

Opioid Antagonists, Naloxone & Naltrexone — Aids for Pain Management

An Overview of Clinical Evidence



INNOVATIONS

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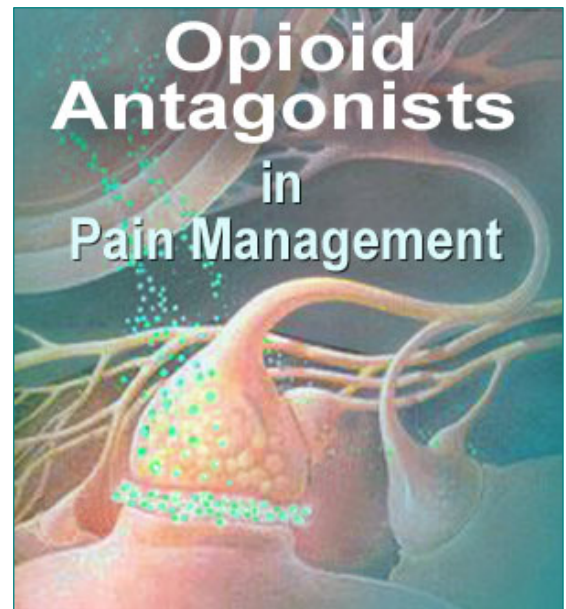
Achieving effective, durable, and safe pain relief, especially in patients with chronic and/or severe pain conditions, can be a clinical challenge. For many types of pain, prescription opioids are among the most effective analgesics [Fine and Portenoy 2004]. However, there could be concerns about the development of opioid tolerance or adverse effects, and in some cases opioids seem to worsen pain (eg, hyperalgesia) [Compton 2008; DuPen et al. 2007; Stein et al. 2003]. For certain difficult conditions, such as fibromyalgia or neuropathies, opioids alone are sometimes considered of limited effectiveness [Chou et al. 2009].

Healthcare providers interested in pain management must be alert to new or novel approaches that help to overcome deficiencies of opioids, such as treatment-limiting side effects, and as aids in relieving difficult-to-treat pain conditions. In this regard, there is a growing body of evidence suggesting potential benefits of opioid antagonists.

Opioid antagonists — in particular, naloxone and naltrexone — have been available and studied for decades as agents that displace opioid molecules from their neuroreceptors, and block opioids from attaching to and activating those receptors. Such qualities can be of important benefit, as short-acting antagonists like naloxone are used effectively to quickly reverse toxic effects of opioid overmedication or overdose.

Laboratory research and clinical trials have demonstrated the unexpected, paradoxical effects of opioid antagonists as adjuvants for enhancing rather than attenuating analgesic effects of opioids like morphine, oxycodone, and others. Further benefits of opioid antagonists, as monotherapy, for better managing certain chronic pain conditions also have been discovered.

This paper provides an overview of naloxone and naltrexone pharmacology, and briefly examines some of the theoretical foun-



Available evidence suggests that the opioid antagonists naloxone and naltrexone offer potential benefits for enhancing opioid analgesia and as monotherapy for managing certain challenging pain conditions.

Graphic above modified from an illustration by Carol Donner, NIDA, undated.

dations of opioid antagonists for pain management. Available evidence from the literature describing opioid-antagonist therapy in adult humans, as portrayed in case examples or clinical trials, is reviewed and summarized. It must be understood, however, that opioid antagonists are not yet FDA-approved as adjuvant analgesics or for other pain management purposes, so their uses described in this report are off-label. Further investigations to assess the safety and efficacy of these applications would be appropriate.



The contents of this report are for educational purposes and are not intended to endorse or promote the off-label prescribing of any drugs. Practitioners are advised to study the available evidence and use professional discretion in their prescribing decisions.

Opioid Antagonist Pharmacology

Opioid antagonists have been available for many decades and are well known for their applications in addiction treatment (naltrexone) and as an antidote for opioid overdose (naloxone). The first report of agents having opioid antagonist-like properties was in 1915, when N-allylnorcodeine was observed to block the respiratory-depressant effects of morphine and heroin. The opioid antagonist nalorphine was synthesized in the 1940s; however, it also had partial agonist activity and its unsettling effects on mood (causing dysphoria) discouraged widespread use for treating opioid intoxication or overdose [Gonzales and Brogden 1988; Zimmerman and Leander 1990].

In 1960, naloxone was synthesized as a more potent and less toxic antagonist than nalorphine. Naloxone produces no dysphoria but it has a short duration of action and poor oral bioavailability due to high first-pass hepatic metabolism; it is 15 times more potent by injection than by mouth. The need for a long-acting opioid antagonist as a treatment for addiction, by blocking the euphoric effects of illicit opioids for an extended period of time, motivated the development of naltrexone in 1963. This antagonist has reasonably good oral bioavailability, a long duration of action, and twice the potency of naloxone [see **Table 1**: Crabtree 1984; Gonzales and Brogden 1988; Reisine and Pasternak 1996].

The development of these agents was facilitated by the interesting fact that relatively minor structural changes could convert an opioid agonist drug into one with antagonist actions; that is, blocking various opioid receptors and preventing their activation. Thus, morphine was transformed into nalorphine, and oxycodone into either naloxone or naltrexone. A more recent development, nalmefene, is a pure mu-receptor antagonist that is at least equipotent with naloxone but longer acting, with a duration of action between naloxone and naltrexone. Additional antagonists that are selectively active at other opioid receptors have been developed largely for experimental purposes [Barsan 1989; Reisine and Pasternak 1996; Zimmerman and Leander 1990].

Naloxone and naltrexone are the two opioid antagonists that have been most extensively studied and are commercially available today. They are FDA-approved for the treatment of alcoholism or opioid addiction (naltrexone; eg, Trexan®, Revia®, Depade®) or opioid overdose (naloxone; eg, Narcan®). A long-acting, high-dose depot form of naltrexone (Vivitrol®) for intramuscular injection also is approved for addiction therapy. These antagonists also are being

	Naltrexone	Naloxone
Chemical Formula	C ₂₀ H ₂₃ NO ₄	C ₁₉ H ₂₁ NO ₄
Oral Bioavailability	Up to 40%	2% (high absorption but extensive first-pass metabolism)
Metabolism	Hepatic	Hepatic
Peak Concentration	1–2 hours	10 minutes
Half-life	Up to 14 hrs (oral)	30–81 min. (IV, IM)
Duration of Action	Up to 24+ hrs	1–4 hrs
Excretion	Renal	Renal, Biliary

Sources: Crabtree 1984; Gonzales and Brogden 1988; Reisine and Pasternak 1996

used or tested as ingredients in specially formulated opioid analgesics to deter their misuse or abuse (see **Side Box**).

