Ultra-low-dose opioid antagonists to enhance opioid analgesia

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ABSTRACT

This article will review decades of science contributing to current interest in opioid excitatory pharmacology. A long history of clinical confusion provided the stimulus for recent, detailed in vivo and in vitro investigations of the neuropharmacologic mechanisms involved in analgesic and hyperalgesic actions of opioid agonists and antagonists. Following the discovery of central nervous system opioid excitatory-hyperalgesic processes in animals, detailed neuronal cell culture experiments established opioid receptor/G protein/adenylate cyclase neurobiochemical mechanisms for bimodal inhibitory versus excitatory actions of opioids. Once this novel model was available to explain the cellular mechanisms responsible for the duality of opioid actions, clinical translation of this technology began to emerge, with a primary focus on selective antagonism of opioid excitatory actions with concomitant low-dose opioid antagonists. Encouraging results from recent animal and clinical studies will be discussed as further evidence that therapeutic pain management may be improved through enhancement of opioid agonist analgesia by cotreatment with ultra-low-dose opioid antagonists that selectively attenuate opioid-mediated hyperalgesia.

Key words: chronic pain, opioid agonists, opioid antagonists, adjuvant analgesics, cancer pain, hyperalgesia, analgesia

INTRODUCTION

Opioid therapy is recommended and effective for most patients with moderate or severe cancer pain[1,2] and has been used in recent years for analgesia in patients with chronic nonmalignant pain. While opioids are often effective in the long-term treatment of chronic cancer and nonmalignant pain, they are not without side effects or other limitations.[3] Tolerance to opioid analgesia may occasionally limit such medications' usefulness in patient care. Patients treated with opioids for chronic pain may exhibit a paradoxical increase in sensitivity to pain, recently described as opioid-induced hyperalgesia.[4] It is well recognized that there is tremendous variability in individual patients' analgesic response to a given opioid,[5] which may be due in part to individual differences in terms of the balance of analgesic versus hyperalgesic actions of opioids.

In order to improve opioid analgesia in patients with chronic moderate to severe pain, clinicians use several strategies: 1) combining therapy with other analgesics such as nonsteroidal anti-inflammatories or NMDA receptor antagonists; 2) adding adjuvant analgesic agents such as tricyclic antidepressants, anticonvulsants, oral local anesthetics, or muscle relaxants; 3) rotating to a different opioid; 4) changing the route of opioid administration (for example, from oral to intravenous or spinal); 5) using surgical or anesthetic interventional techniques; or 6) adding nonpharmacological pain therapies such as physical therapy, massage therapy, biofeedback, and acupuncture.[3] All of the above strategies have their limitations, side effects, and contraindications[6-9]; thus, future pain management practice requires development and testing of novel pharmacological approaches to achieve optimal pain relief with minimal side effects for every patient. Selective antagonism of opioid excitatory-hyperalgesic actions with ultra-low-dose opioid antagonists may represent one such novel therapeutic approach and could enable clinical enhancement of opioid agonist analgesic efficacy.[10] Opioids are known to activate stereospecific opioid receptors on cell membranes in the central nervous system (CNS).[11] The exact mechanisms of action are not fully understood, but they are known to involve G protein–adenylate cyclase second-messenger systems. How opioid antagonists could possibly enhance the efficacy of opioid agonist analgesia is the subject of this review article.

The first description of the paradoxical analgesic effect of opioid antagonists dates back 60 years. This review begins with discussion of early human and animal observations and how they provided historical evidence for opioid excitatory actions that inspired the systematic and detailed in vivo and in vitro studies of the last two decades. Literature related to the discovery of opioid excitatory processes will be reviewed as a prelude to the presentation of evidence for our current understanding of the novel neuropharmacologic mechanisms of low-dose opioid antagonists responsible

Table 1. Analgesic potency of nalorphine compared with morphine for postoperative pain*		
Number of patients	Drug and dose/70 kg	Percent pain relief
19	Nalorphine 5 mg	28 percent
35	Nalorphine 10 mg	64 percent
35	Morphine 10 mg	74 percent
*Lasagna and Beecher; 1954. Published with permission of *ASPET*.		

for enhancement of opioid agonist analgesia. Finally, we will summarize the latest clinical evidence supporting use of low-dose opioid antagonists for the treatment of perioperative and chronic pain.

HISTORICAL EVIDENCE

Opioids have been used as analgesics for several millennia, their effects recognized long before opioid receptors were discovered in animals and humans in the early 1970s. While the concept of opioid agonists and antagonists, as related to "multiple opioid receptors,"[12] was not developed until the 1970s, researchers in the 1950s were investigating medications that could antagonize all or part of the effects of morphine. Dr. Harris Isbell, Director of the Public Health Service Addiction Research Center (Lexington, KY), was perhaps the first to suggest, in 1950, that the opioid antagonist nalorphine had analgesic properties in humans and could raise the pain threshold.[13] In the early 1950s, Lasagna and Beecher,[14] working at Massachusetts General Hospital, strove to investigate and develop a combination of opioid analgesic and opioid antagonist that would offer the analgesia of morphine without the undesirable side effects. During their landmark studies, the authors "accidentally" discovered that the opioid antagonist nalorphine was itself an analgesic agent.[15] In an elegant double-blind study of postoperative pain, Lasagna and Beecher[14] noted that while low doses of nalorphine produced analgesia comparable to placebo, higher doses produced significant postoperative pain relief (Table 1). Keats and Telford[16] repeated the Lasagna-Beecher study using a placebo control and found the postoperative analgesic potency of nalorphine to compare with that of 10 mg of morphine.

Studies on the analgesic effects of opioid antagonists were limited over the next 25 years and often gave conflicting results. In 1965, Lasagna[15] reported that among patients with postoperative pain, naloxone had a "strange biphasic quality," exerting the greatest analgesic effect at low doses and becoming antianalgesic at higher doses. McClane and Martin[17] (1967), using a dog model to evaluate opioid analgesics, found that nalorphine produced a partial opioid analgesic response and that naloxone was inactive. The authors suggested that opioid antagonists may have some agonist actions different from, and possibly initiated at a different site than, those of morphine. This mechanism of opioid antagonist analgesic versus hyperalgesic actions still remains under debate.

