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

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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.

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While stimulants remain the mainstay of the treatment of attention-deficit/hyperactivity disorder (ADHD), their use is marred by persistent concerns about abuse potential. In a review of 21 studies representing 113,104 subjects, Wilens et al[1] reported rates of past-year nonprescribed stimulant use ranging from 5% to 9% in grade school–aged and high school–aged children and 5%–35% in college-aged individuals. Lifetime rates of diversion ranged from 16% to 29% of students with stimulant prescriptions asked to give, sell, or trade their medications. The authors concluded that individuals both with and without ADHD misuse stimulant medications.

Recent investigations indicate that stimulants activate brain μ-opioid receptors.[2] Areas of the brain involved in the reward and addiction circuitry, such as the caudate-putamen, nucleus accumbens, frontal cortex, and ventral midbrain, are enriched in opioid receptors.[3] Interactions of opioids and neurotransmitters, including dopamine and norepinephrine, facilitate different aspects of reward circuits. Activation of the μ-opioid receptor is associated with euphoria.[3]

In a mouse model, we found that supratherapeutic but not therapeutic doses of methylphenidate produced conditioned place preference, a well-known animal behavioral model of addiction.[2] Additionally, we found that supratherapeutic but not therapeutic doses of methylphenidate enhanced striatal μ-opioid receptor activity.[2] Finally, we showed that naltrexone, an opioid receptor antagonist, blocked methylphenidate-induced place preference. Thus, we showed that an opioid antagonist can block rewarding effects of methylphenidate.[2]

These findings suggest that adding naltrexone to stimulants may rid stimulants of their addictive potential. However, for such an approach to be useful, it requires the documentation that naltrexone will not interfere with the benefits of stimulants.

The successful treatment of ADHD with the combination of naltrexone and a stimulant could lead to the development of a nonaddictive form of stimulant treatment for ADHD. Such development would facilitate access to a highly effective treatment for ADHD to millions of adults and children who would otherwise be unlikely to use a potentially abusable medication.

Clinical Points

- Animal studies have shown μ-opioid antagonists, such as naltrexone, may minimize the abuse potential of stimulants
- The addition of naltrexone to methylphenidate did not interfere with the clinical effectiveness of methylphenidate for ADHD symptoms.
- Our findings provide support for the concept of combining opioid receptor antagonists with stimulants to provide an effective stimulant formulation with less abuse potential.

The main aim of this study was to assess whether the combination of naltrexone with a stimulant is effective and well tolerated in the treatment of ADHD. To this end, we conducted a 6-week, double-blind, placebo-controlled, randomized clinical trial of naltrexone administered to adults with ADHD receiving open-label treatment with stimulants. Because the pharmacologic effects of naltrexone and methylphenidate are distinct, we hypothesized that the potency of stimulants in reducing symptoms of ADHD would be similar in subjects receiving methylphenidate with and without the coadministration of naltrexone.

METHODS

Subjects

Subjects were outpatient adults with ADHD between 18 and 30 years of age. To be included, subjects had to satisfy full diagnostic criteria for *DSM-IV* ADHD with childhood onset and persistent symptoms based on clinical assessment and confirmed by structured diagnostic interview and the Adult ADHD Investigator Symptom Report Scale (AISRS)[4] score > 20. We excluded potential subjects if they had clinically significant chronic medical conditions, abnormal baseline laboratory values, IQ < 80, delirium, dementia, amnestic disorders, or other clinically unstable psychiatric conditions (ie, bipolar disorder, psychosis, suicidality); were on treatment with other psychotropics; or had seizures or tics during their lifetime or drug or alcohol abuse or dependence within the 12 months preceding the study or a previous adequate trial of methylphenidate. We also excluded pregnant or nursing women. The study was approved by the local ethics committee, written informed consent was obtained, and the study was registered at ClinicalTrials.gov (identifier: NCT01673594).

Procedure

After providing written informed consent, subjects underwent clinical and medical assessments to determine if they had adult ADHD and met study specific requirements. Those who continued to meet inclusion and exclusion criteria were screened for a minimal "liking" response (detailed in the Likability Ratings paragraph). Those qualifying entered the randomized clinical trial.