As noted above, two important features distinguishing naloxone from naltrexone are the very limited oral bioavailability of naloxone and the extended action of naltrexone. Both, naltrexone and naloxone may interact with all classes of opioid receptors [Shader 2003] but they do so most strongly at mu-opioid receptors [Reisine and Pasternak 1996]. However, the typical naltrexone doses used for addiction therapy (50–100 mg/day orally) and naloxone dosing for reversing opioid overdose (0.4–1.0 mg/dose IV or IM) are, in most cases, different from the dosing protocols used in pain management applications (discussed below). In general, the literature refers to doses of antagonists, particularly naltrexone, in the 1 to 5 mg range as “low dose”; whereas, those less than 1 mg, in microgram amounts, are usually designated as “ultralow dose.”

In the interest of abuse deterrence rather than therapeutic enhancement, certain agonist-antagonist combinations have been developed containing a sustained-release opioid with a sequestered antagonist, usually naltrexone. The concept is that the antagonist remains latent and is only released in the event of tampering, such as by crushing or dissolving the product, in an attempt to extract the abusable opioid ingredient. The activated antagonist would then impede desired opioid effects making the product less prone to abuse [Gershell and Goater 2006].

Special Qualities of Opioid Antagonists

In an excellent review of the role opioid antagonists may play in pain management, Sloan and Hamann [2006] note that interest in this topic dates back to the 1950s. It was observed that low doses of the antagonist nalorphine had pain-relieving properties in humans comparable to low-dose morphine in some cases. It was suspected that a combined opioid agonist-plus-antagonist agent might offer significant pain-relief without the undesirable side effects of opioids alone. However, this line of research was not pursued until quite recently.

It was later discovered that naloxone had an analgesic effect at very low doses but no such effect at higher doses. For example, experiments in opioid-naïve human subjects during the 1970s found that “low-dose” naloxone (up to 2 mg) had analgesic effects that were lacking at higher naloxone doses (eg, 7.5 mg and 10 mg) [Sloan and Hamann 2006]. The proposed neurobiological mechanisms behind this are complex and still being defined.

Studies in opioid-free animals have shown that, by causing a transient blockade of opioid receptors, low doses of antagonists stimulate increased production, or upregulation, of mu-opioid receptors in regions of the brain that control pain responses [references in Mannelli et al. 2006]. Therefore, it seems plausible that after antagonist effects wear off — which may take minutes or hours depending on the agent and dose — greater numbers of opioid receptors are available to bind with pain-relieving opioids in the circulatory system, whether externally administered (eg, morphine) or endogenous peptides (eg, endorphins). At the same time, it has been noted that the body responds to the temporary opioid-receptor blockade by producing substantially increased amounts of beneficial natural endorphins [NCI 2007; Smith et al 2007]. However, if the opioid-receptor blockade by antagonist is too extensive or continues too long, these pain relieving benefits are not realized, so the dose and half-life of the particular antagonist are critical factors.

Laboratory experiments further demonstrated that opioid antagonists may help to prevent the potential hyperalgesic (pain enhancing) and other negative effects of opioid pain relievers. At a cellular level, it is believed that exposure to opioid analgesics at certain doses and for prolonged periods of time may lead to aberrant signaling patterns by opioid receptors. These pat-

Low doses of opioid antagonists seem to “reset” the opioid-receptor system, enhancing analgesia while overcoming prior opioid tolerance or hyperalgesia.

terns can be reversed and restored to normal by the actions of opioid antagonists in very low concentrations [Sloan and Hamann 2006; Webster et al. 2006].

The ultimate effects of these mechanisms, demonstrated in animal studies and human trials, appears to be an enhancement by low- or ultralow-dose naloxone or naltrexone of opioid-agonist antinociceptive (pain relieving) efficacy. Along with this, tolerance to and physiologic dependency on opioid agonists, such as morphine and others, may be diminished [Crain and Shen 2000a]. Essentially, appropriately low doses of opioid antagonists have been postulated to “reset” the opioid-receptor system for a period of time [Loitman 2006], which seems analogous to how rebooting a malfunctioning computer clears memory, refreshes the software, and often restores normal function. The best type of antagonist, the optimal dose of it for achieving these effects, and the duration of effects have been explored by various investigators, as described below.

Research on Naloxone in Pain Management

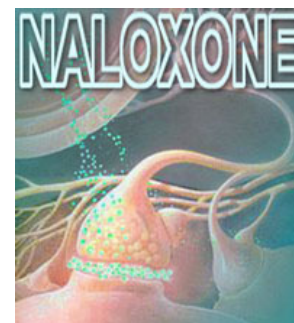
The traditional role of naloxone has been the complete reversal of opioid effects, particularly in cases of opioid overmedication or life-threatening overdose. However, the potentials of this agent in pain management have been described in a number of studies.


Loitman [2006] reported an interesting case series of 3 patients with intractable chronic pain — despite receiving large doses of strong opioids, other medications, and complementary procedures — who underwent a brief and temporary inpatient opioid-receptor reversal (that is, detoxification) procedure with intravenous naloxone (0.6–1.2 mg). This induced rapid withdrawal as the opioids were displaced from their receptors by the antagonist. Distressing withdrawal symptoms were ameliorated by sedation and, after a brief period of time (about 20 minutes), opioid pain relievers were readministered.

All patients responded very positively to the procedure, achieving much greater pain relief than before the brief detoxification and at significantly lower doses of opioid analgesics. Overall, Loitman noted that vastly improved pain relief was achieved in less than one hour on about one-third of the original opioid dose. Although exact mechanisms were unclear, the opioid receptors were thought to have been “reset” (as discussed above), overcoming prior opioid tolerance and/or hyperalgesia.

A number of clinical investigations have suggested potential benefits of ultralow-dose oral naloxone administration for postoperative pain:

- In patients treated with buprenorphine (a mixed agonist-antagonist opioid) postoperatively and experiencing breakthrough pain, the addition of oral ultralow-dose naloxone (0.08–0.4 mg, or 80–400 mcg*) provided effective and long-lasting analgesia (median 22 hrs) [Schmidt et al. 1985]. A more recently reported investigation, by La Vincente and colleagues [2008], also confirmed the enhancement of buprenorphine analgesia by ultralow-dose oral naloxone (exact dose unspecified).
- Oral naloxone alone, either 0.4 or 1.0 mg, produced significant analgesic effects compared with placebo for postoperative dental pain in a trial of 90 patients. In a second trial, oral naloxone (0.4 mg) plus pentazocine (60 mg, a mixed agonist-antagonist opioid) produced greater dental-pain relief than monotherapy with pentazocine (60 mg) or morphine (15 mg). However, naloxone (0.4 mg) plus morphine (8 mg) produced less analgesia than morphine (8 mg) alone, suggesting



 On rare occasions, nausea, vomiting, hypertension, pulmonary edema, tachycardia, arrhythmia, and cardiac arrest have been implicated with naloxone doses as small as 0.1–0.4 mg [Pallasch and Gill 1981, Partridge and Ward 1986].