The 1975 discovery of opioid receptors and endogenous opiates in the human brain led to renewed interest in opioid and opioid antagonist pharmacology. Levine and colleagues[18] (1978) reported that naloxone given to patients with dental pain resulted in significantly greater increases in pain intensity than placebo controls. In retrospect, the naloxone dose used in their study was rather high, and the results support Lasagna's earlier finding of a biphasic response to naloxone for postoperative pain. Levine et al.[19] later published a second study using a dental pain model and also observed this biphasic response to naloxone. That is, naloxone at low doses (0.4 and 2 mg) produced analgesia, while higher doses (7.5 and 10 mg) of naloxone produced the more expected hyperalgesia (Table 2).

The 1970s ended with animal experiments that were inconclusive as to the analgesic action of opioid antagonists. Intracerebral naloxone microinjected into the third ventricle, the medulla, and the periaqueductal gray of the midbrain of rats did not produce a consistent analgesic response.[20] Holaday and Belenky[21] found that low-dose naloxone resulted in analgesia in a rat experimental pain model, while higher naloxone doses produced hyperalgesia, consonant with the experiments of Levine et al.[19] The research of the most recent 25 years has benefited from improved cell culture and receptor pharmacology techniques, with much investigation of low-dose opioid antagonists as possible analgesic agents.

BASIC SCIENCE EVIDENCE

This discussion will first focus on the discovery of opioid excitatory processes and then summarize in vivo animal pain and pharmacology studies, which provided direction for subsequent in vitro electrophysiologic and biochemical investigations. Following that, more current preclinical research will be reviewed, with emphasis on understanding the mechanisms of the analgesia-enhancement effects of low-dose opioid antagonists and an eye toward clinical translations of these concepts that will improve chronic pain management. For the sake of this discussion, opioid antagonist enhancement of analgesia

Table 2. Analgesic dose response of naloxone on postoperative pain[19]	
Postoperative pain score (0 = no pain, 10 = worst pain imaginable)	Naloxone dose (mg)
4	0 (placebo)
2.2	0.4
1.8	2
7	7.5
6.8	10
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will be considered the primary therapeutic innovation and clinical goal. Other potential therapeutic benefits of low-dose opioid antagonists, including decreased opioid side effects, physical dependence, and tolerance, are important but are not our focus. Furthermore, to provide subject clarity the many terms used throughout earlier literature to describe enhanced nociception (i.e., excitation, hyperalgesia, pain enhancement, antianalgesia, pronociception, and allodynia) will be used interchangeably. It is understood that this approach varies from traditional descriptive terminology of pain and does not recognize important differences in nociceptive assays and experimental paradigms.

Discovery and pharmacologic characterization of opioid excitatory processes

While the analgesic actions of opioid agonists have been utilized clinically with confidence since antiquity and studied in detail for over a century, interest in opioid excitatory actions has lagged behind, as has clinical application. Animal and clinical reports that opioid antagonists produce both analgesia and hyperalgesia provided the most important "paradoxical" observations and have driven the considerable effort toward understanding the neuropharmacologic mechanisms of opioid excitatory actions.[15,19-25]

Four decades' worth of preclinical pharmacologic evidence for opioid excitatory actions indicates that systemic opioid agonists and antagonists produce either analgesia or hyperalgesia in several animal models of nociception. The earliest direct pharmacologic demonstration of opioid agonist excitatory actions resulted from experiments in the decerebrate and spinalized decerebrate dog.[26,27] Profound hyperalgesic actions of opioid agonists were demonstrated using changes in skin-twitch reflex following brainstem drug infusions as the experimental paradigm. Further, these studies provided evidence for CNS opioid excitatory processes, since naloxone produced independent analgesic effects and antagonized both the analgesic and hyperalgesic actions of opioid agonists. Both inhibitory and excitatory actions of opioids have been subsequently demonstrated following systemic, intrathecal, and brainstem injections in rodents.

The neuropharmacology of opioid excitatory actions is not fully understood, and description of the phenomena has varied considerably depending upon the experimental model and whether endogenous neuropeptides were studied in combination with exogenous drugs. The research efforts of many investigators have contributed to the current understanding of differential excitatory versus inhibitory actions of opioid agonists and antagonists. Several important neuropharmacologic models have been developed, including 1) brainstem opioid hyperalgesic processes,[26-31] 2) the dual-system hypothesis of pain perception involving a putative endogenous opioid system that is antagonistic to analgesia,[25,32-35] 3) an endogenous dynorphin "antianalgesia" system,[36-40] and 4) presynaptic autoinhibition of endogenous hyperalgesic opioid peptides.[41] Taken together, this diverse literature demonstrates that distinct excitatory versus inhibitory actions of opioid agonists occur at extremely low versus higher doses, respectively. Conversely, antiexcitatory versus anti-inhibitory actions of opioid antagonists occur at extremely low versus higher doses, respectively. The resultant biphasic dose-response curves (Figure 1) for opioid agonists and antagonists demonstrate the concept that opioid drugs elicit hybrid actions on nociception, which depends upon the dynamic balance of CNS excitatory versus inhibitory processes. Although the existence of opioid excitatory processes had been established during the 1980s, there was no model to explain mechanisms of opioid excitatory actions and no direction for future clinical translation of this knowledge.

Opioid antagonist enhancement of opioid agonist analgesia

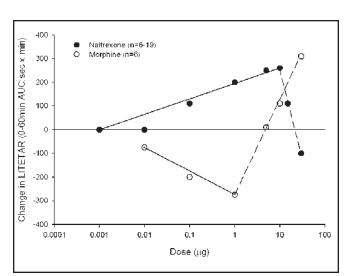In addition to the paradoxical analgesic effects of opioid

Figure 1. Bimodal hyperalgesic vs. analgesic effects of morphine and naltrexone microinjections into the brainstem of rodents. These data demonstrate the concept that opioid drugs elicit hybrid actions on nociception with resultant biphasic dose-response curves for the hyperalgesic (excitatory) vs. analgesic (inhibitory) actions of opioid agonists at extremely low vs. higher doses, respectively. Conversely, antiexcitatory (analgesic) vs. antiinhibitory (hyperalgesic) actions of opioid antagonists occur at extremely low vs. higher doses, respectively.

