Poster # P07.183

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.

Table 1: Participant Demographics

	PBO (N=10)	Ibudilast 20 mg BID (N=10)	Ibudilast 40 mg BID (N=10)
Age	39.4 ± 4.5	38.2 ± 5.3	37.9 ± 4.3
Sex (M/F)	9/1	8/2	9/1
Ethnicity (B/W/Other)	2/3/5	3/1/6	4/5/1
Preferred Route of Heroin Use (IN/IV)	7/3	4/6	4/6
Amount Spent per Day on Heroin ($)	61.5 ± 13.1	47.0 ± 21.2	58.5 ± 36.6
Avg # of Years Using Heroin	15.2 ± 6.2	12.8 ± 7.5	12.9 ± 6.5

Table 2. Study Design

Week	1*	2*	3
Maintenance Drugs	Morphine (30 mg QID, PO)	Morphine (30 mg QID, PO)	Placebo (0 mg QID, PO)
Test Drugs	Placebo (0 mg BID, PO)	Placebo (0 mg BID, PO) Ibudilast (20 or 40 mg BID, PO)**	Placebo (0 mg BID, PO) Ibudilast (20 or 40 mg BID, PO)**
Endpoints	Safety Withdrawal Analgesia* Subjective Effects*	Safety Withdrawal Analgesia* Subjective Effects*	Safety Withdrawal

*Laboratory Sessions
**Participants were randomized to either Pbo, Ibudilast 20 mg, or Ibudilast 40 mg

Study Design

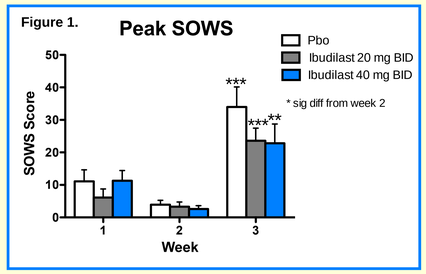
On days 1-14, participants received oral morphine (30 mg QID). Subjects were randomized 1:1:1 (n=10 each) to placebo, low-dose (20 mg BID, 40 mg/day), or high-dose ibudilast (40 mg BID, 80 mg/day) on day 8. Assessment of oxycodone-induced subjective, analgesic, and physiological effects were measured 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, & 25 mg were administered 45 min apart (cumulative doses of 0, 25, and 50 mg).

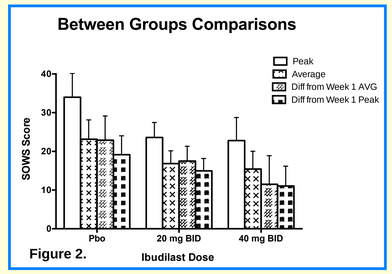
Conflicts of Interest Disclosure

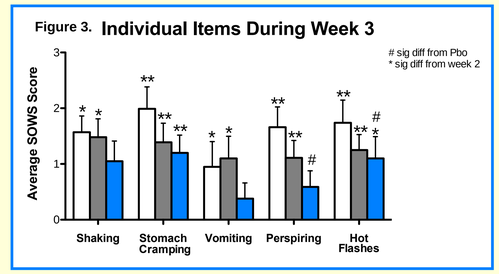
MediciNova, Inc. provided study medication for this study, and NIDA provided funding for it. The authors have no other conflicts of interest to declare.

Subjective Opiate Withdrawal Scale (SOWS)

(Figures 1-3)

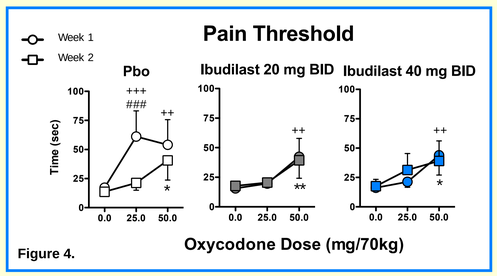


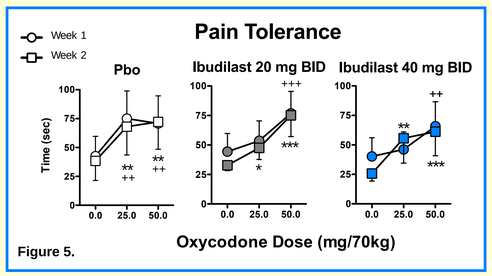


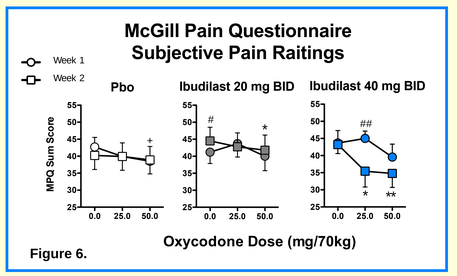


Cold Pressor Test (CPT)

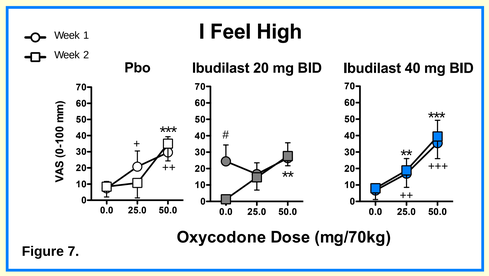
(Figures 4-6)



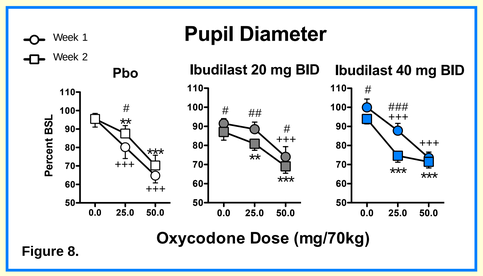




Subjective Effects



Physiological Measures



sig diff btwn week 1 and wk 2
+ sig diff from 0.0 mg Oxy during week 1
* sig diff from 0.0 mg Oxy during week 2
(Fig. 4, 5, 6, 7, 8)
1 symbol: p<0.05, 2 symbols: p<0.01, 3 symbols p<0.001

Table 3. Statistics

Figure	Main Effect	Interaction
4 and 5	Oxy Dose, p<0.001	- Oxy Dose x Week x Ibudilast Dose p< 0.10
6	Oxy Dose, p< 0.05	- Week x Ibudilast Dose p <0.10 - Oxy Dose x Week x Ibudilast Dose p< 0.05 - Oxy Dose x Week p< 0.05
7	Oxy Dose, p< 0.001	- Oxy Dose x Ibudilast Dose p< 0.10 - Oxy Dose x Week x Ibudilast Dose p< 0.05
8	Oxy Dose, p< 0.001	- Oxy Dose x Ibudilast Dose p< 0.05 - Oxy Dose x Week x Ibudilast Dose p< 0.05

Results

Figures 1 and 2.
Although total SOWS scores were not significantly different between active ibudilast and placebo, they tended to be lower in the active dose groups.

Figure 3.
Individual items on the SOWS revealed a significant difference between ibudilast and placebo: perspiring and hot flashes were reduced by 40 mg BID ibudilast compared to placebo (p< 0.05).

Figures 4-6.
Pain threshold and tolerance were not affected by ibudilast, but subjective ratings of pain were significantly reduced by 40 mg BID ibudilast during week 2 compared to week 1.

Figure 7.
Oxycodone-induced ratings of "I Feel High" were not altered by ibudilast.

Figure 8.
Oxycodone-induced pupil constriction was greater in the active ibudilast groups during week 2 compared to week 1, suggesting reduced tolerance.

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 miotic effects of oxycodone. The mechanism by which ibudilast produces these changes is unclear and further clinical validation is warranted.