buprenorphine formulations show considerable potential for use in chronic pain treatment.

PENTAZOCINE

TALWIN Nx5 contains pentazocine hydrochloride, USP, equivalent to 50 mg base and naloxone hydrochloride,
USP, equivalent to 0.5 mg base. It is formulated for oral administration. Pentazocine has the following structural formula:

\[
\text{HO} \quad \text{CH} \quad \text{OH}
\]

It is a potent analgesic which when administered orally in a 50 mg dose appears equivalent in analgesic effect to 60 mg (1 grain) of codeine. Onset of significant analgesia usually occurs between 15 and 30 minutes after oral administration, and duration of action is usually 3 hours or longer. Onset and duration of action and the degree of pain relief are related both to dose and the severity of pretreatment pain. Pentazocine weakly antagonizes the analgesic effects of morphine and meperidine; in addition, it produces incomplete reversal of cardiovascular, respiratory, and behavioral depression induced by morphine and meperidine. Pentazocine has about 1/50 the antagonistic activity of nalorphine. It also has sedative activity. The presence of naloxone in TALWIN Nx will prevent the effect of pentazocine if the product is misused by injection. Studies in animals indicate that naloxone does not affect pentazocine analgesia when the combination is given orally. If the combination is given by injection, the action of pentazocine is neutralized. TALWIN Nx is indicated for the relief of moderate to severe pain. Some patients previously given opioids, including methadone, for the daily treatment of opioid dependence, have experienced withdrawal symptoms after receiving pentazocine. Patients receiving therapeutic doses of pentazocine have experienced hallucinations (usually visual), disorientation, and confusion, which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. There have been some reports of dependence and of withdrawal symptoms with orally administered pentazocine. The usual initial adult dose is 1 to 2 tablets every 3 or 4 hours. Total daily dosage should not exceed 12 tablets. Tolerance to the analgesic effect of pentazocine has also been reported only rarely. However, there are no peer-reviewed reports on the long-term experience with the oral administration of TALWIN Nx, but anecdotally no adverse effects have been observed by the authors from long-term use.

BUPRENORPHINE

Suboxone (CIII) is a sublingual tablet that contains buprenorphine HCl and naloxone HCl dihydrate at a ratio of 4 to 1, buprenorphine, naloxone (ratio of free bases). Subutex is a sublingual tablet that contains buprenorphine HCl. Suboxone is available as sublingual tablets containing 2 mg of buprenorphine with 0.5 mg of naloxone and 8 mg of buprenorphine with 2 mg of naloxone. Subutex is available as 2 mg and 8 mg of buprenorphine sublingual tablets. Buprenorphine has the following structure:

\[
\text{HO} \quad \text{CH} \quad \text{OH}
\]

Molecular weight: 504.09

Buprenorphine 0.3 mg i.m. is approximately equivalent to 10 mg morphine sulfate i.m. in analgesic and respiratory depressant effects in adults. Pharmacological effects occur as soon as 15 minutes after intramuscular injection and persist for 6 hours or longer. Peak pharmacologic effects usually are observed at 1 hour. Although buprenorphine may be classified as a partial agonist, under the conditions of recommended use it behaves very much like a classical mu agonist. One unusual property of buprenorphine observed in in vitro studies is its very slow rate of dissociation from its receptor. This could account for its longer duration of action than morphine, the unpredictability of its reversal by opioid antagonists, and its low level of manifest physical dependence. Buprenorphine demonstrates opioid antagonist activity and has been shown to be equipotent with naloxone as an antagonist of morphine in the mouse tail flick test. Buprenorphine is indicated for the relief of moderate to severe pain.

