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Do Opiate Antagonists Interfere with the Clinical Benefits of Stimulants in ADHD? A Double-Blind, Placebo-Controlled Trial of the Mixed Opioid Receptor Antagonist Naltrexone

Address Correspondence To: Thomas J. Spencer, MD; Massachusetts General Hospital, 55 Fruit Street, Warren 705, Boston, MA, 02144; Tel: 617-724-3883; Fax: 617-724-3742; spencer@helix.mgh.harvard.edu.

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Thomas J. Spencer, MD^{1,2}, Pradeep Bhide, PhD³, Jinmin Zhu, PhD³, Stephen V. Faraone, PhD^{4,5}, Maura Fitzgerald, MPH¹, Amy M. Yule, MD^{1,2}, Mai Uchida, MD^{1,2}, Andrea E. Spencer, MD^{1,2}, M Anna Hall, BA¹, Ariana J. Koster, BS¹, and Joseph Biederman, MD^{1,2}

¹Pediatric Psychopharmacology and Adult ADHD, Massachusetts General Hospital, Boston, MA;

²Department of Psychiatry, Harvard Medical School, Boston, MA;

³Department of Neuroscience, Florida State University, Tallahassee, FL;

⁴Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY;

⁵K.G.Jebesen Centre for Psychiatric Disorders, Department of Biomedicine, University of Bergen, Bergen, Norway

Abstract

Objective: Methylphenidate (MPH) activates mu opioid receptors, which are linked to euphoria. Mu 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 MPH is well-tolerated while preserving the clinical benefits of stimulants in subjects with ADHD.

Method: We conducted a six-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 MPH. **(January 2013 to June 2015)** Spheroidal Oral Drug Absorption System (SODAS)–MPH was administered BID and titrated to ~1 mg/kg/day over three weeks and continued for three 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 (IR) MPH. The primary outcome measure was The Adult ADHD Investigator Symptom Report Scale (AISRS).

Results: Thirty-seven subjects who experienced stimulant-induced (mild) euphoria on a baseline visit were started in the open trial of SODAS MPH and randomized to 50 mg naltrexone or placebo. Thirty-one subjects completed through Week 3, 25 through Week 6. Throughout six weeks of blinded naltrexone and open MPH treatment, the co-administration of naltrexone with MPH did not interfere with the clinical effectiveness of MPH for ADHD symptoms. Additionally, the combination of naltrexone and MPH did not produce an increase in adverse events over MPH alone.

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

Keywords

ADHD; Stimulants; Substance Abuse

INTRODUCTION

While stimulants remain the mainstay of the treatment of 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 to range from 5% to 9% in grade school- and high school-age children and 5% to 35% in college-age 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 opioid mu 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 noradrenaline, facilitate different aspects of reward circuits. Activation of the μ opioid receptor (MOPR) is associated with euphoria.³

In a mouse model we found that supra therapeutic but not therapeutic doses of methylphenidate (MPH) produced conditioned place preference, a well-known animal behavioral model of addiction.² Additionally, we found that supra therapeutic but not therapeutic doses of MPH enhanced striatal MOPR activity.² Finally we showed that Naltrexone, an opioid receptor antagonist, blocked MPH-induced place preference. Thus we showed that an opioid antagonist could block rewarding effects of MPH.

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 non-addictive 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 medicine.

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 six-week, double-blind, placebo-controlled, randomized clinical trial of naltrexone administered to adults with ADHD receiving open-label treatment with stimulants. Because the pharmacological effects of naltrexone and MPH are distinct, we hypothesized that the potency of stimulants in reducing symptoms of ADHD would be similar in subjects receiving MPH with and without the co-administration of naltrexone.