* In most of the literature, ultralow-dose applications of antagonists are usually expressed in microgram amounts. However, since the more well-known applications of naloxone and naltrexone are in milligram increments, doses in this paper are converted from micrograms to milligrams (1 mcg = .001 mg).

that analgesia augmentation by naloxone is influenced by the type and dose of opioid [Levine et al. 1988].

- In a study involving postoperative IV PCA (patient-controlled analgesia), 60 patients received morphine under patient control, plus either placebo or naloxone — 0.00025 mg/kg/h or 0.001 mg/kg/h — via steady IV infusion. Good pain relief was experienced in all groups; however, side effects (nausea, vomiting, pruritus) were reduced by naloxone at either dose and consumption of PCA morphine was significantly reduced by the lowest naloxone dose, suggesting a morphine-enhancement effect of the antagonist [Gan et al. 1997].
- Other postoperative trials compared IV PCA morphine alone versus IV PCA morphine plus an IV naloxone bolus (0.8 mg) administered with each morphine dose (which was equivalent to 0.38 mg/kg/hr of naloxone on average). In the 92 patients studied, investigators found no differences between groups in pain relief, side effects, or morphine consumption [Sartain et al. 2003]. Comparing this study with the Gan et al. [1997] trial above suggests that a *continuous* naloxone infusion rather than bolus, and at doses of naloxone that are less than in this study, may be required to accrue beneficial effects during naloxone/morphine PCA.
- A more recently reported case series, incorporating intravenous nalbuphine (5 mg) plus naloxone (0.2 mg IV), used postoperatively in 4 women undergoing outpatient gynecological procedures, found improved analgesia with this mixture [Gordon et al. 2007].
- In a case report, a patient with chronic refractory pain following laminectomy was treated with an intrathecal combination of morphine (2 mg) and ultralow-dose naloxone (.000020 mg; that is, 20 nanograms). Dramatic pain relief began within 20 minutes, peaked at 1 hour, and persisted with repeated infusions. Up to 80% improvement was reported by the patient while receiving an intrathecal infusion of 5 mg morphine plus .000050 mg naloxone daily during a 3-year followup period [Hamann et al. 2008].

The trials in postoperative patients suggest that combining low-dose naloxone with opioid agonists can be safe and enhance effectiveness of the analgesic. PCA-based studies further suggest that the augmentation of opioid-agonist effects during PCA is best with sustained ultralow-level antagonism of opioid receptors versus the more complete and intermittent blockade of those receptors by a somewhat higher dose of naloxone [Sloan and Hamann 2006].

Naloxone for Opioid-induced Constipation

Another proposed application of low-dose opioid antagonists has been to help prevent or relieve opioid-induced constipation that can be a problematic side effect of long-term opioid analgesics. Meissner et al. [2009] recently reported a clinical trial in 202 patients receiving oxycodone for chronic noncancer pain. Subjects administered 40, 60, or 80 mg/day of extended-release oxycodone were randomized to also receive either 10, 20, or 40 mg/day of extended-release oral naloxone or placebo.

There was no loss of oxycodone analgesic efficacy in patients administered naloxone at any of these higher doses, probably due to naloxone's limited oral bioavailability. However, bowel function significantly improved with increasing naloxone dose, and there were no unexpected adverse events. A 2:1 dose ratio of oxycodone/naloxone was judged as most efficacious. Other large, randomized, placebo-controlled trials had found the same favorable results in patients with chronic noncancer pain and back pain [Simpson et al. 2008; Vondrackova et al. 2008]. A combination product — using extended-release oxycodone and extended-release

naloxone; 2:1 ratio — was recently approved for marketing in Europe under the name Targin®, with an emphasis on its benefits for providing equipotent oxycodone analgesia while ameliorating opioid-induced constipation [Targin 2009]. Also see **Box**.

Two relatively new and specialized opioid antagonists, methylnaltrexone (Relistor®) and alvimopan (Entereg®), have been introduced for managing opioid-induced constipation. These agents block only peripheral opioid receptors in the gut. And, unlike naloxone and naltrexone, these antagonists do not cross the blood-brain barrier, so their actions potentially reverse opioid-induced constipation without precipitating withdrawal symptoms or altering analgesic qualities of opioids [Goodheart and Leavitt 2006].

The FDA approved oral alvimopan in 2008 to accelerate the restoration of normal bowel function in hospitalized adult patients who have undergone partial large or small bowel resection surgery [FDA 2008a]. At about the same time, methylnaltrexone bromide was FDA-approved as an injectable medication to help restore bowel function in adult patients with advanced illness who are receiving analgesic opioids on a continuous basis [FDA 2008b].

Applications of Naltrexone in Pain Management

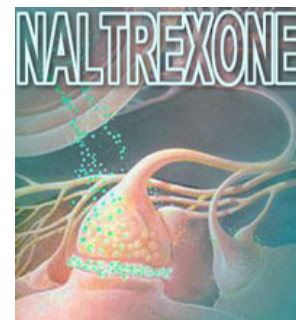
As a longer-acting, orally-bioavailable antagonist, naltrexone is easy to administer and may offer advantages over naloxone. In opioid-tolerant animals, naltrexone was shown to produce increased response to morphine [Gonzales and Brogden 1988], possibly by upregulating the opioid-receptor system [Crabtree 1984]. Also of interest, animal experiments suggest that very low doses of naltrexone appear to enhance opioid analgesia to a greater extent when the amount of opioid drug is actually reduced [Crain and Shen 2000b, 2001], which proposes an opioid-sparing effect in humans. A number of investigations in human subjects have explored the potential of low- or ultralow-dose naltrexone as an opioid adjuvant and as monotherapy for the management of several pain-related conditions.