Treating Chronic Pain

The mixed agonist-antagonist analgesics have not had a major role in the treatment of chronic pain, but the use of Suboxone is gaining popularity. Pentazocine, the first and most widely used of this group of drugs has two major limitations: by mouth it is not a strong analgesic and its use is associated with psychotomimetic side effects in 10 to 20 percent of patients. Buprenorphine is the most useful of the agonist-antagonists in chronic
pain patients. It is potent, long-acting (6 to 9 hours) and effective when given sublingually. However, it has a limited effective dose range (analgesic ceiling at 32 mg sublingual per day) and produces the same side effects as morphine-like drugs, possibly more frequently at equianalgesic doses. It may be used in the treatment of cancer pain, or in patients with chronic arthritides or other forms of chronic noncancer pain who require a potent conventional analgesic, as an alternative to the weak opioids or to morphine in low doses. Suboxone has an additional prescribing advantage because it has the analgesic potency of the class II controlled substances but it is scheduled as a class III controlled substance. The Drug Enforcement Administration (DEA) “X” license is not required when it is prescribed as a pain medication. The Drug Addiction Treatment Act of 2000 expanded treatment for opioid dependence into mainstream medical practice. It specifies several ways in which physicians can qualify to prescribe and dispense buprenorphine in their offices for the treatment of opioid dependence. A practitioner who wants to use buprenorphine for substance abuse treatment must apply for a waiver and meet all of the requirements under 21 U.S.C. § 823(g)(2)(B). The DEA will then assign an additional identification number to the practitioner who will then have 2 DEA numbers. The additional number will be the same as the first except an X will precede the number. It would seem advisable to get the “X” license if one is treating patients with a dual diagnosis of chronic pain and addiction. This is because if the patient can be classified as an opiate addict, then one would be treating chronic pain and the opioid addiction.

Practical Considerations

Major limitations of agonist-antagonists include a "ceiling" on their ability to provide analgesia and restricted routes of administration. Although agonist-antagonists have a ceiling on the severity of opioid-induced respiratory depression, when the analgesic ceiling is reached, any increase in dose will not increase pain relief. This is why they are inappropriate for severe, escalating pain, and are not recommended as first-line analgesics for any pain. Unlike buprenorphine, the strict agonist-antagonist require cessation of [mu]-analgesics for 24 to 48 hours. They appear to produce more respiratory depression and they appear to be less acceptable analgesics attributed to their psychotomimetic effects.

Buprenorphine differs from most opioid analgesics in several ways that may favor its use in patients with drug abuse histories. Compared to typical [mu]-agonist opioids, buprenorphine appears to produce less physical dependence,10 abuse liability,9 and respiratory depression.11 In addition, buprenorphine blocks the euphoric effects of [mu]-agonist12 and has a longer duration of analgesia (6 to 8 hours), thus requiring infrequent self-administration.11 The main problem in switching to buprenorphine therapy for the treatment of pain is that it can precipitate withdrawal from [mu]-agonist opioids.13

As a mu opioid partial agonist, buprenorphine may act as a mu agonist or antagonist depending on the pharmacological test, the degree of receptor activation required to produce agonist effects,14,15 and the dosage. When buprenorphine, with its high affinity for the mu receptor, displaces a full agonist with greater intrinsic activity from that mu receptor, the activation produced by buprenorphine is less. Buprenorphine has low intrinsic activity (and high affinity) at the mu receptor. That is, it binds tightly to this receptor, but it does not "turn on" this receptor as completely as a full mu-opioid agonist. Conversely, buprenorphine has no intrinsic activity (but high affinity) at kappa receptors. These differing effects at mu and kappa receptors have been used to explain the unusual pharmacologic effects of buprenorphine, including its bell-shaped dose-response curve (Figure 1). It has been suggested that at low doses, mu effects predominate, while at higher doses kappa antagonist effects offset mu effects, resulting in a descending limb to the dose-response curve.16

As noted above, because of its partial-agonist properties, buprenorphine can precipitate signs and symptoms of opioid withdrawal in some patients physically dependent on opioids. In opioid-dependent individuals, buprenorphine at low doses will substitute for other opioids (ie, function as an opioid agonist). However, under appropriate conditions buprenorphine

Figure 1. Hypothetical dose–effect curve for buprenorphine. As the dose increases (horizontal axis) the effect increases (vertical axis) to a maximum (M) and then the effect decreases as the dose is further increased.
at high doses can precipitate an opioid withdrawal syndrome.\textsuperscript{17-22}

Initiation of agonist–antagonist treatment or switching from opioids to agonist-antagonist can be performed as per the buprenorphine initiation protocol.\textsuperscript{23}

The following recommendations are the proper way to use buprenorphine.\textsuperscript{24}

The degree of withdrawal precipitated by buprenorphine in opioid-dependent individuals is determined by the dose of buprenorphine, dose of maintenance opioid, and time since last dose of maintenance opioid.\textsuperscript{21,22,25-27}