METHOD

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 an Adult ADHD Investigator Symptom Report Scale (AISRS⁴) score > 20. We excluded potential subjects if they had clinically significant chronic medical conditions,

abnormal baseline laboratory values, I.Q. <80, delirium, dementia, amnesic disorders, other clinically unstable psychiatric conditions (i.e., bipolar disorder, psychosis, suicidality), were on other psychotropics, had seizures or tics, drug or alcohol abuse or dependence within the twelve months preceding the study, or previous adequate trial of MPH. We also excluded pregnant or nursing females. The study was approved by the local ethics committee, written informed consent was obtained, and the study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (identifier: NCT01673594).

Procedure

After 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 below). Those qualifying entered a randomized clinical trial.

This was a six-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)–MPH administered BID and titrated to ~1 mg/kg/day 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 01/2013 to 07/2015.

Inclusion and Exclusion Criteria

Inclusion Criteria: (1) Male and female outpatients; (2) age 18–30; (3) diagnosis of ADHD by DSM-IV, per clinical evaluation and confirmed by structured interview; (4) likeability response (> 5) on Question #2 of the Drug Rating Questionnaire-Subject (DRQ-S^{5–7}) after an initial test dose of 60 mg of immediate release (IR) MPH; (5) baseline ADHD severity of > 20 on the Adult ADHD Investigator Symptom Report Scale (AISRS⁴); (6) able to participate in blood draws and to swallow pills; (7) subjects must be considered reliable reporters, must understand the nature of the study and must sign an informed consent document.

Exclusion Criteria: (1) Any current (last month), non-ADHD Axis I psychiatric conditions; (2) Hamilton Depression Scale (HAM-D)⁸ > 16, Beck Depression Inventory (BDI)⁹ > 19, or Hamilton Anxiety Scale (HAM-A)¹⁰ > 21; (3) any clinically significant chronic medical condition; (4) any cardiovascular disease or hypertension; (5) clinically significant abnormal baseline laboratory values; (6) I.Q. < 80; (7) organic brain disorders; (8) seizures or tics; (9) pregnant or nursing females; (10) clinically unstable psychiatric conditions (i.e. suicidal behaviors, psychosis); (11) current or recent (within the past year) substance abuse/dependence; (12) patients on other psychotropics; (13) current or prior adequate treatment with MPH; (14) known hypersensitivity to MPH; (15) current opioid use (by history and urine screen) or potential need for opioid analgesics during the study; (16) acute hepatitis or liver failure.

Screening procedures—Screening procedures were divided into two parts. All subjects underwent the following procedures: clinical assessments, medical history, structured interview, neuropsychological battery, physical examination, vital signs, urine pregnancy test for females, 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 IR MPH (see below).

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 Axis I DSM IV psychopathology by clinical assessment. All subjects were assessed with the Structured Clinical Interview for DSM-IV (SCID) supplemented with modules from the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-E) to assess childhood DSM-IV disorders (ADHD, ODD, CD).¹¹

ADHD Rating Scale Severity Scales:

AISRS & CGI: The Adult ADHD Investigator Symptom Report Scale (AISRS⁴) is the validated, standard 18-item, DSM-IV symptom assessment used for FDA approval of medications for adult ADHD.^{12, 13} 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 collected the Clinical Global Impression (CGI) Scale,¹⁴ a widely used rating scale to measure the overall severity and improvement. There are two subscales: the Global Severity (GS) (1=not ill, to 7= extremely ill) and the Global Improvement (GI) (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.¹⁴

Likeability Ratings—At a pre-baseline assessment for eligibility, subjects were tested for a subjective response to a 60 mg dose of immediate-release (IR) MPH. At least one response of > 5 on Question 2 (Do you like the drug effect?) of the Drug Rating Questionnaire at one time point after taking the IR-MPH dose (and not with placebo) was required for participation in the study. Constituent elements of the DRQ scale 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 MPH.^{5–7}

Placebo controlled, randomized clinical trial of naltrexone—Study subjects underwent six weeks of open treatment with SODAS-MPH. Naltrexone masked placebo was matched to an identically appearing naltrexone formulation. Each eligible subject was randomized to receive either active naltrexone and active SODAS-MPH or placebo (naltrexone masked) and active SODAS-MPH for a six-week period.