Crohn's Disease

In 2007, successful results of the first clinical trial of low-dose naltrexone for active Crohn's disease were published by investigators at the Pennsylvania State University College of Medicine [Smith et al. 2007]. In an open-label study, 17 patients were administered low-dose oral naltrexone (4.5 mg/day at bedtime) for 12 weeks. Statistically significant improvements were found in CDAI (Crohn's Disease Activity Index) scores and quality of life indicators, increased rates of remission, and decreases in inflammatory markers in serum. Overall, 89% of patients exhibited a favorable response to naltrexone therapy, 67% achieved remission, and 2 subjects with open fistulas had closure. Side effects of therapy were reportedly minimal, with sleep disturbances in 7 patients most common. Reportedly, the National Institutes of Health has granted funding for this same group of researchers to conduct a larger placebo-controlled trial.

Irritable Bowel Syndrome

Kariv et al. [2006] reported an open-label pilot study of ultralow-dose naltrexone (0.5 mg/day) in 42 patients with confirmed irritable bowel syndrome (IBS). During 4 weeks of treatment and 4 weeks of followup, global assessments of symptom relief improved in about three-quarters of the subjects (76%) and mean numbers of pain-free days per week were modestly but significantly increased from baseline. Naltrexone therapy was well tolerated, without any significant adverse reactions.



! Administering larger doses of naltrexone to patients maintained on pure opioid agonists for pain can result in withdrawal signs and symptoms. These may be more sustained than those encountered with naloxone due to the longer half-life of naltrexone and its significant concentrations in the central nervous system.

Despite this initial success, a large, Phase III multi-center, randomized, placebo-controlled trial of oral naltrexone for treating IBS in 600 women was discontinued early due to unacceptable outcomes [Pain Therapeutics 2005]. Naltrexone demonstrated a favorable safety profile, and patients reported statistically meaningful relief of painful IBS symptoms during the second month of treatment compared with placebo. However, these beneficial effects did not persist into the third month, which was the primary endpoint of interest. Possibly, a critical factor was that this trial (and the one by Kariv et al. above) used 0.5 mg/day of naltrexone, which is well below the 4.5 mg every night that others have recommended as monotherapy [described at LDNinfo.org 2009; Smith et al. 2007; also see, fibromyalgia, below].

Fibromyalgia

Low-dose naltrexone (LDN) has been purportedly used off-label for the treatment of fibromyalgia for some time, and a small clinical study (n=10) funded by the American Fibromyalgia Syndrome Association (AFSA) was conducted in 2007 at the Stanford University Systems Neuroscience and Pain Lab [SNAPL 2008]. Details and results of this single-blind trial of LDN for the treatment of fibromyalgia have not been published (as of February 2009), but according to some reports the outcomes were successful and the majority of study participants asked to continue on drug therapy after the conclusion of the study [4.5 mg/day oral naltrexone, per correspondence with researcher S. Mackey, 1/28/09]. Side-effects were essentially nonexistent, except for 3 reports of mild sleep disturbance [also see, LDN for Fibromyalgia 2009].

Enrollment is ongoing, as of January 2009, for a large double-blind, placebo-controlled trial of LDN for fibromyalgia [ClinicalTrials.gov 2008]. While the exact mechanisms of naltrexone benefits for fibromyalgia are unknown, the researchers suggest it is possible that low doses of the drug block receptors on glial cells that are responsible for fibromyalgia symptoms [SNAPL 2008]. Previously, *in vitro* experiments on tissue cultures had shown that very low concentrations of opioid antagonists stimulated nerve tissue growth and the response of certain nerve tissues to the favorable effects of endogenous opioid peptides [Ilyinsky et al. 1987]. Hypothetically at least, these combined effects may play a role in the rejuvenation of nerve tissues that become sensitized or deranged in fibromyalgia syndrome.

More recently, neuroimaging studies (via positron emission tomography or PET) found that patients with fibromyalgia had significantly reduced availability of mu-opioid receptors in specific brain regions known to modulate pain, as compared with healthy control subjects [Harris et al. 2007]. The investigators suggested this as a possible explanation for why exogenous opioids generally have reduced effectiveness in fibromyalgia. Low-dose naltrexone, by upregulating the opioid-receptor system, might increase the body's responsiveness to endogenous opioid peptides in helping to relieve fibromyalgia pain. Whether or not adjuvant LDN therapy also could improve patient response to exogenous opioid analgesics has not been reported.

Neuropathic Pain

Recently reported laboratory experiments, and a case example, suggest benefits of opioid antagonists in ameliorating neuropathic pain. Prior investigations demonstrated that activated spinal cord glial cells (microglia and astrocytes) contribute importantly to neuropathic pain; although, how nerve irritation or injury activate glia is still undefined. In rodents, Hutchinson et al. [2008] found that isomers of naloxone and naltrexone can suppress microglial activation and aid in reversing neuropathic pain. Similarly, investigators recently described analgesic enhancement by an oxycodone/ultralow-dose naltrexone combination administered orally or spinally in a rodent model of neuropathic pain [Largent-Milnes et al. 2008].

The potential for ultralow-dose naltrexone to benefit neuropathic pain conditions needs further exploration.

Other positive effects on nerve tissues had been reported much earlier by Ilvinsky and colleagues [1987, described above].

There has been at least one case report of positive effects of antagonists for reducing neuropathy in humans. Cruciani et al. [2003] described a patient with chronic painful diabetic neuropathy being treated unsuccessfully with methadone. The addition of ultralow-dose oral naltrexone (0.002 mg/day) dramatically improved pain relief and, at the same time, allowed a 16% reduction in methadone dose.

Based on laboratory experiments and the very limited clinical evidence, low- or ultralow-dose naltrexone might potentially benefit reflex sympathetic dystrophy (RSD, also known as complex regional pain syndrome or CRPS). However, this has not been reported in the literature, and the role of the nervous system in this syndrome and its appropriateness as a target for treatment require further definition [Bennett and Brookoff 2006].

Naltrexone Combined with Opioid Agonists

Successful Phase II [Chindalore et al. 2005] and Phase III [Webster et al. 2006] trials have been completed on a combination oxycodone plus ultralow-dose naltrexone product. In the first trial, 243 patients with chronic, painful osteoarthritis were administered placebo, oxycodone QID (4x/day), or oxycodone + 0.001 mg naltrexone (Oxytrex™) either QID or BID (2x/day) [Chindalore et al. 2005]. The total daily oxycodone dose (titrated up to 80 mg/day or less) was the same in all treatment groups on average, but the Oxytrex groups additionally received either 0.002 or 0.004 mg naltrexone per day. Oxytrex BID (ie, oxycodone + 0.002 mg/day naltrexone) provided significantly superior pain relief compared with oxycodone alone QID, Oxytrex QID, or placebo.