This was a 6-week, double-blind, placebo-controlled, randomized clinical trial of naltrexone 50 mg (or placebo) daily in young adults with ADHD receiving unblinded, open treatment with Spheroidal Oral Drug Absorption System (SODAS)–methylphenidate administered twice daily and titrated to about 1 mg/kg/d over 3 weeks depending on response and adverse effects. Informed consent was obtained from subjects after the study procedures and possible side effects were fully explained. This study was approved by the institutional review board at Massachusetts General Hospital and was conducted from January 2013 to July 2015.

Inclusion and Exclusion Criteria

Inclusion criteria. Inclusion criteria were as follows: (1) male and female outpatients; (2) age of 18–30 years; (3) diagnosis of ADHD by *DSM-IV*, per clinical evaluation and confirmed by structured interview (see Assessments section); (4) likability response (> 5) on question 2 of the Drug Rating Questionnaire, Subject version (DRQ-S)[5–7] after an initial test dose of 60 mg of immediate-release methylphenidate; (5) baseline ADHD severity score > 20 on the AISRS[4]; (6) ability to participate in blood draws and to swallow pills; and (7) ability to reliably report effects of treatment, understand the nature of the study, and sign an informed consent document.

Exclusion criteria. (1) Any current (last month), non-ADHD Axis I psychiatric conditions; (2) Hamilton Depression Scale (HDRS)[8] score > 16, Beck Depression Inventory (BDI)[9] score > 19, or Hamilton Anxiety Scale (HARS)[10] score > 21; (3) any clinically significant chronic medical condition; (4) any cardiovascular disease or hypertension; (5) clinically significant abnormal baseline laboratory values; (6) IQ < 80; (7) organic brain disorders; (8) seizures or tics; (9) pregnant or nursing women; (10) clinically unstable psychiatric conditions (ie, suicidal behaviors, psychosis); (11) current or recent (within the past year) substance abuse or dependence; (12) taking other psychotropic medications; (13) current or prior adequate treatment with methylphenidate; (14) known hypersensitivity to methylphenidate; (15) current opioid use (by history and urine screen) or potential need for opioid analgesics during the study; or (16) acute hepatitis or liver failure.

Screening Procedures

Screening procedures were divided into 2 parts. All subjects underwent the following procedures: clinical assessments, medical history, structured interview, neuropsychological battery, physical examination, vital signs, urine pregnancy test for women, electrocardiogram, urinalysis, and urine drug test. The second component of the screening consisted of testing for the experience of at least minimal euphoria with a test dose of immediate-release methylphenidate (see the Likability Ratings paragraph).

Assessments

Socioeconomic status/background. A brief demographic interview was conducted to estimate socioeconomic status as well as to collect information about any educational accommodations and any past head injuries or head trauma.

Assessment of ADHD and comorbid psychopathology. At study entry, we confirmed the diagnosis of ADHD

and potentially exclusionary comorbid *DSM-IV* Axis I psychopathology by clinical assessment. All subjects were assessed with the Structured Clinical Interview for *DSM-IV* (SCID)[11] supplemented with modules from the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-E)[12] to assess childhood *DSM-IV* disorders (ADHD, oppositional defiant disorder, and conduct disorder).

ADHD Rating Scale Severity Scales. The AISRS[4] is the validated, standard 18-item *DSM-IV* symptom assessment used for US Food and Drug Administration approval of medications for adult ADHD.[13,14] The AISRS has language specific to the adult manifestation of symptoms and numerous probes for each item. As a secondary measure of ADHD, each week we also administered the Clinical Global Impressions scale (CGI),[15] a widely used rating scale to measure the overall severity and improvement. There are 2 subscales: Severity of Illness (CGI-S) (1 = not ill to 7 = extremely ill) and Global Improvement (CGI-I) (1 = very much improved to 7 = very much worse). This scale has been used extensively in psychopharmacology research and has been shown to be drug-sensitive.[15]

Likability Ratings (Drug Feeling Visit)

At a prebaseline assessment for eligibility, subjects were tested for a subjective response to a 60-mg dose of immediate-release methylphenidate. At least 1 response of >5 on question 2 ("Do you like the drug effect?") of the DRQ-S at 1 time point after taking the immediate-release methylphenidate dose (and not with placebo) was required for participation in the study. Constituent elements of the DRQ-S have been standardized by comparison to responses to known drugs of abuse and validated against observer ratings and physiologic changes.[5] This measure and related scales have been used in over 27 published studies assessing the abuse liability of methylphenidate.[5–7]

Placebo-Controlled, Randomized Clinical Trial of Naltrexone

Study subjects underwent 6 weeks of open treatment with SODAS methylphenidate. Naltrexone-masked placebo was matched to an identically appearing naltrexone formulation. Each eligible subject was randomly assigned to receive either active naltrexone and active SODAS methylphenidate or placebo (naltrexone masked) and active SODAS methylphenidate for a 6-week period.