antagonists already discussed, several studies found paradoxical hyperalgesic effects of opioid agonists[4] when they were given chronically or acutely in low doses. Researchers also found that low-dose naloxone enhanced the analgesic actions of opioid agonists.[42-44] To take clinical advantage of this evolving knowledge required a succinct pharmacologic model consistent with established neurobiochemical mechanisms of opioid actions. During a decade-long series of experiments, Crain and Shen[45-66] (Albert Einstein College of Medicine in the Bronx) studied the effects of opioid agonist and antagonist cotreatment of nociceptive sensory neurons in vitro and in vivo in mice. This systematic research effort produced an innovative "bimodal opioid modulation" neurobiochemical model which provides a foundation for future therapeutic applications related to opioid excitatory pharmacology. Electrophysiologic studies of opioids on dorsal root ganglion (DRG) sensory neuron cultures demonstrated not only known opioid inhibitory (analgesic) actions mediated by Gi- and Go-coupled opioid receptors but also previously unrecognized excitatory actions mediated by Gs-coupled opioid receptors.[45,58-60,67] Detailed description of complex electrophysiologic experiments is beyond this review, and our discussion will focus on fundamental concepts that bring more clarity to potential clinical applications. A simplified diagram for the "bimodal modulation" model of opioid actions is presented in Figure 2; more detailed descriptions of this model are presented in research articles on the subject.[45-69]

Briefly, opioid agonists are proposed to act acutely via bimodal modulation of neuronal membrane calcium-versus-potassium conductance and resultant action potential duration (APD) of DRG sensory neurons.[45,55] This bimodal modulation of APD is influenced by activation of neuronal membrane opioid receptors that are coupled to interconvertible intracellular G protein–adenylate cyclase second-messenger systems. Because opioid receptors are abundantly distributed on the membranes of cell bodies as well as on the axonal terminals of immature nociceptive DRG neurons in culture, an opioid-induced decrease in the duration of the Ca^{2+}-dependent component of the DRG neuron APD will result in decreased presynaptic release of transmitters mediating afferent pain signals to the spinal cord. Conversely, an opioid-induced increase in the APD will increase presynaptic transmitter release, resulting in increased pain signals. Depending upon the dynamic state of the G protein system, modulation of the APD by opioid agonists may occur in either Gi- or Go-coupled inhibitory (analgesia) or Gs-coupled excitatory (hyperalgesia) modes. APD modulation by this dynamic system is further influenced by acute versus chronic opioid agonist exposure and relative affinities of opioids for the inhibitory versus excitatory forms of the opioid membrane receptor.[46,55,59] In the DRG electrophysiologic assay, low concentrations of bimodal opioid agonists have excitatory actions, high concentrations produce inhibitory effects, and intermediate concentrations result in hybrid/variable effects. Selective blockade of opioid agonist excitatory effects was demonstrated by cotreatment with picomolar concentrations of naloxone or naltrexone. This selective antagonism of opioid excitatory receptors resulted in attenuation of the excitatory action of opioid agonists and enhancement of their inhibitory (analgesic) potency.[48,57,64] These in vitro studies provided insight toward clinical translation of opioid excitatory pharmacology and future improvement in clinical efficacy and safety of opioid narcotics.

Subsequent behavioral tail-flick assays in mice by Crain and Shen[48,55-57,66] confirmed the analgesia-enhancement effects of low-dose opioid antagonists on opioid agonist analgesia. Other investigators have demonstrated enhancement of opioid agonist analgesic potency via low-dose opioid antagonists in animal studies, although the magnitude and character of the response are influenced somewhat by experimental variables (i.e., rodent species, gender, age, nociceptive assay, and dose).[70-79] Figure 3 presents an exemplary time-action curve for the morphine analgesia-enhancing effects of a low-dose opioid antagonist in a rodent model of nociceptive pain. More recent preclinical in vitro and in vivo laboratory studies are further refining our understanding of the neurobiochemical mechanisms of opioid excitatory pharmacology, as well as of the efficacy of low-dose opioid agonists and antagonists in models of neuropathic pain syndromes.[73-79]
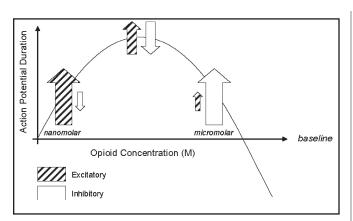
Figure 2. Bimodal modulation model of opioid agonist actions on membrane APD of DRG sensory neurons. Electrophysiologic studies of opioids on DRG sensory neuron cultures demonstrate both opioid inhibitory (analgesic) actions (mediated by Gi- and Go-coupled opioid receptors) and excitatory actions (mediated by Gs-coupled opioid receptors). Published with permission of *JPSM* and Elsevier.

CURRENT CLINICAL EVIDENCE

A handful of clinical studies and observations from the past 25 years have suggested that opioid antagonists may enhance opioid agonist analgesia. During clinical evaluation of the postoperative analgesic effects of buprenorphine, Schmidt and colleagues[42] treated patients exhibiting breakthrough postoperative pain with naloxone (80 to 400 μg), resulting in long-lasting pain relief (median duration of 22 hours). Levine and colleagues[43] examined the possible analgesic actions of naloxone using a human model of dental pain. In their earliest study, 90 patients with postoperative dental pain were given either 400 μg or 1,000 μg doses of naloxone in a double-blind manner. Compared with placebo controls, naloxone (400 and 1,000 μg) produced a significant decrease in pain intensity, suggesting an analgesic effect on naloxone's part. Subsequent clinical studies by this group examined the opioid-enhancing effect of naloxone for pentazocine and morphine in 105 patients, using the same double-blind postoperative dental pain model. The combination of 400 μg of naloxone with 60 mg pentazocine produced significantly greater analgesia than pentazocine or 15 mg of morphine alone, suggesting an opioid-enhancing effect of naloxone. The combination of 400 μg of naloxone with 8 mg of morphine, however, produced less analgesia than morphine administered alone. Although this apparent discrepancy between naloxone's analgesia-enhancement effects with pentazocine and morphine was not readily explained, the authors speculated that the analgesia-enhancing effect of naloxone was opioid specific.

