The Mixed Opioid Receptor Antagonist Naltrexone Mitigates Stimulant-Induced Euphoria:

A Double-Blind, Placebo-Controlled Trial of Naltrexone

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ABSTRACT

Objective: Supratherapeutic doses of methylphenidate activate μ-opioid receptors, which are linked to euphoria. This study assessed whether naltrexone, a mixed μ-opioid antagonist, may attenuate the euphoric effects of stimulants, thereby minimizing their abuse potential 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 (January 2013 to June 2015). Spheroidal Oral Drug Absorption System methylphenidate (SODAS-MPH) was administered twice daily, was titrated to ~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 an oral test dose of 60 mg of immediate-release methylphenidate (IR-MPH). The primary outcome measure was Question 2 (Liking a Drug Effect) on the Drug Rating Questionnaire, Subject version, which was assessed after oral test doses of 60 mg of IR-MPH were administered after the third and sixth weeks of treatment with SODAS-MPH.

Results: Thirty-seven subjects who experienced stimulant-induced (mild) euphoria at a baseline visit were started in the open trial of SODAS-MPH and randomized to naltrexone 50 mg/d or placebo. Thirty-one subjects completed through week 3, and 25 completed through week 6. Naltrexone significantly diminished the euphoric effect of IR-MPH during the heightened-risk titration phase (primary outcome; first 3 weeks) ($\chi^2 = 5.07$, $P = .02$) but not the maintenance phase (weeks 4–6) ($\chi^2 = 0.22$, $P = .64$) of SODAS-MPH treatment.

Conclusions: Preclinical findings are extended to humans showing that naltrexone may mitigate stimulant-associated euphoria. Our findings provide support for further studies combining opioid receptor antagonists with stimulants to reduce 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.[1] Wilens et al[1] reported rates of past-year nonprescribed stimulant use ranging from 5%–35% in college-aged individuals. Individuals at greatest risk are those with preexisting conduct or substance use disorders.[1]

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 (MOPR) 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] as well as enhanced striatal MOPR activity.[2] We showed that naltrexone, an opioid receptor antagonist, blocked methylphenidate-induced place preference. Thus, an opioid antagonist can block rewarding effects of methylphenidate in a mouse model. Naltrexone is a mixed opiate antagonist that is currently approved by the US Food and Drug Administration for the treatment of opioid use disorder as well as the treatment of alcoholism.

In a previous publication,[4] we showed that the coadministration of naltrexone with Spheroidal Oral Drug Absorption System methylphenidate (SODAS-MPH) was well tolerated and did not interfere with the clinical benefits of methylphenidate. Yet, whether the coadministration of naltrexone to methylphenidate attenuates stimulant-induced euphoric effects and drug abuse liability in humans remained to be established.

The main aim of this study was to assess whether the coadministration of naltrexone to

Clinical Points

- Animal studies have shown that μ-opioid antagonists, such as naltrexone, may minimize the abuse potential of stimulants.
- In our study of adults with ADHD, the addition of naltrexone to daily methylphenidate decreased abuse potential (subjective "liking") during the heightened-risk titration phase but not the maintenance phase.
- Our findings provide support for the concept of combining opioid receptor antagonists with stimulants to provide an effective stimulant formulation with less abuse potential.

treatment with a stimulant would attenuate stimulant-induced euphoria. To this end, we conducted a 6-week, double-blind, placebo-controlled, randomized clinical trial of naltrexone in adults with ADHD receiving open-label treatment with therapeutic oral doses of SODAS-MPH. We used an enriched sample approach in which we included only participants who experienced euphoria with a test dose of immediate-release methylphenidate (IR-MPH). Because there may be a period of heightened risk for euphoric effects during a titration phase when the dose of SODAS-MPH is being increased, we tested subjective response to IR-MPH in 2 periods: after 3 weeks of titration of SODAS-MPH and again at week 6 after an additional 3 weeks of stable treatment with SODAS-MPH. On the basis of its pharmacologic properties, we hypothesized that treatment with naltrexone would attenuate methylphenidate-induced euphoria in general and during the titration phase in particular.