Titration of SODAS methylphenidate. Study subjects were started on 20 mg of SODAS methylphenidate twice daily for week 1, which was then increased to 30 mg twice daily by week 2 and to 40 mg twice daily by week 3, based on response and adverse effects, up to a maximum daily dose of 80 mg/d (about 1 mg/kg/d). In weeks 4–6, treatment was continued at the highest tolerated dose (≤ 80 mg/d).

Response to ADHD. ADHD response was defined as a ≥ 30% reduction from baseline in AISRS[4] and a CGI-I score of 1 or 2 (very much or much improved), per prior National Institute of Mental Health–funded and industry-funded large-scale published studies.[13,14]

Statistical Analysis

We compared demographics, clinical features, and adverse events among the placebo and naltrexone groups using Student t tests and Pearson χ^2 tests for parametric data and Wilcoxon rank sum and Fisher exact tests for nonparametric data. Analyses of outcomes of the 6-week clinical trial were performed using mixed-effects Poisson regression, linear regression, Wilcoxon signed rank tests, and Fisher exact tests. Regression models used robust standard errors to account for the repeated measures on each subject.

We performed a non-inferiority test to evaluate whether naltrexone + methylphenidate was significantly non-inferior to placebo + methylphenidate in the treatment of ADHD. We used a non-inferiority analysis (as described by Walker and Nowacki[16]) instead of a simple *t* test comparison of differences since we were not testing whether the 2 therapies were different but whether methylphenidate with naltrexone was inferior to methylphenidate without naltrexone. First, we defined our non-inferiority margin as a difference of 5 points in total score on the AISRS between naltrexone + methylphenidate and placebo + methylphenidate. We chose a 5-point difference because we estimated that this would represent a small clinical difference. We then used a *t* test to compare the difference score with the non-inferiority margin to show that the difference between the 2 groups was greater than the margin. To further show non-inferiority, we compared the lower bound of the 95% confidence interval with the non-inferiority margin.

All tests were 2-tailed and performed at an α level of .05. We did not control for any demographic or clinical characteristics since none reached statistical significance. Analyses were performed using Stata (version 14, StataCorp, LP, College Station, Texas).