Clinical interest in the possible enhancement of opioid analgesic effects by low-dose opioid antagonists has been stimulated by anecdotal case reports and encouraging
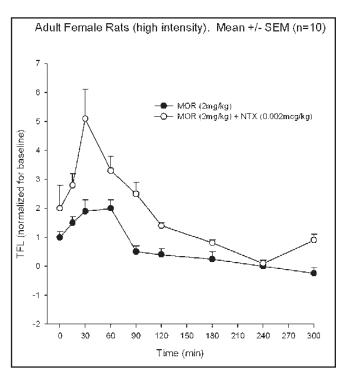

Figure 3. Exemplary time-action curves for the morphine-analgesia-enhancing effects of low-dose opioid antagonist in a rodent model of nociceptive pain. Behavioral tail-flick assays in mice and rats confirm the analgesia-enhancement effects of low-dose opioid antagonists on opioid agonist analgesia.

results from several clinical studies using different "analgesia efficacy versus side effects" paradigms.

Case reports

Cruciani et al.[10] published a case report demonstrating the analgesia-enhancing effect of the oral opioid antagonist naltrexone with methadone in a patient with chronic and resistant painful diabetic neuropathy. The addition of oral naltrexone 1 μg BID resulted in dramatic pain relief, accompanied by a 16 percent dose reduction of methadone.

Another case report describes a patient with chronic refractory pain who was treated with combined intrathecal morphine and low-dose opioid antagonist (naloxone).[80] After multiple treatment modalities failed to relieve severe post-laminectomy radicular pain, the patient remained in excruciating pain, with related depressive symptoms. The patient was treated with a combination of intrathecal morphine (2 mg) and low-dose naloxone (20 ng) to test the concept that selective antagonism of excitatory opioid receptor function at the level of the spinal cord may provide relief for this type of chronic neuropathic pain. Within 15 to 30 minutes, the patient reported onset of persistent pain relief, particularly over the most aggravated region of referred lower extremity pain (40 to 50 percent reduction in visual
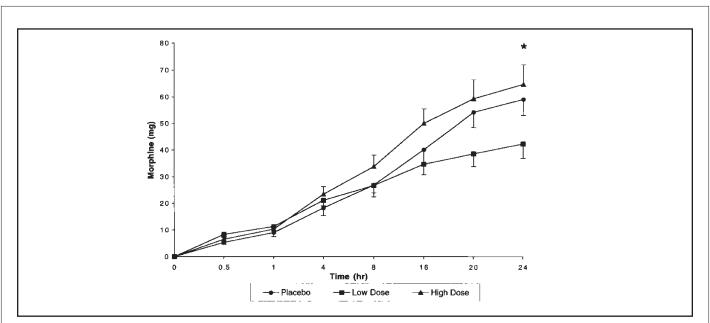
Figure 4. Mean (SEM) cumulative postoperative morphine dose vs. time. *p < 0.05 for both low-dose or high-dose naloxone regimens compared with placebo. Published with permission of *Anesthesiology*.

analogue score one hour after the dose). Following 48 hours of close clinical observation of repeated intrathecal trials, a continuous intrathecal infusion of morphine with ultra-low-dose naloxone was initiated, and acceptable pain control was maintained through this method. The enhanced analgesia (60 to 80 percent improvement by patient report) provided by small doses of intrathecal morphine and naloxone continued for several months.

Clinical studies

Perioperative pain. Low doses of opioid antagonists have enhanced, diminished, or had no effect on morphine analgesia in the perioperative setting, depending upon the drug administration regimen and pharmacokinetic characteristics of the studied antagonist. Gan and colleagues[81] studied the effects of naloxone when combined with patient-controlled analgesia (PCA) morphine for control of narcotic side effects and post-hysterectomy pain. Surgical patients received either a 0.25 µg/kg/h or 1 µg/kg/h dose of naloxone as a double-blind infusion for postoperative pain, allowing unlimited PCA morphine for pain relief and using a placebo control group. While the study objective was to reduce opioid-related side effects with the naloxone infusion, the authors discovered by serendipity that although all groups of patients had excellent pain relief, the cumulative (over 24 hours) PCA morphine doses were the lowest in the low-dose naloxone group (Figure 4). This opioid-sparing effect of naloxone suggested a morphine-analgesia-enhancing effect of naloxone, and the authors proposed that "the conventional understanding of naloxone acting as a direct postsynaptic opioid antagonist may be flawed."[81]

Joshi and colleagues[82] used a similar postoperative pain model to investigate the opioid-related side effects of a long-acting oral opioid antagonist, nalmefene. At the end of surgery, patients received either one of two doses of nalmefene or a saline placebo, and all patients had access to PCA morphine for postoperative pain relief. The study showed that although morphine consumption was similar in all groups, patients who received nalmefene had significantly lower pain scores during the 24-hour study period.

Sartain and colleagues[83] recently completed a double-blind study of postoperative pain using PCA morphine for pain relief, comparing morphine alone with morphine plus naloxone 13 µg given with each PCA bolus dose. They found no difference in pain relief or total 24-hour morphine dose between the two groups. Of note, this study differs from the previous work of Gan et al.[81] in that slightly higher doses of naloxone were given, and naloxone was given in boluses rather than as a continuous infusion. The authors concluded that if low-dose naloxone is to have opioid-enhancing effects, it should be given as an infusion or long-acting oral agent. Using a similar study design, Cepeda et al.[84] reported no clinical benefit, and an increase in morphine consumption, when naltrexone 13 µg was added to each PCA morphine bolus. In contrast to the single-gender and single-surgery study by Sartain et al.,[83] this study recruited male and female patients undergoing a variety of surgical procedures.

In a prospective, double-blind, randomized, placebo-controlled clinical trial of postoperative pain in children, continuous low-dose naloxone infusions were added to PCA morphine.[85] Low-dose naloxone infusions sustained morphine-induced analgesia, reducing the incidence and severity of opioid-induced side effects. The authors concluded that when PCA morphine is chosen for the treatment of postoperative pain, clinicians should consider starting a concomitant low-dose naloxone infusion.

