

## **The effects of the opiate neutral antagonist 6b-naltrexol in opiate dependent subjects**

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### ***Abstract:***

**Background:** Complications of prescription opioids include abuse and constipation. The molecular pharmacology of 6b-Naltrexol (6bN), a neutral opioid antagonist, suggested it might attenuate  $\mu$ -agonist effects without precipitating opiate withdrawal (OWD), decreasing abuse liability if co-formulated with  $\mu$ -analgesics, and reverse opiate constipation, without compromising analgesia.

**Methods:** In this proof-of-concept, placebo-controlled, blinded study 4 (3F, 1M) opiate-dependent subjects (on 19-70 mg/day methadone) received ascending doses of 6bN (0.05, 0.15, 0.50 & 1.0 mg, over 15 mins IV). The primary endpoint was precipitated OWD; all subjects were screened with naloxone 50  $\mu$ g IV before 6bN exposure to assure tolerability of OWD. Measures included vital signs (HR and BP), Visual Analog Scales (VAS) of 'any' 'good' and 'bad' drug effect; 'opiate withdrawal'; 'sickness'; the Objective and Subjective OWD Scales (SOWS, OOWS), oral-cecal transit time (OCTT, measured by expired H<sub>2</sub> after 10 gm po lactulose), and laxation. Dose escalation was terminated for VAS OWD >25. PK profiles were obtained with the 1.0 mg dose; results are pending.

**Results:** Three subjects (all F) received the maximal 1.0 mg of 6bN; the one M reached stopping criteria at 0.5 mg. No subject would have been advanced beyond 1 mg due to significant abdominal distress. Although 6bN produced abdominal discomfort and withdrawal symptoms no significant changes in VAS measures of OWD, total SOWS and OOWS scores, or HR and BP occurred. 0.15 mg 6bN accelerated OCTT in 2 subjects; >0.5 mg produced laxation within 20 minutes in 3/4 subjects; naloxone did not produce laxation.

**Conclusions:** 6bN acts as a neutral opiate antagonist, is less potent than naloxone in precipitating OWD and produces laxation. These features suggest that a combination formulation of 6bN with an opioid analgesic could attenuate opiate-induced constipation and decrease abuse of  $\mu$ -opioids.

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