METHODS

Subjects

Subjects were medication-naive 18- to 30-year-old adults with ADHD who were preselected for having experienced euphoria with a test dose of IR-MPH and were willing to reliably participate and understood all study procedures. Main exclusion criteria included any current non-ADHD clinically significant psychiatric condition, any chronic or clinically significant medical illness, current or recent substance abuse/dependence or psychotropic use, current or prior adequate treatment with methylphenidate, or a known hypersensitivity to methylphenidate. 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 (ClinicalTrials.gov identifier: NCT01673594).

Assessments

Sociodemographic assessment. A brief interview was conducted to collect information on education and occupation to estimate socioeconomic status, as well as information about educational accommodations.

Assessment of ADHD and comorbid psychopathology. An expert clinician assessed the diagnosis of ADHD and exclusionary comorbid Axis I *DSM-IV* disorders. Subjects were also assessed with the Structured Clinical Interview for *DSM-IV* Axis I Disorders[5] supplemented with modules from the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-E)[6] to assess childhood *DSM-IV* disorders.

AISRS and CGI. The Adult ADHD Investigator Symptom Rating Scale (AISRS)[7] is a validated *DSM-IV* investigator-rated assessment widely used in clinical trials of adults with ADHD.[8,9] The Clinical Global Impression (CGI) Scale for ADHD[10] is a rating scale used to measure the overall severity of ADHD and has been shown to be drug-sensitive in psychopharmacology research.[10]

Drug Rating Questionnaire. The Drug Rating Questionnaire, Subject version (DRQ-S) is a simple questionnaire used to measure factors in abuse liability. Each subscale (Feeling, Liking, Disliking) is a Likert scale (1–29).[11] This measure and related scales have been used in over 27 published studies assessing the abuse liability of methylphenidate.[12,13]

Study Procedures

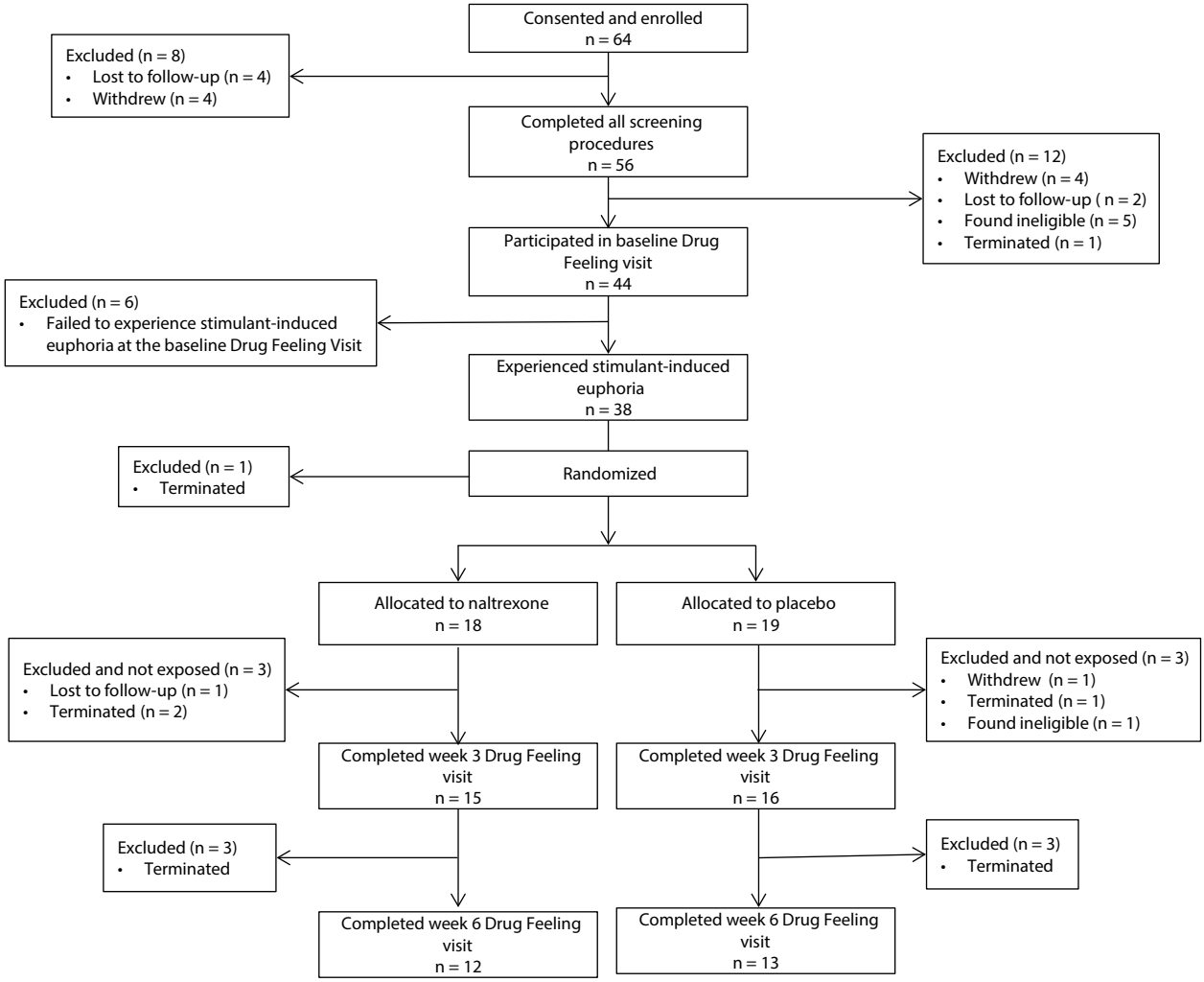
Eligible subjects were randomized to 50 mg of naltrexone daily (active or placebo) and entered a 6-week, open-label treatment protocol with daily, therapeutic doses of long-acting SODAS-MPH. At baseline and at the end of weeks 3 and 6, subjects underwent 1-day likability assessments with single supratherapeutic doses (60 mg) of IR-MPH and then (IR-MPH) placebo (order randomized). On the likability assessment days, the subjects took their blinded doses of naltrexone (active or placebo) but did not take SODAS-MPH on those days.

