Opiate Antagonists Do Not Interfere with the Clinical Benefits of Stimulants in ADHD: A Double-Blind, Placebo-Controlled Trial of the Mixed Opioid Receptor Antagonist Naltrexone.


Abstract

OBJECTIVE:
Methylphenidate activates μ-opioid receptors, which are linked to euphoria. μ-Opioid antagonists, such as naltrexone, may attenuate the euphoric effects of stimulants, thereby minimizing their abuse potential. This study assessed whether the combination of naltrexone with methylphenidate is well-tolerated while preserving the clinical benefits of stimulants in subjects with attention-deficit/hyperactivity disorder (ADHD).

METHODS:
We conducted a 6-week, double-blind, placebo-controlled, randomized clinical trial of naltrexone in adults with DSM-IV ADHD receiving open treatment with a long-acting formulation of methylphenidate from January 2013 to July 2015. Spheroidal Oral Drug Absorption System (SODAS) methylphenidate was administered twice daily, was titrated to approximately 1 mg/kg/d over 3 weeks, and was continued for 3 additional weeks depending on response and adverse effects. Subjects were adults with ADHD preselected for having experienced euphoria with a test dose of immediate-release methylphenidate. The primary outcome measure was the Adult ADHD Investigator Symptom Report Scale (AISRS).

RESULTS:
Thirty-seven subjects who experienced stimulant-induced (mild) euphoria at a baseline visit were started in the open trial of SODAS methylphenidate and randomly assigned to naltrexone 50 mg or placebo. Thirty-one subjects completed the study through week 3, and 25 completed through week 6. Throughout 6 weeks of blinded naltrexone and open methylphenidate treatment, the coadministration of naltrexone with methylphenidate did not interfere with the clinical effectiveness of methylphenidate for ADHD symptoms. Additionally, the combination of naltrexone and methylphenidate did not produce an increase in adverse events compared with methylphenidate alone.

CONCLUSIONS:
Our findings provide support for the concept of combining opioid receptor antagonists with stimulants to provide an effective stimulant formulation with less abuse potential.

TRIAL REGISTRATION:
ClinicalTrials.gov identifier: NCT01673594.