



ENHANCING THE USE OF OPIOIDS IN PAIN  
MANAGEMENT: ANTINOCICEPTIVE  
POTENTIATION WITH OPIOID  
AGONIST/ANTAGONIST COMBINATIONS

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## **Abstract**

While opioids are the most effective and widely used class of drug for the management of moderate to severe pain, their use may be limited by adverse effects that are unpleasant and potentially dangerous. Research is increasingly directed towards strategies to improve the use of opioids in pain management, investigating methods by which the analgesia afforded by an opioid may be enhanced, while minimising adverse effects. One approach that has produced promising findings in animal studies and some clinical reports is the combination of an opioid agonist and “ultra-low” (nanomole) doses of an opioid antagonist. A recent animal study reported that antinociception may be significantly enhanced with the combination of the partial opioid agonist/antagonist buprenorphine and ultra-low doses of the antagonist naloxone. The central aim of the studies described herein was to investigate the effect of this drug combination on response to experimental nociceptive stimuli and the incidence and severity of adverse effects among healthy volunteers.

The first study established normative responses to two commonly used nociceptive tests, the cold pressor and electrical stimulation tests, in 100 healthy volunteers. The effect of buprenorphine on nociceptive test performance had not previously been determined, therefore a dose-ranging study of buprenorphine was conducted to establish a dose-response relationship. The subsequent two studies investigated the effect of a range of buprenorphine:naloxone IV dose ratios (5:1, 10:1, 12.5:1, 15:1, 20:1 and 25:1) on nociception and adverse effects among healthy volunteers. These studies are the first to investigate the combination of buprenorphine and ultra-low dose antagonist in humans, and the first to assess the agonist:antagonist combination in an experimental model of human nociception. Antinociception was significantly enhanced with the combination of buprenorphine and naloxone in the 12.5:1 and 15:1 ratios. Moreover, this enhanced

antinociception occurred *without* a simultaneous increase in adverse effects and indeed with a *reduction* in the severity of some effects. An agent that produces greater analgesia and reduces adverse effects has the potential to overcome some of the barriers that limit the use of opioids in pain management. The current findings indicate that further investigation of this drug combination is warranted.