RESULTS

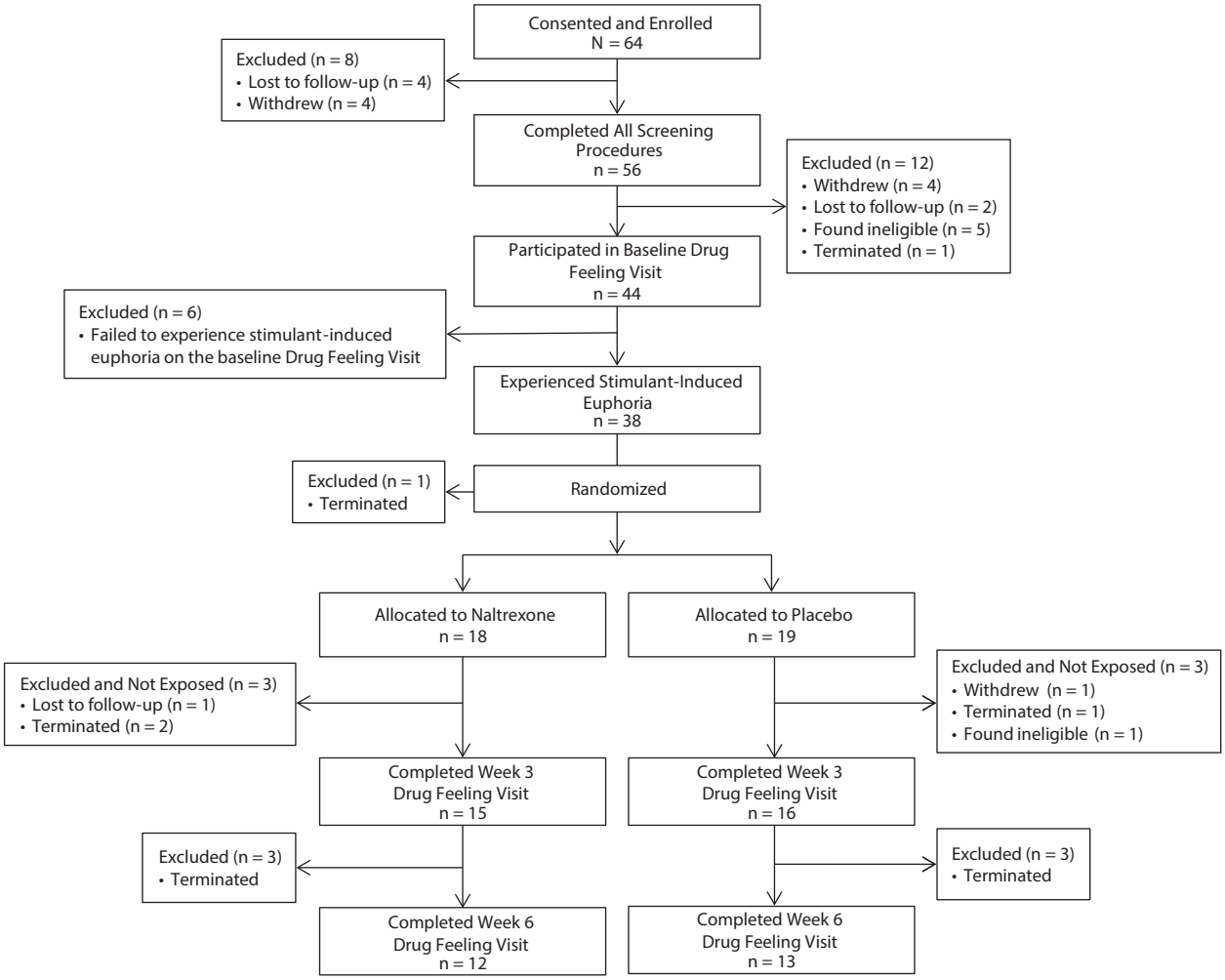
Subjects

Randomized subjects were medication-naive adults (aged 18 to 30 years) with ADHD preselected by the experience of euphoria with a test dose of immediate-release methylphenidate. Based on our preliminary work with a 40-mg dose of immediate-release methylphenidate, we expected that 38% of adults with ADHD would experience at least mild euphoric effects from therapeutic oral doses of methylphenidate.[17]

As depicted in Figure 1, 64 subjects provided consent and were enrolled. Fifty-six subjects completed all screening procedures. Forty-four subjects participated in the baseline Drug Feeling Visit, of whom 38 experienced stimulant-induced euphoria. Of those 38, 37 were started in the open trial of methylphenidate and randomly assigned to naltrexone or placebo. Thirty-one subjects completed to week 3. Twenty-five subjects completed through week 6.

Thirty-nine subjects did not complete the study for various reasons. We found that 12 subjects were ineligible

Figure 1. CONSORT Diagram



after they provided consent due to cardiovascular concerns about using stimulant treatment, a positive urine drug screen, comorbidity, or failure to experience stimulant-induced euphoria (n = 6/44) on the baseline Drug Feeling Visit. A total of 23 subjects withdrew or were later dropped due to the demanding time commitment of participating in the study or to relocation. Finally, 4 subjects were terminated from the study during the treatment phase due to adverse events. Of these subjects, 1 developed negative mood side effects, 1 was discovered to have previously asymptomatic lymphoma, 1 experienced a recurrence of her peptic stress ulcers, and 1 subject experienced nausea and vomiting.

Demographic and Clinical Characteristics of Randomized Sample

There was no significant difference in age, weight, or sex between the naltrexone and placebo groups (Table 1). There was no significant difference in baseline ADHD severity on the AISRS. Mean ratings of anxiety symptoms on the HARS and depression symptoms on the HDRS and BDI were low and did not significantly differ between the 2 groups (Table 1).