Titration of SODAS-MPH: Study subjects were started on 20 mg SODAS-MPH BID for Week 1, then increased to 30 mg BID by Week 2, and then increased to 40 mg BID by Week 3, based on response and adverse effects, up to a maximum daily dose of 80 mg/day (~ 1 mg/kg/day). In Weeks 4–6 they were continued at the highest tolerated dose (80 mg/day).

Response to ADHD: As previously used, ADHD Response was defined as a 30% reduction from baseline in Adult ADHD Investigator Symptom Rating Scale (AISRS⁴) and a CGI-Improvement of 1 or 2 (very much or much improved), per prior NIMH-funded and industry-funded, large-scale published studies.^{12, 13}

Statistical Analysis

We compared demographics, clinical features, and adverse events among the placebo and naltrexone groups using Student's t-tests and Pearson's χ^2 tests for parametric data and Wilcoxon rank-sum and Fisher's exact tests for non-parametric data. Analyses of outcomes of the six-week clinical trial were performed using mixed-effects Poisson regression, linear regression, Wilcoxon signed-rank tests, and Fisher's 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 + MPH was significantly non-inferior to placebo + MPH in the treatment of ADHD. As described by Walker et al.,¹⁵ we used a non inferiority analysis vs. a simple t-test comparison of differences since we were not testing whether the two 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 five points between naltrexone + MPH and placebo + MPH in total score on the AISRS. We chose a five-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 two groups was greater than the margin. To further show this, we compared the lower bound of the 95% confidence interval with the non-inferiority margin.

All tests were two-tailed and performed at the 0.05 alpha level. We did not control for any demographic or clinical characteristics since none reached statistical significance. Analyses were performed using Stata® (version 14).

RESULTS

Subjects

Randomized subjects were medication-naïve adults (age 18 to 30) with ADHD preselected by the experience of euphoria with a test dose of IR MPH. Based on our preliminary work with a 40 mg dose of IR MPH, we expected that 38% of adults with ADHD would experience at least mild euphoric effects from therapeutic oral doses of MPH.¹⁶

As depicted in Figure 1, 64 subjects were consented and enrolled. Fifty-six subjects completed all screening procedures. Forty-four subjects participated in the baseline Drug Feeling Visit, of which thirty-eight experienced stimulant-induced euphoria. Of those 38, 37

were started in the open trial of MPH and randomized 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 twelve subjects were ineligible after they consented 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 twenty-three subjects withdrew or were later dropped due to the demanding time commitment of participating in the study or to relocation. Finally, four subjects were terminated from the study during the treatment phase due to adverse events. Of these subjects, one developed negative mood side effects, one was discovered to have previously asymptomatic lymphoma, one experienced a recurrence of her peptic stress ulcers, and one 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. Average ratings of anxiety symptoms on the HAM-A and depression symptoms on the HAM-D and BDI were low and did not significantly differ between the two groups (Table 1).

ADHD Treatment

The average final dose of methylphenidate was 67 ± 19 mg/day. The optimal dose was 80 mg for 17/31 (55%) of the subjects. Six weeks of open MPH produced significant clinical improvement of ADHD symptoms ($t = -14.13$, $df = 24$, $P < 0.001$). During the six weeks of open MPH treatment, assignment to six weeks of concurrent naltrexone or placebo did not have a significant effect on the efficacy of MPH treatment for ADHD symptoms ($\chi^2 = 1.61$, $df = 6$, $P = 0.95$). Average scores on the AISRS did not significantly differ for those on naltrexone compared to those on placebo over the six weeks of the study (Figure 2). Furthermore, there was no significant difference in the drop-out rates for subjects on naltrexone versus those on placebo (20% vs. 18%; Fisher's exact, $P = 1.00$). Conducting a completers-only analysis, six weeks of naltrexone did not have a significant effect on the efficacy of MPH treatment for ADHD symptoms ($\chi^2 = 2.16$, $df = 6$, $P = 0.90$).