Likability Assessment Procedures

Subjects were tested for a euphoric effect in response to an oral 60-mg bolus dose of IR-MPH under double-blind conditions. On Likability Assessment days, the MGH Research Pharmacy assigned the randomization of the order of IR-MPH administration (active-placebo, placebo-active). Likability was assessed 3 times: (1) at prebaseline assessment for eligibility; (2) titration phase: at the end of week 3, when subjects are expected to have reached the optimal and tolerated dose of SODAS-MPH; and (3) maintenance phase: at the end of the clinical trial (week 6). At the week 3 and week 6 visits, subjects took their naltrexone (or placebo) in the morning but did not take SODAS-MPH (for that day only).

At the prebaseline visit, subjects received 1 oral blinded test dose (60 mg) of IR-MPH (active/placebo) in the morning and the other treatment in the afternoon (order randomized) and completed the DRQ-S hourly for 4 hours after each dose. On subsequent likability assessment days (end of week 3 and end of week 6), subjects did not take the usual SODAS-MPH but did receive their blinded, randomized dose of naltrexone or placebo in the morning

Figure 1. CONSORT Diagram



and then a blinded test dose (60 mg IR-MPH or placebo) in the morning and afternoon (order randomized). They completed the DRQ-S hourly for 4 hours after each dose.

Open-Label Treatment With SODAS-MPH

All study subjects underwent 6 weeks of open treatment with SODAS-MPH administered twice daily.

Titration phase. Subjects were started on 20 mg SODAS-MPH twice daily and were 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 (~1 mg/kg/d).

Maintenance phase. In weeks 4–6, they were continued at the highest tolerated dose (≤ 80 mg/d).

Placebo-Controlled, Randomized Clinical Trial of Naltrexone

The MGH Research Pharmacy assigned randomization for (daily) naltrexone (active vs placebo; 50:50) to eligible and consenting subjects for a 6-week period combined with the open treatment with SODAS-MPH. Naltrexone-masked placebo was matched to an identically appearing naltrexone formulation in lactose-filled capsules.