Patients dependent on methadone 60 mg/day (but not 30 mg/day) show a significant increase in total withdrawal scores following an acute 8 mg sublingual solution dose of buprenorphine when administered 40 hours after the last methadone dose.\textsuperscript{21} In patients maintained on methadone 30 mg/day, intramuscularly administered doses of buprenorphine (0.5 to 8 mg) do not precipitate opioid withdrawal when buprenorphine is administered 20 hours after the last dose of methadone.\textsuperscript{26} However, they do produce mild antagonist-like effects when administered 2 hours following the maintenance dose of methadone.\textsuperscript{19} In another study, subjects maintained on daily oral methadone (25 to 45 mg/day, mean 35 mg), and abruptly transferred to 2 mg of daily sublingual buprenorphine solution, showed mild withdrawal symptoms.\textsuperscript{25} This probably reflects that the low dose of buprenorphine used only partially suppressed methadone withdrawal rather than precipitated withdrawal.

Prior to administering the initial buprenorphine dose, consideration should be given to three important factors. These factors include: (1) the time since last opioid use (theoretically, a partial agonist opioid should be most effective and demonstrate the least antagonist effects when the patient is experiencing slight opioid withdrawal); (2) the type of opioid dependence (ie, long- or short-acting opioid); and (3) the degree or level of opioid physical dependence. The shorter acting the opioid of dependence, the longer time since last opioid use, and the lower the level of physical dependence, the higher the initial dose can be.\textsuperscript{28}

The likelihood of a buprenorphine- or buprenorphine/naloxone-induced precipitated withdrawal increases as the time interval since last opioid ingestion decreases. Mild precipitated withdrawal has been observed at a time interval of 2 hours since last opioid dosing.\textsuperscript{19} Because of this potential, patients transferring from short-acting opioids (ie, street heroin) should be instructed to abstain from illicit opioid use for at least 4 hours prior to administration of the first buprenorphine dose. If the patient's drug use history is vague or inconsistent, or if acute opioid effects are suspected, the first dose should be delayed for at least 4 hours or until mild withdrawal signs or symptoms are observed or reported.

Induction onto buprenorphine from short-acting opioids such as heroin should be easy to accomplish, and reports of buprenorphine-induced precipitated withdrawal in abusers dependent upon heroin have been extremely uncommon. Induction onto buprenorphine from long-acting opioids can be more problematic, possibly because of kinetic differences in long- and short-acting full mu-opioid agonists. A longer time interval between methadone and subsequent buprenorphine dosing is recommended depending on the dose of methadone. In controlled studies of subjects maintained on 20 to 40 mg of daily methadone, the transition to buprenorphine is less difficult and can generally be initiated 24 hours after the last dose of methadone.\textsuperscript{29-31} Successful titration with higher maintenance doses of methadone, such as 40+ mg/day, have been achieved (L. Amass, E. Strain, personal communication, 30 October 2002). For higher doses of methadone, the transition to buprenorphine may be made more tolerable by delaying initiation of buprenorphine therapy for more than 24 hours after the last dose of methadone\textsuperscript{32} or rapidly lowering the dose of methadone and offering supportive therapy with ancillary medications prior to buprenorphine induction.\textsuperscript{33}

Patients with a level of physical dependence on long-acting opioids equivalent to >40 mg/day of methadone should ideally reduce their opioid use to the equivalent of 40 mg/day or less of methadone prior to initiating buprenorphine therapy. Some patients with higher levels of daily opioid use can be inducted onto buprenorphine safely provided they are abstinent for a sufficient time period to result in clinically apparent withdrawal symptoms.\textsuperscript{33-36} However, these patients should be prepared in advance for the possibility of some mild discomfort during the first few days of buprenorphine induction.

After taking a clinical history that includes time since last opioid use, and type and amount of opioid used, the appropriate initial dose of buprenorphine can be selected. An initial dose of buprenorphine 4 mg or buprenorphine/naloxone 4/1 mg is recommended followed in 3 to 4 hours with additional dose of up to 4 mg (or 4/1 mg) if indicated. On subsequent days, the dose of buprenorphine/naloxone should be increased to 12/
3–16/4 mg/day. During this period of dose induction, patients may need to attend the clinic or doctor's office on a daily basis for dose adjustment and clinical monitoring. Table 1 provides guidance for selecting the optimal dose of buprenorphine based on the patient's self-reported opioid use.