The difference in AISRS total score between naltrexone + MPH and placebo + MPH was 0.92 with a 95% confidence interval of -3.82 to 5.67 . The lower bound of the 95% confidence interval is above the non-inferiority margin and the difference between naltrexone + MPH and placebo + MPH is significantly different from the non-inferiority margin ($P = 0.02$). Thus, we can conclude that naltrexone + MPH is not inferior to placebo + MPH.

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. When corrected 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). In order to interpret the Week 6 average weight data, is important to note that, by chance, two subjects in the naltrexone group were about 50 pounds heavier than the next heaviest person at baseline. When those two are removed, the average Week 6 weights are 147.4 ± 23.1 and 141.4 ± 22.5 pounds for the placebo and naltrexone groups respectively.

Adverse Events

Of the 21 types of adverse events (AEs) reported, there were only significant differences in the rates of palpitations/tachycardia and decreased appetite between the naltrexone and placebo groups (palpitations/tachycardia: 0% vs. 6%, Fisher's exact, $P = 0.01$; decreased appetite: 13% vs. 3%, $\chi^2 = 5.98$, $df = 1$, $P = 0.02$) (Table 3). There was no significant difference in the mean number of AEs reported by those on naltrexone versus placebo (4.75 vs. 6.73 ; $t = -1.37$, $df = 29$, $P = 0.18$).

DISCUSSION

This double-blind, randomized clinical trial showed that the combination of naltrexone with methylphenidate (MPH) was highly effective in the treatment of ADHD and was well-tolerated. The observed benefits were indistinguishable in subjects receiving MPH 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 non-addictive stimulant treatment for ADHD.

In a previous study we reported that 38% of adults experienced a mild euphoric effect to a single dose of 40 mg IR MPH.¹⁶ In this study we found that 78% of adults experienced a mild euphoric effect to 60 mg IR MPH. 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 MPH on ADHD symptoms was equally robust in subjects receiving MPH with and without the co-administration 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 MPH in reducing ADHD symptoms has been documented in the literature,¹⁷ it has never before been documented with the concomitant administration of naltrexone with MPH. These results show that the co-administration of naltrexone does not diminish the benefits expected with MPH treatment.

With few exceptions, the concomitant administration of naltrexone did not affect the tolerability of robust dosing of MPH as measured by either spontaneously reported adverse events (AEs) or dropout rates. However, of the 21 categories of AEs 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 on naltrexone or on placebo (Table 2). Of note, naltrexone has been reported to substantially reduce the heart rate increase that is characteristic of alcohol intoxication.¹⁸

Although the co-administration of MPH and naltrexone is novel, both MPH and naltrexone are established medicines 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.¹⁹ While widely used to treat alcohol and opioid use disorders, the main concern about naltrexone is a potential for chemical hepatitis (elevated liver enzymes) at higher doses. In several studies, supratherapeutic naltrexone doses of 300 mg/day have led to transient, reversible elevations in serum transaminases in some subjects. While monitoring of hepatic health is important when naltrexone is prescribed, to date no cases of hepatic failure due to naltrexone have been reported and the black box warning has been removed.²⁰

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 (PNE).²¹ This mouse model has brain, biochemical, and behavioral changes highly consistent with what has been documented in humans with ADHD. These included low fronto-cortical dopamine turnover, behavioral symptoms of inattention, impulsivity and hyperactivity, and pharmacological response to therapeutic doses of MPH. Using this PNE mouse, our team made the important and novel discovery relating activation of the opioid system to high doses of MPH activated mu 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 pharmacological 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 MPH 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 paper 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 five 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 rate of drop out was similar in groups treated with naltrexone and placebo, the rate of drop out may affect generalizability of the findings.

Treatment with MPH was open-label and not blinded. However, we were not testing the tolerability or effectiveness of stimulants, but the tolerability and effectiveness of the co-administration of naltrexone with a stimulant. As noted above, MPH 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 Caucasian 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, in this controlled study, the effects of MPH were equally potent and indistinguishable with and without the co-administration of naltrexone. If confirmed, these findings could lead to the development of a non-addictive 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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Clinical Points

- Animal studies have shown Mu 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.