Statistical Analysis

We compared demographics and clinical features among the placebo and naltrexone groups using Student *t* tests and Pearson χ^2 tests for parametric data and Wilcoxon rank sum tests for nonparametric data. Analyses pertaining to likability testing days and the 6-week clinical trial were performed using mixed-effects Poisson regression, linear regression, Wilcoxon signed rank tests, and Spearman correlations. Regression models used robust standard errors to account for the repeated measures on each subject. We performed backward selection to arrive at the final mixed-effects Poisson regression models used to examine feeling a drug effect, euphoria, and dysphoria at weeks 3 and 6. All models started with the following variables: naltrexone, IR-MPH, session (morning or afternoon), hours (1–4), the IR-MPH × naltrexone interaction, the IR-MPH × hours interaction, the IR-MPH × session interaction, the naltrexone × hours interaction, and the

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

Characteristic	Placebo (n = 16)	Naltrexone (n = 15)	Test Statistic	*P* Value
Age, y	24.4 ± 3.2	25.1 ± 2.9	$t = -0.63$	.53
Gender, male, n (%)	8 (50)	6 (40)	$\chi^2 = 0.31$	.58
Weight, lb	154.7 ± 23.2	162.5 ± 41.1	$z = -0.20$	.84
HARS	3.9 ± 3.5	7.0 ± 8.3	$z = -0.86$	.39
HDRS	2.8 ± 3.6	4.7 ± 6.0	$z = -0.75$	.45
BDI	2.4 ± 2.1	4.5 ± 4.4	$z = -0.92$	.34
AISRS	36.4 ± 9.0	38.5 ± 9.8	$z = -0.61$	.54
DRQ-S				
Feel Effect	5.4 ± 5.5	5.4 ± 5.9	$z = 0.14$	.89
Euphoria	5.9 ± 6.1	6.1 ± 7.4	$z = 0.57$	.57
Dysphoria	1.9 ± 2.9	1.7 ± 1.9	$z = -0.86$	.39

[a]Data are presented as mean ± SD unless otherwise noted.
Abbreviations: AISRS = Adult ADHD Investigator Symptom Rating Scale; BDI = Beck Depression Inventory; DRQ-S = Drug Rating Questionnaire, Subject version; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale.

IR-MPH × naltrexone × hours interaction. Insignificant higher-order variables were removed from the model successively until only those that were significant at the .05 α level remained. We kept the IR-MPH × naltrexone interaction term in all models regardless of significance because it was our effect of interest. All tests were 2-tailed and performed at the .05 α level. We did not control for any demographic or clinical characteristics since none reached statistical significance. Analyses were performed using Stata (version 14; StataCorp LLC, College Station, Texas).

A priori analyses included the effects of naltrexone on methylphenidate-induced detection, euphoria, and dysphoria in the titration phase (week 3) and maintenance phase (week 6). The primary outcome analysis was the effect of naltrexone on methylphenidate-induced euphoria in the titration phase (week 3).

RESULTS

Subjects

As depicted in Figure 1, 64 subjects provided written informed consent and enrolled. Fifty-six subjects completed all screening procedures. Forty-four subjects participated in the baseline Drug Feeling Visit, of which 86% (38/44) experienced stimulant-induced euphoria. Of those 38, 37 were started in the open trial of SODAS-MPH and randomized to naltrexone or placebo. Thirty-one subjects completed through week 3, and 25 subjects completed through week 6.

Thirty-nine subjects did not complete the study for various reasons. Six subjects were ineligible after they consented due to cardiovascular concerns about using stimulant treatment, a positive urine drug screen, or comorbidity. An additional 6 (of 44) subjects failed to experience stimulant-induced euphoria 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 due 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 reoccurrence of her peptic stress ulcers, and 1 experienced nausea and vomiting. In no case were the adverse events judged to be due to naltrexone.

Demographic and Clinical Characteristics of Randomized Sample

As described in Table 1, there were no significant differences in age, weight, or sex between the naltrexone and (naltrexone) placebo groups. There also were no significant differences in baseline ADHD severity on the AISRS or in ratings of anxiety symptoms (Hamilton Anxiety Rating Scale[14]) and depression symptoms (Hamilton Depression Rating Scale[15] and Beck Depression Inventory[16]). Furthermore, prebaseline ratings for feelings of any effect, euphoria, and dysphoria on the DRQ-S did not significantly differ between the naltrexone and placebo groups (Table 1).