Table 1. Demographic and Clinical Characteristics of Subjects Who Completed Through at Least Study Week 3[a]

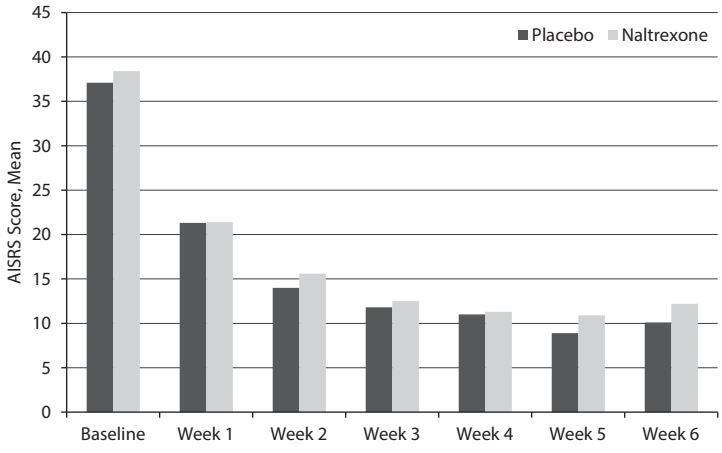
Characteristic	Placebo (n = 16)	Naltrexone (n = 15)	Test Statistic	*P* Value
Age	24.4 (3.2)	25.1 (2.9)	$t = -0.63$	.53
Male, n (%)	8 (50)	6 (40)	$\chi^2 = 0.31$	.58
Weight, lb[b]	154.7 (23.2)	162.5 (41.1)	$z = -0.20$	.84
HARS score	3.9 (3.5)	7.0 (8.3)	$z = -0.86$	.39
HDRS score	2.8 (3.6)	4.7 (6.0)	$z = -0.75$	.45
BDI score	2.4 (2.1)	4.5 (4.4)	$z = -0.92$	.34
AISRS score	36.4 (9.0)	38.5 (9.8)	$z = -0.61$	.54

[a]Data are presented as mean (SD) unless otherwise noted.
[b]70.2 (10.5) kg for the placebo group and 73.7 (18.6) kg for the naltrexone group.
Abbreviations: AISRS = Adult ADHD Investigator Symptom Report Scale; BDI = Beck Depression Inventory; HARS = Hamilton Anxiety Scale; HDRS = Hamilton Depression Rating Scale.

ADHD Treatment

The mean (SD) final dose of methylphenidate was 67 (19) mg/d. The optimal dose was 80 mg for 17 (55%) of the 31 subjects. Six weeks of open methylphenidate treatment produced significant clinical improvement in ADHD symptoms ($t_{24} = -14.13$, $P < .001$). During the 6 weeks of open methylphenidate treatment, assignment to 6 weeks of

Figure 2. Mean AISRS Scores for the Placebo and Naltrexone Groups During the 6 Weeks of the Clinical Trial



Abbreviations: ADHD = attention-deficit/hyperactivity disorder, AISRS = Adult ADHD Investigator Symptom Report Scale.

concurrent naltrexone or placebo had no significant effect on the efficacy of methylphenidate treatment for ADHD symptoms ($\chi^2_6 = 1.61$, $P = .95$). Mean scores on the AISRS did not significantly differ for those on naltrexone treatment compared to those on placebo over the 6 weeks of the study (Figure 2). Furthermore, there was no significant difference in the dropout rates for subjects on naltrexone treatment versus those on placebo (20% vs 18%; Fisher exact test, $P = 1.00$). Per a completers-only analysis, 6 weeks of naltrexone did not have a significant effect on the efficacy of methylphenidate treatment for ADHD symptoms ($\chi^2_6 = 2.16$, $P = .90$).

The difference in AISRS total score between naltrexone + methylphenidate and placebo + methylphenidate was 0.92, with a 95% confidence interval (CI) of −3.82 to 5.67. The lower bound of the 95% CI is above the non-inferiority margin, and the difference between naltrexone + methylphenidate and placebo + methylphenidate is significantly different from the non-inferiority margin ($P = .02$). Thus, we can conclude that naltrexone + methylphenidate is not inferior to placebo + methylphenidate.

Table 2. Vitals at Week 6 Controlling for Baseline Measures

Variable	Placebo (n = 13)[a]	Naltrexone (n = 12)[a]	Test Statistic	*P* Value
Weight, lb[b]	147.4 (23.1)	156.8 (41.2)	$t_{22} = 0.38$	.71
Pulse, BPM	78.0 (13.3)	77.0 (6.8)	$t_{22} = -0.73$	.47
Systolic blood pressure, mm Hg	114.8 (5.6)	118.8 (12.7)	$t_{22} = 1.11$	.28
Diastolic blood pressure, mm Hg	72.6 (8.7)	73.5 (9.0)	$t_{22} = 0.42$	.68

[a]Values shown as mean (SD).
[b]66.9 (10.5) kg for the placebo group and 71.1 (18.7) kg for the naltrexone group.
Abbreviation: BPM = beats per minute.