The Phase III trial enrolled 719 patients with chronic back pain using essentially the same treatment protocol as above [Webster et al. 2006]. All active-treatment groups achieved comparable pain relief, although the addition of naltrexone in Oxytrex allowed significantly lower consumption of that combination drug than with oxycodone alone. Patients receiving Oxytrex BID also experienced significantly less constipation, somnolence, and/or pruritus than subjects in the other active-treatment groups.

The potential benefits of such agonist/antagonist combinations seems promising; however, this may depend on the type of opioid and/or the naltrexone dose. In an experimental trial in healthy humans, using a thermal discomfort test, the addition of 0.25, 0.5, or 1.0 mg of oral naltrexone neither aided nor deterred analgesic effects of oral hydrocodone [Cantilena et al. 2004]. These findings are very preliminary, and the naltrexone doses in this study were many-fold larger than in the Oxytrex formulation, so further research on combination products seems warranted.

Hamann and Sloan [2007] reported a clinical pilot study to assess the analgesic efficacy of ultralow-dose oral naltrexone combined with intrathecal morphine infusions in patients with chronic, refractory nonmalignant pain. Subjects being administered continuous intrathecal morphine were randomized in double-blind fashion to receive either oral placebo (n=5) or oral naltrexone — 0.1 mg (n=3) or 0.01 mg (n=7) — every 12 hours for 7 days. The group receiving 0.1 mg BID (0.2 mg/day total) of adjuvant naltrexone exhibited significant reductions in pain intensity and greater pain relief compared with placebo; whereas, the 0.01 mg BID naltrexone dose (0.02 mg/day total) was ineffective. There were no serious adverse events or evidence of opioid withdrawal, and side effects were minor and similar across all treatment groups (eg, headache, nausea, sedation, dry mouth).

Potential benefits of combining naltrexone with opioid agonists seems promising for enhancing analgesia while reducing side effects; however, this may depend on the type of opioid and/or the naltrexone dose.

Aid for Opioid Tapering

Another interesting application has been the use of very low doses of naltrexone to diminish withdrawal signs/symptoms in patients being tapered from long-term opioid therapy. Mannelli et al. [2006] describe a study in methadone-maintained patients administered ultralow-dose oral naltrexone (0.125 – 0.250 mg/dose) during inpatient opioid detoxification. Overall signs of withdrawal were repressed, even as naltrexone doses were increased daily, and the opioid-tapering process was completed without adverse incidents or patient discomfort.

A larger (n=174), randomized, placebo-controlled study by this group [Mannelli et al. 2008], found similar benefits of ultralow-dose oral naltrexone (0.125 mg or 0.250 mg/dose) combined with tapered methadone doses during a 6-day outpatient detoxification protocol. Naltrexone-treated patients experienced milder withdrawal symptoms and reduced opioid craving compared with placebo-group subjects. There were no treatment-related adverse events reported.

Extensions of LDN Theory & Application

Besides the potential advantages of opioid antagonists for pain management described above, off-label low-dose naltrexone (LDN) protocols have been reported as benefitting a number of important immunological and neurological disorders. This is believed due at least in part to the observation that many body tissues, including virtually every cell of the body's immune system, have receptors that are routinely stimulated by endogenous opioid peptides — including endorphins and enkephalins [Machelska and Stein 2002]. Therefore, by acting at those receptors, LDN has been demonstrated as possibly having important capabilities to modulate the immune system and promote healing [LDNinfo.org 2009; NCI 2007].

Therapeutic implications of LDN date back to the mid-1980s when researcher Bernard Bihari, MD, in New York discovered its beneficial effects in the newly emerging disease of HIV/AIDS [reported in NCI 2007]. In subsequent years, Bihari found that LDN appeared to stem the progress of every autoimmune disease in which it was tested. The agent also has been attributed as benefitting a long list of neurodegenerative and other disorders, many of which have pain as a significant symptom, including Parkinson's disease, amyotrophic lateral sclerosis (ALS), and primary progressive multiple sclerosis [Gironi et al. 2008].

In very limited clinical investigations, LDN has been shown to halt disease progression in certain cancers and to reduce symptoms of autism [LDNinfo.org 2009]. Some authors have recently suggested that, since LDN can upregulate endogenous opioid activity, it may have a role in promoting stress resilience and emotional well-being, as well as the amelioration of depression [Brown and Panksepp 2008].

The typical therapeutic dosage range for LDN in these applications is from 1.75 mg to 4.5 mg taken at bedtime. It has been suggested that doses below this range are likely to have little effect for neurodegenerative and other disorders, while doses above this range could block endogenous opioid peptides for too long a period of time and interfere with naltrexone's effectiveness [LDNinfo.org 2009].

The actions of low-dose naltrexone on endogenous-opioid receptors, may have important capabilities for modulating the immune system and promoting healing in various immunological and neurological disorders.

Prescribing Opioid Antagonists

Opioid antagonists are non-scheduled drugs that may be prescribed by any appropriately licensed healthcare provider. However, low- or ultralow-dose formulations of naloxone and naltrexone are not commercially available and must be specially compounded by pharmacies equipped for this purpose.

The website, LDNinfo.org, under the editorial direction of David Gluck, MD, provides recommendations regarding the ordering of low-dose naltrexone [LDNinfo.org 2009]. Apparently, low-dose naltrexone prescriptions in 1 mg to 5 mg doses are being filled by many local and mail order pharmacies, and Gluck notes that a 30-day supply of 4.5 mg naltrexone capsules may cost from \$15 to \$38 (USD).

He specifies that pharmacies should be instructed to *not* provide naltrexone in slow-release (SR) or timed-release form. Furthermore, calcium carbonate fillers should not be employed in compounding capsules because they may interfere with naltrexone absorption.

The website also cautions that it is important that the compounding pharmacy has a reputation for consistent reliability in the quality and accuracy of opioid antagonist preparations that it delivers.* In one investigation, the FDA found significant error rates in compounded prescriptions produced at randomly selected pharmacies. More than a third (34%) of sampled products failed one or more standard quality tests performed by the FDA, including inadequate potency in 90% of the failing products [FDA/CDER 2003].

Recommendations are lacking regarding where to order naloxone or naltrexone in ultralow, microgram doses (<1.0 mg). However, contacts with several compounding pharmacies confirm that both naltrexone and naloxone powders are readily available and most of those pharmacies are well-equipped to prepare doses in any amounts specified [author's correspondence during January 2009]. Presumably, the same cautions as above would apply to ultralow-dose formulations; ie, avoidance of slow-release formulations and calcium carbonate fillers.