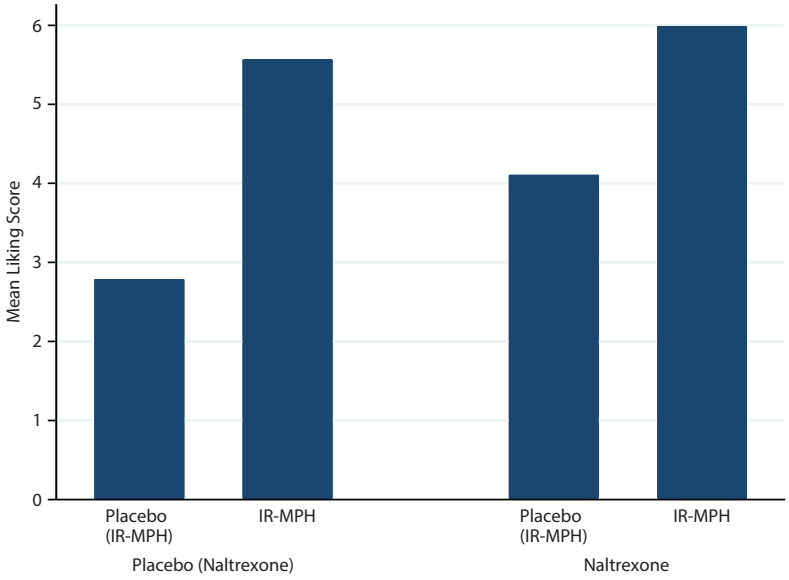
Week 3 DRQ-S Findings

Feeling a Drug Effect (detection). The final model for Feeling a Drug Effect at week 3 included naltrexone, IR-MPH, session, hours, the IR-MPH × hours interaction, the naltrexone × hours interaction, and the IR-MPH × naltrexone interaction. Although the effect of naltrexone on IR-MPH–associated Feeling a Drug Effect did not reach our a priori threshold for statistical significance ($\chi^2 = 3.65$, $P = .06$), the trend favored naltrexone (lower feeling). There was less difference in average Feeling a Drug Effect score between the IR-MPH and (IR-MPH) placebo groups for those on naltrexone (difference = 1.92) compared to those on (naltrexone) placebo (difference = 2.65). Additionally, average Feeling a Drug Effect scores significantly differed by session (AM and PM), with higher ratings in the PM hours compared to those in the AM hours (5.15 vs 3.88; $\chi^2 = 4.61$, $P = .03$).

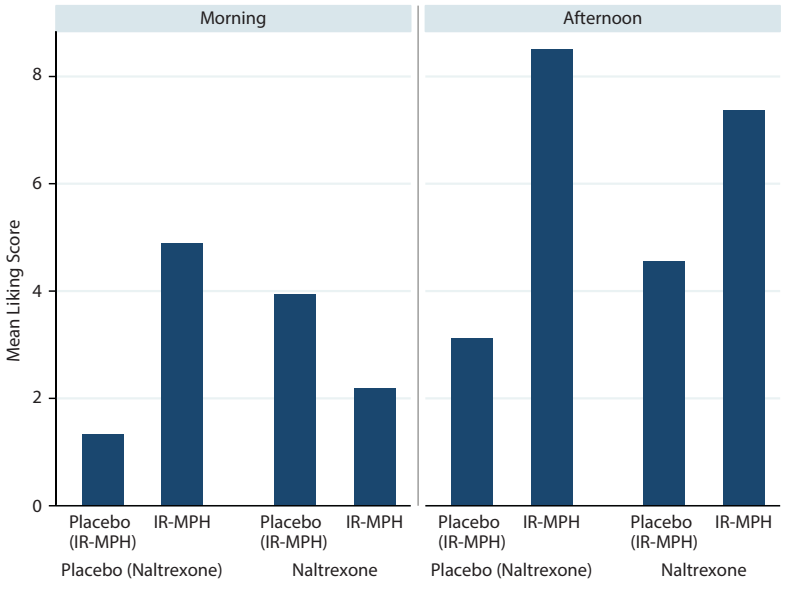
Liking a Drug Effect (euphoria). For Liking a Drug, the final model included naltrexone, IR-MPH, baseline euphoria, hours, session, and the IR-MPH × naltrexone interaction. Baseline Liking a Drug Effect was significantly associated with week 3 liking ($z = 4.99$, $P < .001$). Controlling for baseline findings, the effect of IR-MPH on Liking a Drug Effect significantly differed between (naltrexone) placebo and naltrexone groups ($\chi^2 = 5.07$, $P = .02$). There was less difference in average Liking a Drug Effect scores between the IR-MPH and (IR-MPH) placebo groups for those on naltrexone compared to those on (naltrexone) placebo (Figure 2A). In addition, average Liking a Drug Effect scores were significantly higher during the afternoon session compared to the morning session (5.33 vs 3.80; $\chi^2 = 6.31$, $P = .01$). A 3-way interaction between IR-MPH, naltrexone, and session revealed that naltrexone suppressed the Liking a Drug Effect score significantly more when IR-MPH was given in the morning compared to when IR-MPH was administered in the afternoon ($\chi^2 = 5.20$, $P = .02$) (Figure 2B). In addition, we found that the difference in average Liking a Drug Effect scores between the IR-MPH and (IR-MPH)