Table 3. Adverse Events[a]

Adverse Event Category	Event Frequency, No. (%)[b] Placebo	Naltrexone	Test Statistic	*P* Value
Agitated/irritable	0 (0)	4 (4)	Fisher	.13
Anxious/worried	3 (4)	1 (1)	Fisher	.32
Autonomic (drool/sweat)	3 (4)	2 (2)	Fisher	.65
Cardiovascular (palpitations/ tachycardia)	**5 (7)**	**0 (0)**	**Fisher**	**.01**
Cold/infection/allergies	5 (7)	2 (2)	Fisher	.24
Decreased appetite	**2 (3)**	**13 (13)**	**$\chi^2 = 5.98$**	**.02**
Decreased energy	1 (1)	4 (4)	Fisher	.39
Dermatologic	0 (0)	1 (1)	Fisher	1.00
Dizzy/lightheaded	1 (1)	0 (0)	Fisher	.43
Extrapyramidal symptoms	1 (1)	0 (0)	Fisher	.43
Headache	15 (20)	19 (19)	$\chi^2 = 0.01$	.91
Increased energy	0 (0)	2 (2)	Fisher	.51
Insomnia	13 (17)	12 (12)	$\chi^2 = 0.91$	.34
Mucosal dryness	1 (1)	4 (4)	Fisher	.39
Musculoskeletal	5 (7)	5 (5)	Fisher	.75
Nausea/vomit/diarrhea	9 (12)	16 (16)	$\chi^2 = 0.62$	.43
Neurologic	0 (0)	1 (1)	Fisher	1.00
Other	4 (5)	3 (3)	Fisher	.46
Sad/down	2 (3)	5 (5)	Fisher	.70
Sedation	1 (1)	0 (0)	Fisher	.43
Tense/jittery	5 (7)	7 (7)	$\chi^2 = 0.01$	.91

[a]Boldface indicates a statistically significant difference ($P < .05$).
[b]Percentages are of the total number of adverse events within the treatment group (placebo: 76 events; naltrexone: 101 events).

Vital Signs

Effects of treatment on blood pressure, heart rate, and weight were consistent with known effects of therapeutic doses of stimulant medications in adults. After correction for baseline, there were no significant differences at week 6 between the naltrexone and placebo groups for blood pressure, heart rate, and weight (Table 2). To interpret the week 6 mean weight data, it is important to note that, by chance, 2 subjects in the naltrexone group were about 50 pounds heavier than the next heaviest person at baseline. When data for those 2 patients are removed, the mean (SD) week 6 weights are 147.4 (23.1) and 141.4 (22.5) lb (66.9 [10.5] and 64.1 [10.2] kg) for the placebo and naltrexone groups, respectively.

Adverse Events

Of the 21 types of adverse events reported, there were significant differences in the rates of only palpitations/tachycardia and decreased appetite between the naltrexone and placebo groups (palpitations/tachycardia: 0% vs 7%, Fisher exact test, $P = .01$; decreased appetite: 13% vs 3%, $\chi^2_1 = 5.98$, $P = .02$) (Table 3). There was no significant difference in the mean number of adverse events reported by those on naltrexone treatment versus placebo (4.75 vs 6.73; $t_{29} = -1.37$, $P = .18$).

DISCUSSION

This double-blind, randomized clinical trial showed that the combination of naltrexone with methylphenidate was highly effective in the treatment of ADHD and was well-tolerated. The observed benefits were indistinguishable in subjects receiving methylphenidate with and without naltrexone. If confirmed, these results could pave the way

for the development of a non-abusable, highly effective novel formulation of a nonaddictive stimulant treatment for ADHD.

In a previous study,[17] we reported that 38% of adults experienced a mild euphoric effect with a single 40-mg dose of immediate-release methylphenidate. In this study, we found that 86% of adults experienced a mild euphoric effect to 60 mg immediate-release methylphenidate. While it is possible that the difference in euphoric response is due to dose, more work is required to replicate these results.