**Compounding pharmacies must use an analytical balance (pictured) with a very high degree of precision and without fluctuations or loss of product. For extremely low doses, below the sensitivity of a scale, an aliquot may be used. This involves adding active ingredient measured to the limits of the scale plus a proportional amount of diluent to make a "stock" supply of known strength. From this, the exact amount containing the desired dose of active ingredient is withdrawn and packaged.*

Summary & Conclusions

Select applications of naloxone and naltrexone may offer novel and potentially effective approaches for resolving difficult pain management challenges. **Table 2** on the next page briefly summarizes the applications, doses, and outcomes in research on adult human subjects that were described in more detail above.

Both of these agents have passed animal and clinical toxicity studies, and are FDA-approved for applications other than those described in this paper. Therefore, it is not surprising that they have exhibited favorable safety profiles when applied at low- and ultralow-dose levels, with few if any reports of adverse events or side effects at these doses when used individually as monotherapy or in combination with opioid analgesics.

Explanatory mechanisms of action behind the benefits of opioid antagonists in pain management are still under investigation. A significant body of laboratory research, in animals or tissue cultures, suggests that the opioid-receptor system is very complex, affecting a variety of tissue and cell types, and with functions extending beyond antinociception (ie, pain-relief). It appears that blockade of opioid receptors exerted by very small concentrations of naloxone or naltrexone may stimulate a cascade of actions at the cellular and molecular levels that may contribute to their multiple beneficial effects. Some of those proposed actions were briefly de-

Table 2: Summary - Opioid Antagonists for Pain in Human Trials/Cases

(See text for further discussion.)

Application	Antagonist Dose	Clinical Outcome	Reference
Naloxone (IV, Intrathecal, or Oral – as specified)			
Brief opioid detoxification for intractable pain.	0.6–1.2 mg IV (ca. 20 minutes).	Significant pain relief at lower opioid doses. Requires close monitoring.	Loitman 2006
+ Buprenorphine for postop breakthrough pain.	0.08–0.4 mg oral.	Effective, long-lasting analgesia	Schmidt et al. 1985; La Vincente et al. 2008
Monotherapy for acute postop dental pain.	0.4 or 1.0 mg oral.	Significant analgesia compared with placebo.	Levine et al. 1988
+ Pentazocine (60 mg) for dental pain.	0.4 mg oral.	Greater analgesia than monotherapy with pentazocine or 15 mg morphine.	Levine et al. 1988
+ PCA morphine postop.	0.00025 or 0.001 mg/kg/h steady infusion IV.	Reduced side effects and lower morphine consumption versus placebo	Gan et al. 1997
+ PCA morphine postop.	0.8 mg dose/IV bolus (= 0.38 mg/kg/h on average).	No benefit.	Sartain et al. 2003
+ Nalbuphine (5 mg IV) postop.	0.2 mg IV.	Improved analgesia.	Gordon et al. 2007
+ Intrathecal morphine (5 mg) for intractable chronic pain.	0.000050 mg/day intrathecal during followup.	Significantly improved ongoing pain relief.	Hamann et al. 2008
+ Oxycodone (chronic noncancer pain; chronic back pain).	10, 20, 40 mg/d oral.	No loss of analgesia, improved bowel function at 2:1 oxycodone/naloxone ratio.	Meissner et al. 2009; Simpson et al. 2008; Vondrackova et al. 2008
Naltrexone (Oral)			
Crohn's Disease.	4.5 mg/day.	Favorable response in 89% of patients.	Smith et al. 2007
Irritable Bowel Syndrome (IBS).	0.5 mg/day.	Pain/symptom relief during first 2 months.	Kariv et al. 2006
Fibromyalgia.	4.5 mg/day.	Unknown, but anecdotal reports favorable.	SNAPL 2008
Neuropathic Pain (combined with methadone).	0.002 mg/day.	Improved analgesia at lower methadone dose.	Cruciani et al. 2003
+ Oxycodone (Oxytrex®) for osteoarthritis or chronic back pain.	0.002 mg/day.	Reduced opioid consumption and side effects, including resolution of opioid-induced constipation.	Chindalore et al. 2005; Webster et al. 2006
+ Hydrocodone (experimental).	0.25, 0.5, or 1.0 mg.	No beneficial effect.	Cantilena et al. 2004
+ Intrathecal morphine for chronic noncancer pain.	0.2 mg/day.	Reduced pain intensity, improved pain relief	Hamann and Sloan 2007
Opioid (methadone) tapering.	0.125 or 0.250 mg in multiple doses/day.	Reduced withdrawal symptoms and opioid craving compared with placebo.	Mannelli et al. 2006, 2008

scribed in this paper.

For the most part, clinical research to date on low- or ultralow doses of opioid antagonists in humans has been limited. Except for several larger, controlled trials, reports in the literature have included small numbers of patients or represented case examples. Collectively, the research appears to offer some suggestions for the application and dosing of naloxone or naltrexone, but there are no well-established or standardized protocols when it comes to their use in pain management. Still, the available evidence, as summarized in **Table 2**, does propose a number of general possibilities that may be of interest to pain practitioners and their adult patients:

1. Brief detoxification via IV naloxone for difficult cases of opioid-unresponsive intractable pain, opioid tolerance, or suspected opioid-induced hyperalgesia.
2. Ultralow-dose oral naloxone combined with various opioid agonists for managing acute postoperative pain.
3. Adjuvant ultralow-dose naloxone (continuous IV infusion) combined with patient controlled analgesia (PCA) postoperatively.
4. Ultralow-dose naltrexone (oral) or naloxone (intrathecal) as a component of intrathecal opioid analgesia for difficult cases of intractable pain.
5. Ultralow-dose naltrexone combined with opioid agonists to provide an opioid-sparing effect, offering equivalent pain relief at lower opioid doses.
6. Oral ultra-low dose naloxone or naltrexone combined with oral opioid analgesics to help prevent or reverse opioid-induced constipation and potentially ameliorate other opioid side effects.
7. Ultralow-dose naltrexone to help facilitate more comfortable opioid-agonist tapering.
8. Low-dose naltrexone monotherapy for Crohn's disease, and possibly for fibromyalgia and short-term treatment of irritable bowel syndrome.

Certainly, further research, including large-scale clinical trials, are needed to better understand the capabilities and safety of opioid antagonists for treating pain conditions of various types. Meanwhile, healthcare providers interested in using low- or ultralow-dose naloxone or naltrexone would need to cautiously prescribe these agents off-label for compounding at properly equipped pharmacies.

Clearly, the type of antagonist (naloxone or naltrexone), mode of administration (oral, IV, IT), the dose (low or ultralow), the pain disorder being treated, comorbidities, and concurrent opioid analgesia can all interact to make important differences. For example, the first commercial agonist/antagonist combination products — Targin, approved in Europe, and Oxytrex, in development — have used vastly differing doses of either naloxone or naltrexone, respectively, due to the dissimilar oral bioavailabilities of the two antagonists.