Figure 2. Poisson Regression Model Predicting Liking a Drug Effect at Week 3, Controlling for Baseline Euphoria

A. IR-MPH × Naltrexone Interaction (N = 31)[a]



B. IR-MPH × Naltrexone × Session Interaction (N = 31)[b]

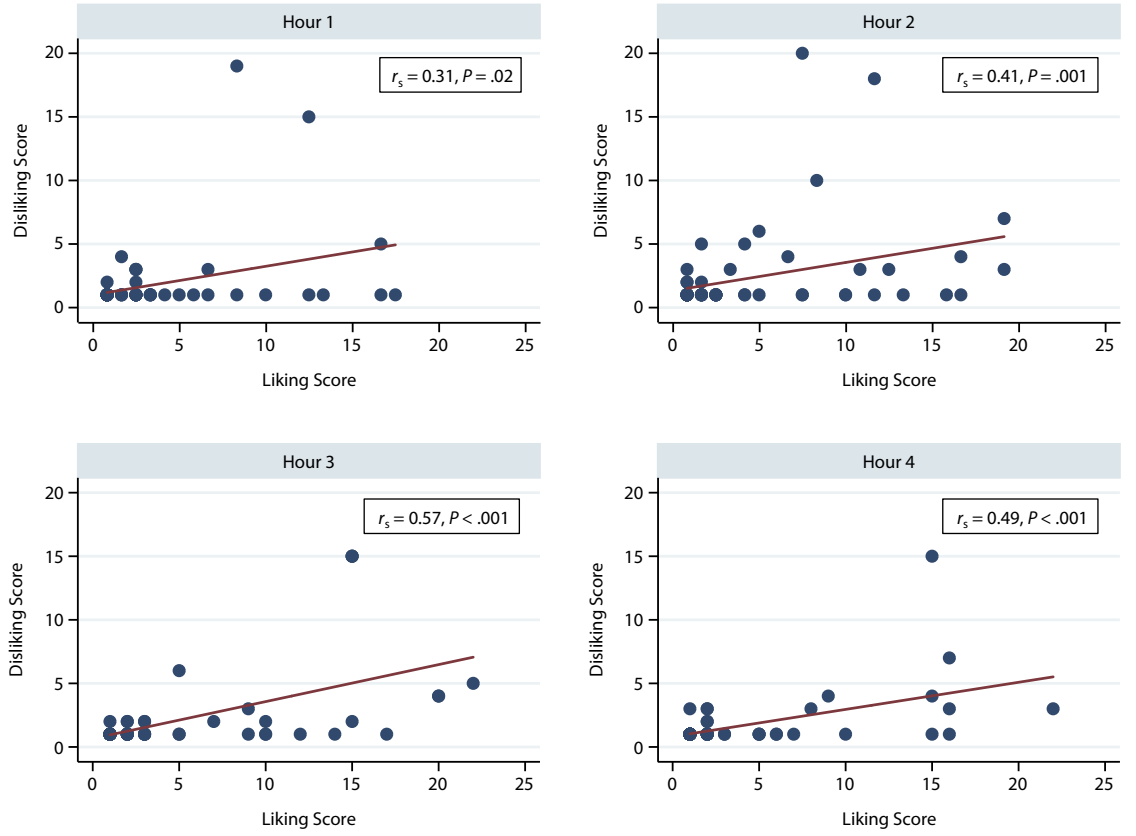


[a]There was a significant interaction between IR-MPH and naltrexone ($P = .02$).
[b]There was a significant interaction between IR-MPH, naltrexone, and session ($P = .02$).
Abbreviation: IR-MPH = immediate-release methylphenidate.

placebo groups was decreased at week 3 (difference = 2.35) compared with baseline (difference = 6.45) regardless of naltrexone ($\chi^2 = 4.20$, $P = .04$).