The observed response to methylphenidate on ADHD symptoms was equally robust in subjects receiving methylphenidate with and without the coadministration of naltrexone. AISRS scores decreased from a highly symptomatic score of 38.4 (9.1) at baseline to a score of 10.5 (5.7) at endpoint, which corresponds to scores associated with remission of ADHD symptoms. While the high degree of effectiveness of methylphenidate in reducing ADHD symptoms has been documented in the literature,[18] it has never before been documented with the concomitant administration of naltrexone with methylphenidate. These results show that the coadministration of naltrexone does not diminish the benefits expected with methylphenidate treatment.

With few exceptions, the concomitant administration of naltrexone did not affect the tolerability of robust dosing of methylphenidate as measured by either spontaneously reported adverse events or dropout rates. However, of the 21 categories of adverse events captured, there were significant differences in the rates of palpitations/tachycardia (less in the naltrexone group) and decreased appetite (greater in the naltrexone group). While lower rates of palpitations and tachycardia were noted with naltrexone, in our study heart rate is not different between the naltrexone and placebo groups (Table 2). Of note, naltrexone has been reported to substantially reduce the heart rate increase that is characteristic of alcohol intoxication.[19]

Although the coadministration of methylphenidate and naltrexone is novel, both methylphenidate and naltrexone are established medications with decades of clinical use behind them and excellent safety records. Early concerns about potential cardiovascular safety of stimulants have been addressed by large pharmacoepidemiologic studies that reported no increase in serious cardiovascular events in stimulant-exposed patients in 2,579,104 person-years of follow-up, including 373,667 person-years of current use of ADHD drug.[20] While naltrexone is widely used to treat alcohol and opioid use disorders, the main concern about its use is a potential for chemical hepatitis (elevated liver enzymes) at higher doses. In several studies, supratherapeutic naltrexone doses of 300 mg/d have led to transient, reversible elevations in serum transaminases in some subjects. While monitoring of hepatic health is important when naltrexone is prescribed, no cases of hepatic failure due to naltrexone have been reported to date, and the black box warning has been removed.[21]

This study has important strengths. Its main hypothesis originated from our translational program starting with the development of an ecologically informative animal model of ADHD caused by prenatal nicotine exposure.[22] This mouse model has brain, biochemical, and behavioral changes highly consistent with what has been documented in humans with ADHD. These changes included low frontocortical dopamine turnover, behavioral symptoms of inattention, impulsivity and hyperactivity, and pharmacologic response to therapeutic doses of methylphenidate. Using this prenatal nicotine exposure mouse, our team made the important and novel discovery relating activation of the opioid system to high doses of methylphenidate, which activated μ-opioid receptors and induced conditioned place preference in rodents, a well-known animal model of addiction.[2] These effects were reversed with the mixed opiate antagonist naltrexone. Considering the well-documented pharmacologic effects of naltrexone in blocking opiate receptors in humans, it can be expected to block opiate receptors and may mitigate abuse potential. The key outstanding question addressed in this study was whether the concomitant use of naltrexone with methylphenidate interferes with the known benefits of stimulants in ADHD, and this study showed that it does not.

Our findings should be viewed in light of some limitations. The current study does not address whether naltrexone decreases ratings of euphoria. This issue will need to be addressed in future reports. Our non-inferiority test assumed that anything smaller than a mean 5-point difference between groups on the AISRS is not clinically significant. The sample size is relatively small. We would need a larger sample size to demonstrate that the combined treatment is non-inferior under the assumption of a smaller non-inferiority margin. Although the dropout rate was similar in groups treated with naltrexone and placebo, the dropout rate may affect generalizability of the findings.

Treatment with methylphenidate was open-label and not blinded. However, we were not testing the tolerability or effectiveness of stimulants, but the tolerability and effectiveness of the coadministration of naltrexone with a stimulant. As noted above, methylphenidate treatment produced a highly clinically significant and indistinguishable effect on ADHD symptoms with or without naltrexone. Our study was restricted to adults. Thus, our findings cannot be extrapolated to a younger population. Because the sample was largely white and referred, our findings do not generalize to community samples or other ethnic groups.

Our findings may prove to be particularly useful for ADHD patients with substance use disorder. Future studies should investigate the effects of naltrexone and stimulants in patients with ADHD and substance use disorder.

Despite these limitations, the effects of methylphenidate in this controlled study were equally potent and indistinguishable with and without the coadministration of naltrexone. If confirmed, these findings could lead to the development of a nonaddictive form of stimulant treatment for ADHD. Such a development would facilitate access to a highly effective treatment for ADHD to millions of subjects who otherwise would be unlikely to use a potentially abusable medicine.

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