Hopefully, other opioid analgesics incorporating naloxone or naltrexone for pain management applications will be formally tested and developed. Whether or not sponsors will come forward to initiate the necessary but costly clinical trials and seek appropriate regulatory-agency approvals remains to be seen.

As monotherapy, the development of FDA-approved formulations of low- and ultralow-dose naloxone or naltrexone used alone for pain management purposes may face some formidable hurdles. For example, at a U.S. government-sponsored conference [NCI 2007], it was noted

Naloxone and naltrexone are available today and, although they are approved for other applications, it is important that practitioners become aware of the therapeutic options that low- and ultralow-dose opioid antagonists may provide clinically as aids for pain management.

that, “[Low-dose naltrexone] has been presented to big pharmaceutical companies, but there has been little support provided, as LDN is commercially available and it is unclear whether or not there could be patent coverage for a new indication at [the very low dosages].”

In sum, the opioid antagonists naloxone and naltrexone appear to offer promise for helping to achieve more effective pain management in some of the most difficult and challenging situations facing healthcare providers and their adult patients. These agents are available today and, although they are approved for other applications, it is important that practitioners become aware of the therapeutic options that these agents may provide for patient care.

References

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- Barsan WG. Duration of antagonistic effects of nalmeferne and naloxone in opiate-induced sedations for emergency department procedures. *Am J Emerg Med.* 1989;7(2):155-161.
- Bennett DS, Brookoff D. Complex regional pain syndromes (reflex sympathetic dystrophy and causalgia) and spinal cord stimulation. *Pain Med.* 2006;7(Suppl 1):S64-S96.
- Brown N, Panksepp J. Low-dose naltrexone for disease prevention and quality of life. *Med Hypotheses.* 2008 (November 26, epub ahead of print).
- Cantilena Jr. LR, Wright IV C, Miller JC, Messina Jr. JC. Effects of low-dose naltrexone on analgesia produced by hydrocodone. *Clin Pharmacol Ther.* 2004;75:71.
- Chindalore VI, Craven RA, Yu KP, et al. Adding ultralow-dose naltrexone to oxycodone enhances and prolongs analgesia: A randomized, controlled trial of Oxytrex. *J Pain.* 2005;6(6):392-399.
- Chou R, Fanciullo GJ, Fine PG, et al. for the American Pain Society – American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain.* 2009;10(2):113-130.
- ClinicalTrials.gov. Effects of Low Dose Naltrexone in Fibromyalgia [study summary]. 2008. Available at: <http://clinicaltrials.gov/ct2/show/NCT00568555?term=fibromyalgia&rank=63>. Access checked 1/23/09.
- Compton P. The OIH Paradox: Can Opioids Make Pain Worse? *Pain Treatment Topics* [special report]. August 2008. Available online at: http://pain-topics.org/clinical_concepts/comments.php#ComptonOIH. Access checked 2/9/09.
- Crain SM, Shen KF. Acute thermal hyperalgesia elicited by low-dose morphine in normal mice is blocked by ultra-low-dose naltrexone, unmasking potent opioid analgesia. *Brain Res.* 2001;888:75-82.
- Crain SM, Shen KF. Antagonists of excitatory opioid receptor functions enhance morphine's analgesic potency and attenuate opioid tolerance/dependence liability. *Pain.* 2000a;84(2-3):121-131.
- Crain SM, Shen KF. Enhanced analgesic potency and reduced tolerance of morphine in 129/SvEV mice: evidence for deficiency in GM1 ganglioside-regulated excitatory opioid receptor functions. *Brain Res.* 2000b;856(1-2):227-235.
- Crabtree BL. Review of naltrexone, a long-acting opiate antagonist. *Clin Pharm.* 1984;3:273-280.
- Cruciani RA, Lussier D, Miller-Saultz, et al. Ultra-low dose oral naltrexone decreases side effects and potentiates the effect of methadone. *J Pain Symptom Manage.* 2003;25(6):491-494.
- DuPen A, Shen D, Ersek M. Mechanisms of opioid-induced tolerance and hyperalgesia. *Pain Manag Nurs.* 2007;8(3):113-121. Available at: <http://www.medscape.com/viewarticle/562216>. Accessed 2/23/09.
- FDA 2008a. FDA Approves Entereg to Help Restore Bowel Function Following Surgery. *FDA News*, May 2008a. Available at: <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01838.html>. Accessed 2/7/09.
- FDA 2008b. FDA Approves Relistor for Opioid-Induced Constipation. *FDA News*, April 2008b. Available at: <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01826.html>. Accessed 2/7/09.