If there is concern for possible precipitation of an opioid withdrawal syndrome, the first daily dose can be split with the second half administered 3 to 4 hours after the first dose. In most studies, the starting dose of buprenorphine administered on the first day has been 2 mg of sublingual solution. However, single doses of buprenorphine up to 4 mg tablet can be administered without undue concern for causing an opioid withdrawal syndrome in opioid-dependent patients.

Induction onto a dose as high as 16 mg of buprenorphine solution has been accomplished by administering 2, 4, 8, and 16 mg of buprenorphine on days 1 to 4, respectively. A similar induction schedule used buprenorphine combination tablets would be 4/1, 8/2, 12/3, 24/6 mg on days 1 to 4. However, the objective of induction should be to achieve a maintenance dose (ie, 16 mg) as rapid as possible (ie, within 2 to 3 days).

It is possible to successfully transfer a patient from a [mu]-agonist to buprenorphine without precipitating withdrawal or interrupting analgesia. In a previous case report, a patient was switched from morphine to buprenorphine for pain relief and the patient was observed for withdrawal symptoms. The patient was a 35-year-old man suffering from Crohn's disease, a chronic intestinal disorder, who had required many surgeries and was on total parenteral nutrition (intravenous feeding). He also had a history of drug and alcohol abuse. Because he was probably dependent on morphine, it was feared that an abrupt switch to buprenorphine would cause withdrawal.

However, the switch was successfully made. After a gradual reduction in morphine dose, followed by the omission of one morphine injection, resulting in 12 hours of abstinence before the new drug was given, the first dose of buprenorphine was administered. There were only minor withdrawal symptoms after the first dose, and no withdrawal symptoms were noted upon subsequent doses while at the same time there was no interruption in analgesia. Thus some patients can be safely switched to Suboxone in an outpatient setting.

### Table 1. Guidelines for Selecting Doses of Buprenorphine for Treatment of Opiate Dependence (Adapted from Bickel and Amass, 1995)

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Unit of Use, Dose (mg)</th>
<th>Self-Reported Drug Use (4 Times Per Day)</th>
<th>Morphine Equivalent Parenteral Dose (mg), Total Daily Dose (4 Times Per Day)</th>
<th>Methadone Equivalent Oral Dose (mg), Daily</th>
<th>Buprenorphine Equivalent Sublingual Tablet Dose (mg), Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodeone&lt;sup&gt;a&lt;/sup&gt; (Percocet, percocan, rexicodone, oxyl)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5</td>
<td>6-9</td>
<td>40-60 (10-15)</td>
<td>20-30</td>
<td>4</td>
</tr>
<tr>
<td>Hydrocodeone&lt;sup&gt;a&lt;/sup&gt; (Hycodan, others)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5</td>
<td>6-9</td>
<td>40-60 (10-15)</td>
<td>20-30</td>
<td>4</td>
</tr>
<tr>
<td>Codeine&lt;sup&gt;c&lt;/sup&gt;</td>
<td>15</td>
<td>13-20</td>
<td>40-60 (10-15)</td>
<td>20-30</td>
<td>4</td>
</tr>
<tr>
<td>Meperidine&lt;sup&gt;d&lt;/sup&gt; (Demerol)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>50</td>
<td>6-9</td>
<td>40-60 (10-15)</td>
<td>20-30</td>
<td>4</td>
</tr>
<tr>
<td>Hydromorphone&lt;sup&gt;d&lt;/sup&gt; (Dilan-did)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2</td>
<td>2</td>
<td>40-60 (10-15)</td>
<td>20-30</td>
<td>48</td>
</tr>
<tr>
<td>Morphine&lt;sup&gt;e&lt;/sup&gt;</td>
<td>15</td>
<td>6-9</td>
<td>100-120 (25-30)</td>
<td>50-60</td>
<td>16</td>
</tr>
<tr>
<td>Heroin&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Bag&lt;sup&gt;g&lt;/sup&gt;</td>
<td>4-6</td>
<td>40-60 (10-15)</td>
<td>20-30</td>
<td>4</td>
</tr>
</tbody>
</table>

