A Drug Candidate for Improving Opioid Analgesia and Attenuating Dependence and Tolerance: An Exploratory Trial of Ibudilast in Morphine Withdrawal and Analgesia in Heroin Addicts

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Background
Previous animal studies have established that systemic ibudilast (aka MN-166, AV411) administration can improve the analgesic potency and efficacy of opioids such as morphine and oxycodone.

Primary Aim
The primary purpose of the present study was to evaluate the ability of ibudilast to reduce opioid withdrawal symptoms in humans. In addition, we collected preliminary data on the ability of ibudilast to alter the analgesic and subjective effects of oxycodone.

Methods
Thirty non-treatment seeking heroin abusers participated in a 3-week inpatient study examining the effects of ibudilast on opioid withdrawal (Table 1). Safety, withdrawal, analgesic, and abuse-related subjective responses were evaluated during the study. Participants received maintenance doses of morphine (30 mg QID, PO) and placebo (0 mg QID, PO) and one of 3 possible doses of ibudilast (0, 20, or 40 mg BID, PO) each day throughout the study.

Study Design
On days 1-14, participants received oral morphine (30 mg QID). Subjects were randomized 1:1:1 (n=10 each) to placebo, low-dose (20 mg BID, 40 mg/day), or high-dose ibudilast (40 mg BID, 80 mg/day) on day 8. Assessment of oxycodone-induced subjective, analgesic, and physiological effects were measured during separate laboratory sessions prior to ibudilast administration (Day 4) and at treatment steady state (Day 11). During laboratory sessions, oral oxycodone doses of 0, 25, & 50 mg were administered 45 min apart (cumulative doses of 0, 25, and 50 mg).

Subjective Opiate Withdrawal Scale (SOWS) (Figures 1-3)

Cold Pressor Test (CPT) (Figures 4-6)

Subjective Effects

Physiological Measures

Discussion: Ibudilast was well-tolerated by the participants with no SAEs, no discontinuations due to treatment, and no impact on oxycodone-induced respiratory measures relative to placebo. Ibudilast reduced some of the subjective ratings of opioid withdrawal and may reduce tolerance to the analgesic, subjective and micturition effects of oxycodone. The mechanism by which ibudilast produces these changes is unclear and further clinical validation is warranted.

Conflicts of Interest Disclosure
MedicNova, Inc. provided study medication for this study, and NIDA provided funding for it. The authors have no other conflicts of interest to declare.