Disliking a Drug Effect (dysphoria). The final model for Disliking a Drug Effect included naltrexone, IR-MPH, hours, the IR-MPH × hours interaction, the naltrexone × hours interaction, and the IR-MPH × naltrexone interaction. Not controlling for naltrexone, we found that Disliking a Drug Effect ratings did not significantly differ between the IR-MPH and (IR-MPH) placebo groups (2.03 vs 1.82; $\chi^2 = 0.57$, $P = .45$). The effect of IR-MPH on dysphoria did not significantly differ between (naltrexone) placebo and naltrexone groups ($\chi^2 = 0.11$, $P = .75$). There was no difference in average Disliking a Drug Effect score between the IR-MPH and (IR-MPH) placebo groups for those on naltrexone (difference = 0.28) compared to those on placebo (difference = 0.15). Additionally, 3 weeks of open SODAS-MPH treatment did not significantly change the IR-MPH–associated Disliking a Drug Effect score ($\chi^2 = 1.02$, $P = .31$). There was no significant difference in the average

Figure 3. Correlation Between IR-MPH–Associated Euphoria and IR-MPH–Associated Dysphoria by Hour



Abbreviation: IR-MPH = immediate-release methylphenidate.

Disliking a Drug Effect score between the IR-MPH and (IR-MPH) placebo groups at week 3 (difference = 0.21) versus baseline (difference = 0.72).

Euphoria/dysphoria relationship. At week 3, IR-MPH–associated euphoria and dysphoria were positively correlated at each hour (Figure 3) and most strongly so at hour 3 ($r_s = 0.57$; $P < .001$). In contrast, we found no significant correlation between euphoria in the morning and dysphoria in the afternoon ($r_s = -0.02$, $P = .92$).

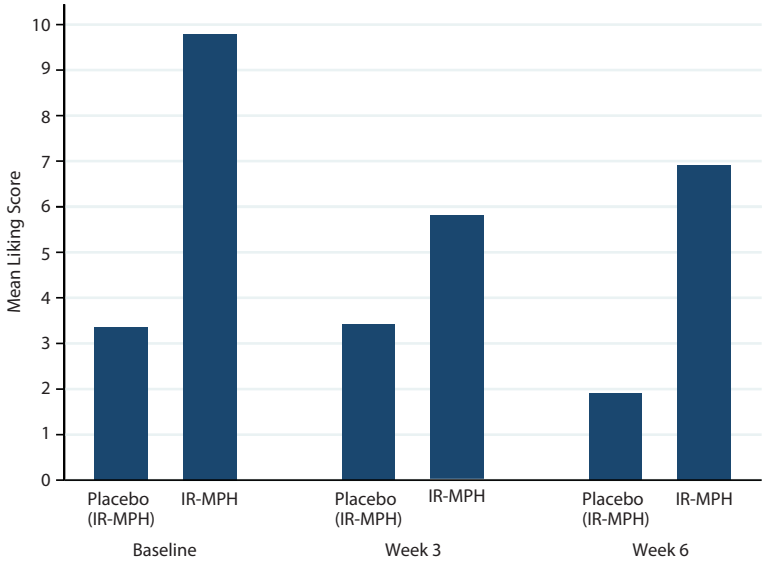
Week 6 DRQ-S Findings

Feeling a Drug Effect (detection). The final model for Feeling a Drug Effect at week 6 included naltrexone, IR-MPH, hours, the IR-MPH × hours interaction, and the IR-MPH × naltrexone interaction. The effect of IR-MPH on Feeling a Drug Effect did not significantly differ between (naltrexone) placebo and naltrexone groups at week 6 ($\chi^2 = 1.14$, $P = .29$). There was no difference in the average Disliking a Drug Effect score between the IR-MPH and (IR-MPH) placebo groups for those on naltrexone (difference = 5.52) compared to those on placebo (difference = 3.15).