- FDA/CDER (U.S. Food and Drug Administration, Center for Drug Evaluation and Research). Report: Limited FDA Survey of Compounded Drug Products. 2003. Available at: <http://www.fda.gov/cder/pharmcomp/survey.htm>. Access checked 1/23/2009.
- Fine PG, Portenoy RK. A Clinical Guide to Opioid Analgesia. New York: McGraw-Hill; 2004. Available online at: <http://www.stoppain.org/pcd/content/forpros/opioidbook.asp>. Access checked 2/9/2009.
- Gan TJ, Ginsberg B, Glass PSA, et al. Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulphate. *Anesthesiology*. 1997;87(5):1075-1081.
- Gershell L, Goater JJ. Making gains in pain. *Nat Rev Drug Discov*. 2006;5:889-880.
- Gironi M, Martinelli-Boneschi F, Sacerdote P, et al. A pilot trial of low-dose naltrexone in primary progressive multiple sclerosis. *Mult Scler*. 2008;14(8):1076-1083.
- Gonzales JP, Brogden RN. Naltrexone: A Review of its pharmacologic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. *Drugs*. 1988;35(3):192-213.
- Gordon AT, Levine JD, Dubois MY, et al. Open-label exploration of an intravenous nalbuphine and naloxone mixture as an analgesic agent following gynecologic surgery. *Pain Med*. 2007;8(6):525-530.
- Hamann S, Sloan PA. Oral naltrexone to enhance analgesia in patients receiving continuous intrathecal morphine for chronic pain: a randomized, double-blind, prospective pilot study. *J Opioid Manag*. 2007;3(3):137-144.
- Hamann S, Sloan PA, Witt W. Low-dose intrathecal naloxone to enhance intrathecal morphine analgesia: a case report. *J Opioid Manag*. 2008;4(4):251-254.
- Harris RE, Clauw DJ, Scott DJ, et al. Decreased central mu-opioid receptor availability in fibromyalgia. *J Neurosci*. 2007;27(37):10000-10006.
- Hutchinson MR, Zhang Y, Brown K, et al. Non-stereoselective reversal of neuropathic pain by naloxone and naltrexone: involvement of toll-like receptor 4 (TLR4). *Eur J Neurosci*. 2008;28(1):20-29.
- Ilyinsky OB, Kozlova MV, Kondrikova ES, Kalentchuk VU, Titov MI, Bespalova ZD. Effects of opioid peptides and naloxone on nervous tissue in culture. *Neuroscience*. 1987;22(2):719-735.
- Kariv R, Tiomny E, Grenshpon R, et al. Low-dose naltrexone for the treatment of irritable bowel syndrome: a pilot study. *Dig Dis Sci*. 2006;51(12):2128-2133.
- La Vincente SF, White JM, Somogyi AA, Bochner F, Chapleo CB. Enhanced buprenorphine analgesia with the addition of ultra-low-dose naloxone in healthy subjects. *Clin Pharmacol Ther*. 2008;83:144-152.
- Largent-Milnes TM, Guo W, Wang HY, Burns LH, Vanerah TW. Oxycodone plus ultra-low-dose naltrexone attenuates neuropathic pain and associated mu-opioid receptor-G(s) coupling. *J Pain*. 2008(8):700-713.
- LDN for Fibromyalgia [online]. 2009. Available at: http://www.ldninfo.org/ldn_trials.htm#InProg. Access checked 1/20/09.
- LDNinfo.org. Low-Dose Naltrexone [website]. 2009. Available at: <http://www.ldninfo.org/>. Access checked 1/24/09.
- Goodheart CR, Leavitt SB. Managing Opioid-Induced Constipation. *Pain Treatment Topics* [special report]. 2006. Available at: http://pain-topics.org/pdf/Managing_Opioid-Induced_Constipation.pdf. Accessed 2/7/09.
- Levine JD, Gordon NC, Taiwo YO, et al. Potentiation of pentazocine analgesia by low-dose naloxone. *J Clin Invest*. 1988;82(5):1574-1577.
- Loitman JE. Enhanced analgesia with opioid antagonist administration. *J Pall Med*. 2006;9(6):1250-1253.
- Machelska H, Stein C. Immune mechanisms of pain control. *Anesth Analg*. 2002;95:1002-1008.
- Mannelli P, Gotthel E, Van Bockstaele EJ. Antagonist treatment of opioid withdrawal: translational low dose approach. *J Addict Dis*. 2006;25(2):1-8.
- Mannelli P, Pratkan AA, Peindl K. Very low dose naltrexone addition in opioid detoxification: a randomized, controlled trial. *Addict Biol*. 2008 [Epub ahead of print].
- Meissner W, Leyendecker P, Mueller-Lissner S, et al. A randomized controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation. *Eur J Pain*. 2009;13(1):56-64.
- NCI (National Cancer Institute). Conference: Low Dose Opioid Blockers, Endorphin and Metenkephalins. Promising Compounds for Unmet Medical Needs. Bethesda, MD; April 20, 2007. Available online at: http://www.lowdosenaltrexone.org/NCI_Conference_Apr_2007.pdf. Accessed 1/18/2009.
- Pain Therapeutics. Pain therapeutics terminates drug candidate for the treatment of irritable bowel syndrome [press release]. December 9, 2005. Available at: <http://investor.paintrials.com/releasedetail.cfm?ReleaseID=297360>. Access checked 1/18/2009.
- Pallasch TJ, Gill CJ. Naloxone associated with morbidity and mortality. *Oral Surgery*. 1981;52:602-603.
- Partridge BL, Ward CF. Pulmonary edema following low-dose naloxone administration. *Anesthesiology*. 1986;65:709-710.

- Reisine T, Pasternak G. Chapter 23: Opioid analgesics and antagonists. In: Hardman JG, Limbird LE, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th ed. New York, NY: McGraw-Hill; 1996: 521-555.
- Sartain JB, Barry JJ, Richardsone CA, et al. Effect of combining naloxone and morphine for intravenous patient-controlled analgesia. *Anesthesiology*. 2003;99(1):148-151.
- Schmidt JF, Chraemmer-Jorgensen B, Pedersen JE, et al. Postoperative pain relief with naloxone. Severe respiratory depression and pain after high-dose buprenorphine. *Anaesthesia*. 1985;40(6):583-586.
- Shader, RI. "Antagonists, Inverse Agonists, and Protagonists." *Journal of Clinical Psychopharmacology*. 2003;23(4):321-322.
- Simpson K, Leyendecker P, Hopp M, et al. Fixed-ratio combination oxycodone/naloxone compared with oxycodone alone for the relief of opioid-induced constipation in moderate-to-severe noncancer pain. *Curr Med Res Opin*. 2008;24(12):3503-3512.
- Sloan P, Hamann S. Ultra-low-dose opioid antagonists to enhance opioid analgesia. *J Opioid Manage*. 2006;2(5):295-304.
- Smith JP, Stock H, Bingaman S, Mauger D, Rogosnitzky M, Zagon IS. Low-dose naltrexone therapy improves active Crohn's disease. *Am J Gastroenterol*. 2007;102(4):820-828.
- SNAPL (Stanford University, Systems Neuroscience and Pain Lab). Low Dose Naltrexone for the Treatment of Fibromyalgia [study summary]. 2008. Available at: <http://snapl.stanford.edu/ldn/>. Access checked 1/27/09.
- Stein C, Schafer M, Machelska H. Attacking pain at its source: new perspectives on opioids. *Nat Med*. 2003;9(8):1003-1008. Available at: <http://www.medscape.com/viewarticle/460435>. Accessed 2/24/09.
- Targin. New treatment for chronic pain sufferers now launching across Europe. *Pharmalive* [online]. January 26, 2009. Available at: <http://www.pharmalive.com/News/index.cfm?articleid=599896>. Accessed 1/27/09.
- Vondrackova D, Leyendecker P, Meissner W, et al. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. *J Pain*. 2008;9(12):1144-1154.
- Webster LR, Butera PG, Moran LV, et al. Oxytrex minimizes physical dependence while providing effective analgesia: A randomized controlled trial in low back pain. *J Pain*. 2006;7(12):937-946.
- Zimmerman DM, Leander JD. Opioid antagonists: structure activity relationships. In: *Drugs of Abuse: Chemistry, Pharmacology, Immunology, and AIDS*. NIDA Res Monogr. 1990;96:50-60. Available at: <http://www.drugabuse.gov/pdf/monographs/96.pdf>. Access checked 1/18/09.

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