Table 3. Effects of low-dose naloxone infusion on morphine MAC-reduction actions

Naloxone dose (ng/kg/hr)	MAC determination (n = number of crossovers per group)	Average DES (percent) (n = number of subjects per group)
Placebo	6.93 ± 0.05 (n = 4)	6.20 ± 0.56 (n = 8)
0.15	4.60 ± 0.60 (n = 3)*	4.53 ± 0.34 (n = 8)
0.46	4.38 ± 0.05 (n = 6)*	4.45 ± 0.20 (n = 8)
4.60	4.54 ± 0.27 (n = 5)*	4.63 ± 0.32 (n = 8)
15.4	5.33 ± 0.88 (n = 3)*	5.28 ± 0.46 (n = 8)

*Significantly different from placebo (one-way ANOVA, p = 0.05); MAC = minimum alveolar concentration; DES = desflurane.

When these PCA-morphine-based clinical studies are considered together, it appears that enhancement of opioid agonist analgesia may be most effective with sustained antagonism versus intermittent blockade of opioid excitatory actions. As seen in preclinical animal studies, several clinical variables may influence the effectiveness of introducing low-dose opioid antagonists to PCA morphine regimens. Importantly, these early postoperative pain studies consistently demonstrate that combining a low-dose opioid antagonist with morphine is safe and may be associated with diminished clinical side effects.

Surgical pain. Recently we completed a pilot study of the effects of low-dose naloxone infusions on the ability of morphine to decrease minimum alveolar concentration (MAC) of a potent volatile anesthetic, desflurane.[86] Patients undergoing abdominal hysterectomy were enrolled in a randomized, double-blind, placebo-controlled study of the effects of extremely low doses of naloxone on the MAC-reduction effects of morphine. Low doses of naloxone consistently enhanced the analgesic effects of morphine, as reflected in decreased MAC of desflurane (Table 3). There were no apparent signs of reduced morphine analgesia, toxicity, or hemodynamic compromise throughout three hours of general anesthesia and completion of the surgical procedures.

Chronic pain. The first large-scale, Phase II, double-blind, placebo-controlled study of low-dose oral naltrexone with oxycodone (Oxytrex) has recently been completed in patients with chronic osteoarthritis pain.[87] This multicenter study evaluated 243 patients randomized to receive placebo, oxycodone QID, Oxytrex (oxycodone plus 1 µg naltrexone) QID, or Oxytrex BID. The daily oxycodone dose was the same for all active treatment groups, although the Oxytrex BID group received only 2 µg/d, compared with 4 µg/d for the Oxytrex QID group. Oxytrex twice daily produced pain relief that was better than that provided by placebo or oxycodone QID (Table 4). No difference between groups was noticed with regard to adverse events or opioid-related side effects. The authors concluded that opioid enhancement by low-dose naltrexone may occur in humans, and longer-treatment trials are ongoing.

In a recently completed Phase III clinical study of patients with chronic low back pain, Oxytrex demonstrated equivalent pain reduction to oxycodone.[88] Patients titrated themselves to adequate analgesia or intolerable side effect. Importantly, Oxytrex maintained equivalent analgesic efficacy, although the doses of oxycodone combined with low-dose naltrexone were significantly lower than of the control oxycodone alone. Several large-scale clinical trials are under way and/or planned for future development of combined low-dose opioid antagonist and opioid agonist formulations.

A pilot clinical trial of combined intrathecal morphine and oral naltrexone in refractory chronic pain has been conducted.[89] Patients with chronic neuropathic pain and indwelling intrathecal drug delivery systems were enrolled in a randomized, double-blind, placebo-controlled study of the effects of extremely low doses of oral naltrexone on pain relief produced by intrathecal morphine. After baseline evaluations were performed using continued intrathecal morphine alone, patients were challenged twice daily, for seven days, with oral placebo or low-dose naltrexone during continued intrathecal morphine infusions. Oral naltrexone exhibited dose-dependent enhancement of intrathecal morphine analgesia that persisted for the entire week. No clinical evidence of decreased intrathecal morphine analgesia (i.e., antagonism) or of serious side effects were observed with the addition of oral naltrexone. Although consistent enhancement of pain relief was observed, the small number of refractory chronic patients studied precludes definitive conclusions about the efficacy of combining low-dose naltrexone with intrathecal morphine. Further studies using this unique clinical model are indicated, but they will be difficult to conduct in this complex patient population.

CONCLUSION

In summary, clinical evidence to support the use of low-dose opioid antagonists as analgesia-enhancing agents has been demonstrated in patients with surgical, postoperative, and chronic neuropathic pain. As in preclinical animal studies, the magnitude of response is

Table 4. Mean (SD) pain intensity scores (0 = no pain, 10 = worst pain imaginable) among patients with chronic osteoarthritis pain treated over three weeks[87]				
Week of treatment	Placebo	Oxycodone QID	Oxytrex QID	Oxytrex BID
Baseline	7.7 (1.3)	7.4 (1.3)	7.7 (1.4)	7.6 (1.4)
Week 3	6.1 (2.8)	5.6 (2.3)	5.7 (2.4)	4.5 (2.4)
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influenced by clinical trial variables, particularly opioid agonist and antagonist dosing regimens. Thus far, there has been no apparent enhanced risk of side effects when low-dose opioid antagonists are combined with clinical doses of opioid agonists or other anesthetics.

An evolving understanding of opioid excitatory pharmacology has been driven by decades of confusing clinical observations followed by focused in vivo and in vitro investigations of the neuropharmacologic mechanisms responsible for the apparent bimodal actions of opioid agonists and antagonists. Dose-dependent inhibitory-analgesic and excitatory-hyperalgesic actions of opioid agonists have been demonstrated in animal and neuronal cell culture experiments. The excitatory versus inhibitory actions of opioids involve dynamic neuronal G protein–adenylate cyclase intracellular biochemical signaling mechanisms. Enhancement of opioid agonist analgesia by low-dose opioid antagonists has been shown in several animal and clinical models of pain. Clinical translation of this novel pharmacology has been focused on enhancement of opioid agonist analgesia by ultra-low-dose opioid antagonists in the treatment of perioperative and chronic pain. Although the clinical paradigms differ, when viewed together the available literature strongly supports the concept that ultra-low-dose opioid antagonists can enhance the analgesic efficacy of opioid agonists. This exciting breakthrough in the therapeutic management of pain deserves further, detailed clinical and laboratory evaluation. While enhanced side effects of the combination of opioid agonists and low-dose opioid antagonists have not been reported, cautious clinical application is warranted while safety and efficacy profiles of combination drug formulations are documented in large, controlled clinical trials.