Figure 1.
CONSORT diagram.

Figure 2.
Average AISRS scores for the Placebo and Naltrexone groups over the six weeks of the clinical trial.

Table 1.

Demographic and clinical characteristics of subjects who completed through at least Week 3.

Characteristic	Placebo N = 16	Naltrexone N = 15	Test Statistic	P-Value
Age	24.4 ± 3.2	25.1 ± 2.9	t = -0.63	0.53
Gender (Male)	8 (50)	6 (40)	$\chi^2 = 0.31$	0.58
Weight (pounds)	154.7 ± 23.2	162.5 ± 41.1	z = -0.20	0.84
HAM-A	3.9 ± 3.5	7.0 ± 8.3	z = -0.86	0.39
HAM-D	2.8 ± 3.6	4.7 ± 6.0	z = -0.75	0.45
BDI	2.4 ± 2.1	4.5 ± 4.4	z = -0.92	0.34
AISRS	36.4 ± 9.0	38.5 ± 9.8	z = -0.61	0.54

Data are presented as mean ± SD or N (%).

AISRS The Adult ADHD Investigator Symptom Report Scale; BDI Beck Depression Inventory; HAM-A Hamilton Anxiety Scale; HAM-D Hamilton Depression Scale

Table 2.

Vitals at week 6 controlling for baseline measures.

	Placebo N = 13	Naltrexone N = 12	Test Statistic	P-Value
Weight (pounds)	147.4 ± 23.1	156.8 ± 41.2	$t_{22} = 0.38$	0.71
Pulse (BPM)	78.0 ± 13.3	77.0 ± 6.8	$t_{22} = -0.73$	0.47
Systolic Blood Pressure (mm Hg)	114.8 ± 5.6	118.8 ± 12.7	$t_{22} = 1.11$	0.28
Diastolic Blood Pressure (mm Hg)	72.6 ± 8.7	73.5 ± 9.0	$t_{22} = 0.42$	0.68

BPM= beats per minute

Table 3.

Adverse Events

AE Category	Event Frequency		Test Statistic	P-Value
	N (%)	Placebo Naltrexone		
Agitated/Irritable	0 (0)	4 (4)	Fisher	0.13
Anxious/Worried	3 (4)	1 (1)	Fisher	0.32
Autonomic: Drool/Sweat	3 (4)	2 (2)	Fisher	0.65
Cardiovascular (palpitations/tachycardia) ^a	5 (7)	0 (0)	Fisher	0.01
Cold/Infection/Allergies	5 (7)	2 (2)	Fisher	0.24
Decreased Appetite ^a	2 (3)	13 (13)	X ² = 5.98	0.02
Decreased Energy	1 (1)	4 (4)	Fisher	0.39
Dermatological	0 (0)	1 (1)	Fisher	1.00
Dizzy/Lightheaded	1 (1)	0 (0)	Fisher	0.43
Extra Pyramidal Sxs	1 (1)	0 (0)	Fisher	0.43
Headache	15 (20)	19 (19)	X ² = 0.01	0.91
Increased Energy	0 (0)	2 (2)	Fisher	0.51
Insomnia	13 (17)	12 (12)	X ² = 0.91	0.34
Mucosal Dryness	1 (1)	4 (4)	Fisher	0.39
Musculoskeletal	5 (7)	5 (5)	Fisher	0.75
Nausea/Vomit/Diarrhea	9 (12)	16 (16)	X ² = 0.62	0.43
Neurological	0 (0)	1 (1)	Fisher	1.00
Other	4 (5)	3 (3)	Fisher	0.47
Sad/Down	2 (3)	5 (5)	Fisher	0.70
Sedation	1 (1)	0 (0)	Fisher	0.43
Tense/Jittery	5 (7)	7 (7)	X ² = 0.01	0.91

^a = P < 0.05