*This table includes selected common opioid agonist medications, which patients may report abusing. The first column describes each medication by generic name with superscripts for references (see below) used to estimate relative analgesic potency and/or comparable (oral vs. parenteral) steady-state blood levels. Selected brand names are noted in parentheses. The second column lists the milligrams of medication per unit of use, which could be either tablets, capsules, caplets, bags, etc. Self-reported drug use is the number of units per use with the assumption that use is 4 times per day (ie, multiply units by a factor of 4 for daily use). Next, morphine equivalents are calculated based on 4 times per day use. Morphine doses are then converted to daily methadone doses. The daily dose of buprenorphine is based on current data from controlled clinical trials and laboratory studies comparing methadone and buprenorphine. Note: Relative analgesic potencies are based on acute and not chronic dosing, as is the case when treating opioid dependence.*
Case Study #1. The patient was a 38-year-old white man with complex regional pain syndrome type II “causalgia” of the left upper extremity status post 10 operations for repair of a complicated left distal radius fracture after a fall 7 years ago. At the time of admission for switching to Suboxone the patient was taking Kadian 100 mg 2 per day, Percocet 10 to 325.6 to 8 per day, Actiq 200 mcg 1 to 4 per day, Gabitril 16 mg 2 per day, Topamax 75 mg 2 per day, Amantadine 100 mg 2 per day, Robaxin 750 mg 2 to 3 per day, Effexor XR 150 mg 3 per day with poor control of his pain. He was using his spinal cord stimulator 24/7. The patient underwent a 3-day inpatient switch to Suboxone. Two weeks after switching, he was taking 8 mg of Suboxone in the AM 4 mg at noon and 4 mg at hs. “I am not drugged anymore! It was the right thing to do.” The patient was off of all narcotics except for Suboxone and he described his pain level on Suboxone as a 3 over 10 on the good days and 8 to 9 over 10 on the bad days.

Case Study #2. The patient was a 60-year-old white woman with chronic low back pain. She had severe dextro scoliosis with central herniated nucleus pulposis (HNP) and severe spinal stenosis at L3-4, herniated nucleous pulposis at L4-5 and degenerated disc at L1-2 and L5-S1. She also had bilateral cervical radicular syndrome with bulging disc at C3-4, osteophytic ridging at C4-5, C5-6, and C6-7. Preoperatively she was being medicated from T9-S1 bilaterally. After surgery she was taking 150 mg 3 per day with poor control of his pain. He was referred to failed neck surgery syndrome and failed back surgery syndrome. He went a 3-day inpatient switch to Suboxone. Two weeks after switching, the patient was taking 8 mg of Suboxone the patient was taking Lortab 10/500 mg 8 per day, which did not control her pain. A trial of Talwin Nx 10 per day did not control her pain. She was also taking Klonopin 1.0 mg 4 per day, Paxil CR 25 mg 1 per day, Sinequan 150 mg 3 at bedtime, Robaxin 750 mg 3 to 8 per day. She was switched to Suboxone as an outpatient. She was instructed to stop her Talwin Nx for 8 hours and then start Suboxone 2 mg sublingual 1 to 2 q 6 hours prn pain. She had no signs and symptoms of withdrawal and at Suboxone 2 mg six per day her pain level decreased to 1 over 10! She said that she was able to do a lot more at home and was very pleased with the medication. This is the best she had done since her spine surgeries 9 years ago.

In the aforementioned peer reviewed articles, opiate to buprenorphine switches/inductions have all been performed as inpatients and thus switching to Suboxone in an outpatient chronic pain management setting should be done with caution. However, there is growing experience with the use of Suboxone for chronic pain, that the switch can be safely done as an outpatient. Anecdotally it has been observed that one-third of patients switched to Suboxone report superior/fantastic analgesia, one-third report no improvement in pain relief but clearing of the sensorium and one-third report increased pain and want to be switched back.

Case Study #3. The patient was a 47-year-old Hispanic woman with chronic intractable pain secondary to failed neck surgery syndrome and failed back surgery syndrome. She was taking Lortab 10/500 mg 8 per day, which did not control her pain. A trial of Talwin Nx 10 per day did not control her pain. She was also taking Klonopin 1.0 mg 4 per day, Paxil CR 25 mg 1 per day, Sinequan 150 mg 3 at bedtime, Robaxin 750 mg 3 to 8 per day. She was switched to Suboxone as an outpatient. She was instructed to stop her Talwin Nx for 8 hours and then start Suboxone 2 mg sublingual 1 to 2 q 6 hours prn pain. She had no signs and symptoms of withdrawal and at Suboxone 2 mg six per day her pain level decreased to 1 over 10! She said that she was able to do a lot more at home and was very pleased with the medication. This is the best she had done since her spine surgeries 9 years ago.

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