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REFERENCES

1. Sloan PA, Moulin DE, Hays H: A clinical evaluation of transdermal therapeutic system fentanyl for the treatment of cancer pain. *J Pain Symptom Manage*. 1998; 16(2): 102-111.

2. Cherny NJ, Chang V, Frager G, et al.: Opioid pharmacotherapy in the management of cancer pain: A survey of strategies used by pain physicians for the selection of analgesic drugs and routes of administration. *Cancer*. 1995; 76(7): 1283-1293.

3. McDonnell FJ, Sloan JW, Hamann SR: Advances in cancer pain management. *Curr Oncol Rep*. 2000; 2(4): 351-357.

4. Angst MS, Clark JK: Opioid-induced hyperalgesia: A qualitative, systematic review. *Anesthesiology*. 2006; 104(3): 570-587.

5. Sloan PA, Slatkin N, Ahdieh H: Effectiveness and safety of oral extended-release oxymorphone for the treatment of cancer pain: A pilot study. *Support Care Cancer*. 2005; 13(1): 57-65.

6. Bannwarth B: Do selective cyclo-oxygenase-2 inhibitors have a future? *Drug Saf*. 2005; 28(3): 183-189.

7. Lossignol DA, Obiols-Portis M, Body JJ: Successful use of ketamine for intractable cancer pain. *Support Care Cancer*. 2005; 13(3): 188-193.

8. Berger A, Hoffman DL, Goodman S, et al.: Therapy switching in patients receiving long-acting opioids. *Ann Pharmacother*. 2004; 38(3): 389-395.

9. Sloan PA: The evolving role of interventional pain management in oncology. *J Support Oncol*. 2004; 2(6): 491-500.

10. Cruciani RA, Lussier D, Miller-Saultz D, 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.

11. Minami M, Satoh M: Molecular biology of the opioid receptors: Structures, functions and distributions. *Neurosci Res*. 1999; 23: 121-145.

12. Martin WR: History and development of mixed opioid agonists, partial agonists and antagonists. *Br J Clin Pharmacol*. 1979; 7 Suppl 3: 273S-279S.

13. Isbell H, Fraser HF: Addiction to analgesics and barbiturates. *J Pharmacol Exp Ther*. 1950; 99(4:2): 355-397.

14. Lasagna L, Beecher HK: The analgesic effectiveness of nalorphine and nalorphine-morphine combinations in man. *J Pharmacol Exp Ther*. 1954; 112(3): 356-363.

15. Lasagna L: Drug interaction in the field of analgesic drugs. *Proc R Soc Med*. 1965; 58(11 Part 2): 978-983.

16. Keats AS, Telford J: Nalorphine, a potent analgesic in man. *J Pharmacol Exp Ther*. 1956; 117(2): 190-196.

17. McClane TK, Martin WR: Effects of morphine, nalorphine, cyclazocine, and naloxone on the flexor reflex. *Int J Neuropharmacol*. 1967; 6(2): 89-98.

18. Levine JD, Gordon NC, Jones RT, et al.: The narcotic antagonist naloxone enhances clinical pain. *Nature*. 1978; 272(5656): 826-827.

19. Levine JD, Gordon NC, Fields L: Naloxone dose dependently produces analgesia and hyperalgesia in postoperative pain. *Nature*. 1979; 278(5706): 740-741.

20. Woolf CJ: Intracerebral naloxone and the reaction to thermal noxious stimulation in the rat. *Brain Res*. 1980; 190(2): 578-583.

21. Holaday JW, Belenky GL: Opiate-like effects of electroconvulsive shock in rats: A differential effect of naloxone on nociceptive measures. *Life Sci*. 1980; 27(21): 1929-1938.

22. Levine JD, Gordon NC: Method of administration determines the effect of naloxone on pain. *Brain Res*. 1986; 365(2): 377-378.

23. Kayan S, Woods L, Mitchell CL: Morphine-induced hyperalgesia in rats tested on the hot plate. *J Pharmacol Exp Ther*. 1971; 177(3): 509-513.

24. Jacquet YF, Lajtha A: Paradoxical effects after microinjection of morphine in the periaqueductal gray matter in the rat. *Science*. 1974; 185(156): 1055-1057.

25. Kayser V, Besson JM, Guilbaud G: Analgesia produced by low doses of the opiate antagonist naloxone in arthritic rats is reduced in morphine-tolerant animals. *Brain Res*. 1986; 371(1): 37-41.

26. Wu K, Martin WR: Effects of naloxone and fentanyl in acutely decerebrated dogs. *Life Sci*. 1982; 31(2): 151-157.

27. Wu K, Martin WR, Kammerling SG, et al.: Possible medullary kappa hyperalgesic mechanism. I. A new role for endogenous opioid peptides in pain perception. *Life Sci*. 1983; 33(18): 1831-1838.

28. Parvini S, Hamann SR, Martin WR: Pharmacologic characteristics of a medullary hyperalgesic center. *J Pharmacol Exp Ther*. 1993; 265(1): 286-293.

29. Hamann SR, Martin WR: Opioid and nicotinic analgesic and hyperalgesic loci in the rat brain stem. *J Pharmacol Exp Ther*. 1992; 261(2): 707-715.

30. Hamann SR, Martin WR: Hyperalgesic and analgesic actions of morphine, U50-488, naltrexone, and (-)-lobeline in the rat brain stem. *Pharmacol Biochem Behav*. 1994; 47(1): 197-201.

31. Bie B, Fields HL, Williams JT, et al.: Roles of alpha1- and alpha2-adrenoceptors in the nucleus raphe magnus in opioid analgesia and opioid abstinence-induced hyperalgesia. *J Neurosci*. 2003; 23(21): 7950-7957.

32. Gillman MA, Lichtigfeld FJ: A pharmacological overview of opioid mechanisms mediating analgesia and hyperalgesia. *Neurol Res*. 1985; 7(3): 106-119.

