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## Opioid Blockers May Aid Problematic-Pain Relief, Research Review Finds

***According to an evidence review from Pain Treatment Topics, opioid antagonists like naloxone and naltrexone -- which block opioid drugs from activating their receptors -- may be surprisingly helpful for relieving difficult-to-treat pain conditions.***

Glenview, IL; March 2009 – Achieving effective, durable, and safe pain relief, especially in patients with chronic and/or severe pain conditions, can be difficult. For many types of pain, prescription opioids are among the most effective analgesics. Yet, there is a growing body of evidence suggesting potential benefits of opioid antagonists, particularly naloxone and naltrexone. This is somewhat unexpected because these drugs displace opioid molecules from their neuroreceptors, and block opioids from attaching to and activating those receptors.

In a peer-reviewed, evidence-based report for *Pain Treatment Topics* (<http://Pain-Topics.org>) editor Stewart B. Leavitt, MA, PhD, describes naloxone and naltrexone pharmacology and the theoretical foundations of opioid antagonists for pain management. Titled **“Opioid Antagonists, Naloxone & Naltrexone -- Aids for Pain Management,”** the 16-page report includes summaries of 17 studies -- case examples and clinical trials – investigating opioid-antagonist therapy in adult humans. The complete report with references can be freely accessed at the Pain-Topics.org website at <[http://pain-topics.org/clinical\\_concepts/innovations.php](http://pain-topics.org/clinical_concepts/innovations.php)>.

Naloxone and naltrexone have been extensively studied in the past, and are FDA-approved for the treatment of alcoholism or opioid addiction (naltrexone) or opioid overdose (naloxone). A long-acting form of naltrexone for intramuscular injection also is approved for addiction therapy. These antagonists also are being used or tested as ingredients in specially formulated opioid analgesics to deter their misuse or abuse.

Leavitt notes, however, “doses of naloxone or naltrexone used in pain management are generally much smaller than in other applications; either in the 1 to 5 mg range, referred to as ‘low dose,’ or less than 1 mg, in microgram amounts, designated as ‘ultralow dose.’ In animal studies and human trials, low- or ultralow-doses of antagonists appear to enhance the pain-relieving efficacy of opioid-agonist analgesics, such as morphine, oxycodone, and others. Along with this, tolerance to and physiologic dependency on opioid analgesics, as well as certain opioid side effects, may

be diminished. Furthermore, low-dose naltrexone has been successfully tested by itself as monotherapy for the management of several pain-related conditions, including Crohn's disease, irritable bowel syndrome, and fibromyalgia."

Explanatory mechanisms of action behind the benefits of opioid antagonists in pain management are still under investigation. Essentially, appropriately low doses of opioid antagonists have been postulated to "reset" the opioid-receptor system for a period of time, which seems analogous to how rebooting a malfunctioning computer clears memory, refreshes the software, and often restores normal function. With opioid-agonist therapy, the body becomes better attuned to the beneficial effects of both external opioids, such as morphine, and naturally occurring internal opioids, such as endorphins.

Clinical research to date on low- or ultralow dose applications of opioid antagonists for pain management in humans has been limited. Still, the available evidence described in this report suggests a number of possibilities that may be of interest to healthcare providers and their patients with pain, including:

- <> Brief detoxification using naloxone for difficult cases of opioid-unresponsive intractable pain, opioid tolerance, or suspected opioid-induced hyperalgesia.
- <> Ultralow-dose naloxone combined with various opioid agonists for managing postoperative pain.
- <> Ultralow-dose naltrexone (oral) or naloxone (intrathecal) as a component of intrathecal opioid analgesia for difficult cases of intractable pain.
- <> Ultralow-dose oral naltrexone combined with opioid agonists to provide an opioid-sparing effect, offering equivalent pain relief at lower opioid doses.
- <> Oral ultra-low dose naloxone or naltrexone combined with oral opioid analgesics to help prevent or reverse opioid-induced constipation and to potentially reduce other opioid side effects.
- <> Ultralow-dose naltrexone to help facilitate more comfortable opioid-agonist tapering.
- <> Low-dose naltrexone monotherapy for Crohn's disease, and possibly for fibromyalgia and short-term treatment of irritable bowel syndrome.

"Although further investigations to assess the safety and efficacy of these applications would be appropriate," Leavitt suggests, "both of these agents have passed animal and clinical toxicity studies, and have been used for years in applications other than those described in this research report. Therefore, it is not surprising that they have exhibited favorable safety profiles when applied at low- and ultralow-dose levels, with few notices of adverse events or side effects at these doses when used individually as monotherapy or in combination with opioid analgesics."

"Naloxone and naltrexone are available today as generic, economically priced drugs, and it is important that practitioners become aware of the therapeutic options that these may provide for patient care," Leavitt concludes. "However, it must be understood that opioid antagonists are not yet FDA-approved for pain management purposes, so low- or ultralow-dose naloxone or naltrexone would need to be cautiously prescribed off-label for compounding at properly equipped pharmacies." \*\*\*

\*\*\* NOTE: 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.

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