33. Gillman MA, Lichtigfeld FJ: Naloxone analgesia: An update. *Int J Neurosci*. 1989; 48(3-4): 321-324.

34. Vaccarino AL, Tasker RAR, Melzack R: Analgesia produced by normal doses of opioid antagonists alone and in combination with morphine. *Pain*. 1989; 36(1): 103-109.

35. Kayser V, Guilbaud G: Dose-dependent analgesic and hyperalgesic effects of systemic naloxone in arthritic rats. *Brain Res*. 1981; 226(1-2): 344-348.

36. Arts KS, Fujimoto JM, Crain SM: Inhibition of the antianalgesic action of dynorphin A in mice by cholera toxin. *Pharmacol Biochem Behav*. 1993; 46(3): 623-629.

37. Fujimoto JM, Fady JJ: Intracerebroventricular physostigmine-induced analgesia: Enhancement by naloxone, beta-funaltrexamine and norbinaltorphimine and antagonism by dynorphin A (1-17). *J Pharmacol Exp Ther*. 1989; 251(3): 1045-1052.

38. Vanderah TW, Gardell LR, Burgess SE, et al.: Dynorphin promotes abnormal pain and spinal opioid antinociceptive tolerance. *J Neurosci*. 2000; 20(18): 7074-7079.

39. Holmes BB, Fujimoto JM: Inhibiting a spinal dynorphin A component enhances intrathecal morphine antinociception in mice. *Anesth Analg*. 1993; 77(6): 1166-1173.

40. Hamann SR, Martin WR: Analgesic actions of dynorphin A(1-13) antiserum in the rat brain stem. *Brain Res Bull*. 1992; 29(5): 605-607.

41. Ueda H, Fukushima N, Kitao T, et al.: Low doses of naloxone produce analgesia in the mouse brain by blocking presynaptic autoinhibition of enkephalin release. *Neurosci Lett*. 1986; 65(3): 247-252.

42. 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.

43. Levine JD, Gordon NC, Taiwo YO, et al.: Potentiation of pentazocine analgesia by low-dose naloxone. *J Clin Invest*. 1988; 82(5): 1574-1577.

44. Bergman SA, Wynn RL, Myers DE, et al.: Low dose naloxone enhances buprenorphine in a tooth pulp antinociceptive assay. *Arch Int Pharmacodyn Ther*. 1988; 291: 229-237.

45. Crain SM, Shen KF: Opioids can evoke direct receptor-mediated excitatory effects on sensory neurons. *Trends Pharmacol Sci*. 1990; 11(2): 77-81.

46. Crain SM, Shen KF: After chronic opioid exposure sensory neurons become supersensitive to the excitatory effects of opioid agonists and antagonists as occurs after acute elevation of GM1 ganglioside. *Brain Res*. 1992; 575(1): 13-24.

47. Crain SM, Shen KF: After GM1 ganglioside treatment of sensory neurons naloxone paradoxically prolongs the action potential but still antagonizes opioid inhibition. *J Pharmacol Exp Ther*. 1992; 260(1): 182-186.

48. Crain SM, Shen KF: Ultra-low concentrations of naloxone selectively antagonize excitatory effects of morphine on sensory neurons, thereby increasing its antinociceptive potency and attenuating tolerance/dependence during chronic cotreatment. *Proc Natl Acad Sci U S A*. 1995; 92(23): 10540-10544.

49. Crain SM, Shen KF: Etorphine elicits unique inhibitory-agonist and excitatory-antagonist actions at opioid receptors on sensory neurons: New rationale for improved clinical analgesia and treatment of opiate addiction. In: Repaka RS, Sorer H (eds.): *Discovery of Novel Opioid Medications, National Institute on Drug Abuse Monograph, 147*. Washington, DC: US Government Printing Office, 1995, pp. 234-268.

50. Crain SM, Shen KF: Chronic morphine-treated sensory ganglion neurons remain supersensitive to the excitatory effects of naloxone for months after return to normal culture medium: An in vitro model of "protracted opioid dependence." *Brain Res*. 1995; 694(1-2): 103-110.

51. Crain SM, Shen KF: Modulatory effects of Gs-coupled excitatory opioid receptor functions on opioid analgesia, tolerance, and dependence. *Neurochem Res*. 1996; 21(11): 1347-1351.

52. Crain SM, Shen KF: Method of simultaneously enhancing analgesic potency and attenuating dependence liability caused by exogenous and endogenous opioid agonists. US Patent No. 5,512,578. US Patent Office, 1996.

53. Crain SM, Shen KF: Method of simultaneously enhancing analgesic potency and attenuating dependence liability caused by morphine and other bimodally acting opioid agonists. US Patent No. 5,580,876. US Patent Office, 1996.

54. Crain SM, Shen KF: GM1 ganglioside-induced modulation of opioid receptor-mediated functions. *Ann N Y Acad Sci*. 1998; 845: 106-125.

55. Crain SM, Shen KF: Modulation of opioid analgesia, tolerance and dependence by Gs-coupled, GM1 ganglioside-regulated opioid receptor functions. *Trends Pharmacol Sci*. 1998; 19(9): 358-365.

56. Crain SM, Shen KF: Antagonists of excitatory opioid receptor functions enhance morphine's analgesic potency and attenuate opioid tolerance/dependence liability. *Pain*. 2000; 84(2-3): 121-131.

57. 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(1): 75-82.

58. Crain SM, Shen KF: Opioids can evoke direct receptor-mediated excitatory as well as inhibitory effects on sensory neuron action potentials. In Harris LS (ed.): *Problems of Drug Dependence: National Institute of Drug Abuse Monograph, 105*. US Government Printing Office, 1991, pp. 34-39.

59. Crain SM, Shen KF, Chalazonitis A: Opioids excite rather than inhibit sensory neurons after chronic opioid exposure of spinal cord-ganglion cultures. *Brain Res*. 1988; 455: 99-109.

60. Shen KF, Crain SM: Dual opioid modulation of the action potential duration of mouse dorsal root ganglion neurons in culture. *Brain Res*. 1989; 491(2): 1227-1242.

61. Shen KF, Crain SM: Cholera toxin-A subunit blocks opioid excitatory effects on sensory neuron action potentials indicating mediation by Gs-linked opioid receptors. *Brain Res*. 1990; 525(2): 225-231.

62. Shen KF, Crain SM: Cholera toxin-B subunit blocks opioid excitatory effects on sensory neuron action potentials indicating that GM1 ganglioside may regulate Gs-linked opioid receptor functions. *Brain Res.* 1990; 531(1-2): 1-7.

63. Shen KF, Crain SM: Chronic selective activation of excitatory opioid receptor functions in sensory neurons results in opioid "dependence" without tolerance. *Brain Res.* 1992; 597(1): 74-83.

64. Shen KF, Crain SM: Antagonists at excitatory opioid receptors on sensory neurons in culture increase potency and specificity of opiate analgesics and attenuate development of tolerance/dependence. *Brain Res.* 1994; 636(2): 286-297.

65. Shen KF, Crain SM: Nerve growth factor rapidly prolongs the action potential of mature sensory ganglion neurons in culture, and this effect requires activation of Gs-coupled excitatory kappa-opioid receptors on these cells. *J Neurosci.* 1994; 14(9): 5570-5579.

66. Shen KF, Crain SM: Biphalin, an enkephalin analog with unexpectedly high antinociceptive potency and low dependence liability in vivo, selectively antagonizes excitatory opioid receptor functions of sensory neurons in culture. *Brain Res.* 1995; 701(1-2): 158-166.

67. Cruciani RA, Dvorkin B, Morris SA, et al.: Direct coupling of opioid receptors to both stimulatory and inhibitory guanine nucleotide-binding proteins in F-11 neuroblastoma-sensory neuron hybrid cells. *Proc Natl Acad Sci U S A.* 1993; 90(7): 3019-3023.

68. Shen KF, Crain SM: Ultra-low doses of naltrexone or etorphine increase morphine's antinociceptive potency and attenuate tolerance/dependence in mice. *Brain Res.* 1997; 757(2): 176-190.

69. Shen KF, Crain SM, Ledeen RW: Brief treatment of sensory ganglion neurons with GM1 ganglioside enhances the efficacy of opioid excitatory effects on the action potential. *Brain Res.* 1991; 559(1): 130-138.

70. Powell KJ, Abul-Husn NS, Jhamandas A, et al.: Paradoxical effects of opioid antagonist naltrexone on morphine analgesia, tolerance, and reward in rats. *J Pharmacol Exp Ther.* 2002; 300(2): 588-596.

71. Cicero TJ, Nock B, Meyer ER: Gender-related differences in the antinociceptive properties of morphine. *J Pharmacol Exp Ther.* 1996; 279(2): 767-773.

72. Hamann SR, Malik H, Sloan JW, et al.: Interactions of "ultra-low" doses of naltrexone and morphine in mature and young male and female rats. *Receptors Channels.* 2004; 10(2): 73-81.

73. Olmstead MC, Burns LH: Ultra-low-dose naltrexone suppresses rewarding effects of opiates and aversive effects of opiate withdrawal in rats. *Psychopharmacology.* 2005; 181(3): 576-581.

74. Wang HY, Friedman E, Olmstead MC, et al.: Ultra-low-dose naloxone suppresses opioid tolerance, dependence and associated changes in mu opioid receptor-G protein coupling and Gbetagamma signaling. *Neuroscience.* 2005; 135(1): 247-261.

75. Vanderah TW, Lai OM, Malan T, et al.: Mechanisms of opioid-induced pain and antinociceptive tolerance: Descending facilitation and spinal dynorphin. *Pain.* 2001; 92(1-2): 5-9.

76. Hamann SR, Wala EP: The effect of very low dose naltrexone on neuropathic pain in rats. *FASEB Journal.* 2003; 17: abstract 138.8.

77. Hamann SR, Hatch NW, Hicks DL, et al.: Ultra-low dose of naltrexone attenuates neuropathic but not acute pain in rats. *FASEB Journal.* 2004; 18: abstract 635.8.

78. Olmstead MC, Burns LH: Ultra-low-dose naltrexone suppresses rewarding effects of opiates and aversive effects of opiate withdrawal in rats. *Psychopharmacology.* 2006 (in press).

79. Leri F, Burns LH: Ultra-low-dose naltrexone reduces rewarding potency of oxycodone and relapse vulnerability in rats. *Pharmacol Biochem and Behav.* 2006 (in press).

80. Hamann SR, Witt WO, Sloan PA: Treatment of refractory post-lumbar laminectomy pain with ultra low-dose intrathecal morphine and naloxone. 2006 (submitted for publication).

81. 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.

82. Joshi GP, Duffy L, Chehade J, et al.: Effects of prophylactic nalmefene on the incidence of morphine-related side effects in patients receiving intravenous patient-controlled analgesia. *Anesthesiology.* 1999; 90(4): 1007-1011.

83. Sartain JB, Barry JJ, Richardson CA, et al.: Effect of combining naloxone and morphine for intravenous patient-controlled analgesia. *Anesthesiology.* 2003; 99(1): 148-151.

84. Cepeda MS, Africano JM, Manrique AM, et al.: The combination of low dose of naloxone and morphine in PCA does not decrease opioid requirements in the postoperative period. *Pain.* 2002; 96(1-2): 73-79.

85. Maxwell LG, Kaufmann SC, Blitzer S, et al.: The effects of small-dose naloxone infusion on opioid-induced side effects and analgesia in children and adolescents treated with intravenous patient-controlled analgesia: A double-blind, prospective, randomized, controlled study. *Anesth Analg.* 2005; 100(4): 953-958.

86. Hamann SR, Wala EP, Rebel A, et al.: Selective antagonism of opioid excitatory receptor systems: A pilot clinical study demonstrating enhancement of morphine analgesia by low-dose naloxone in female patients undergoing elective abdominal laparotomy. American Society of Anesthesiologists Annual Meeting 2006; Abstract 387.

87. Chindalore VL, 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.

88. Webster LR, Butera PG, Moran LV, et al. Oxytrex minimized physical dependence while providing effective analgesia: A randomized controlled trial in low-back pain. *J Pain.* 2006 (in press).

89. Hamann SR, Witt WO, Sloan PA, et al.: Pilot study for treatment of chronic pain with intrathecal morphine in combination with ultra-low dose oral naltrexone. 2006 (submitted for publication).