Liking a Drug Effect (euphoria). The final model for euphoria at week 6 included naltrexone, IR-MPH, hours, the IR-MPH × hours interaction, the naltrexone × hours interaction, the IR-MPH × naltrexone interaction, and the IR-MPH × naltrexone × hours interaction. There was no main effect of the IR-MPH × naltrexone interaction on euphoria at week 6 ($\chi^2 = 0.22$, $P = .64$). There was no difference in the average Liking a Drug Effect score between the IR-MPH and (IR-MPH) placebo groups for those on naltrexone (difference = 5.72) compared to those on placebo (difference = 4.35). The 3-way interaction including IR-MPH × naltrexone × hours shows that the effect of naltrexone and IR-MPH on euphoria varied by hour ($\chi^2_3 = 12.24$, $P = .007$). There was a greater difference in the average Liking a Drug Effect score between the IR-MPH and (IR-MPH) placebo groups for those on naltrexone versus placebo at hour 3 compared to hours 1 (naltrexone: difference = 4.67, placebo: difference = 3.92) and 2 (naltrexone: difference = 4.83, placebo: difference = 6.92). Upon examining the effect of IR-MPH on Liking a Drug Effect across time (baseline, week 3, and week 6), we found a significant interaction between IR-MPH and time regardless of naltrexone ($\chi^2_3 = 6.71$, $P = .03$). The difference in Liking a Drug Effect scores between the IR-MPH and (IR-MPH) placebo groups significantly differed between week 3 and baseline and between week 3 and week 6 (Figure 4).

Disliking a Drug Effect (dysphoria). The final model for dysphoria at week 6 included naltrexone, IR-MPH, hours, the IR-MPH × hours interaction, the naltrexone × hours

Figure 4. Poisson Regression Model Predicting Liking From the IR-MPH × Time Interaction (Week 6 vs Week 3 vs Baseline) (N = 31)[a]



[a]There was a significant interaction between IR-MPH and time ($P = .03$). Week 3 significantly differed from baseline ($P = .04$), and week 6 significantly differed from week 3 ($P = .02$).
Abbreviation: IR-MPH = immediate-release methylphenidate.

interaction, the IR-MPH × naltrexone interaction, and the IR-MPH × naltrexone × hours interaction. There was no main effect of the IR-MPH × naltrexone interaction on dysphoria at week 6 ($\chi^2 = 0.36$, $P = .55$). There was no difference in average Disliking a Drug Effect score between the IR-MPH and (IR-MPH) placebo groups for those on naltrexone (difference = 0.40) compared to those on placebo (difference = 0.67). The 3-way interaction including IR-MPH × naltrexone × hours shows that the effect of naltrexone and IR-MPH on disliking varied by hour ($\chi^2_3 = 13.47$, $P = .004$). There was less difference in the disliking score between the IR-MPH and (IR-MPH) placebo groups for those on naltrexone versus placebo at hour 3 compared to hour 2.

DISCUSSION

The clinical trial aimed to assess whether the mixed opiate antagonist naltrexone, combined with treatment with SODAS-MPH, mitigates stimulant-associated euphoria in adults with ADHD. Our study hypothesis was partially confirmed; naltrexone significantly diminished the euphoric effect of IR-MPH during the titration phase (first 3 weeks) but not the stabilization phase (weeks 4 to 6) of SODAS-MPH treatment.

The titration phase of open-label treatment with SODAS-MPH appears to be a period of heightened vulnerability. These findings are consistent with prior work by us[17] and Volkow et al[18,19] that emphasized the importance of the rate of delivery of stimulants to the brain for abuse liability. Also consistent with this notion is the finding that naltrexone had little effect on euphoria during the last 3 weeks of the trial in which subjects remained on a stable optimized therapeutic dose of SODAS-MPH.

The measures of abuse liability (DRQ-S) consisted of subscales that ranged from 1 to 29. Despite administration of 60 mg of IR-MPH, the subjective responses on these rating scales were in the mild range. It is possible that the experience of euphoria attenuated because the subjects had only mild euphoria at study outset. Our nonsignificant effect for euphoria at week 6 should be viewed with caution due to the possibility of a floor effect, which would have reduced statistical power. Our results are consistent with a previous study[20] that reported decreased subjective effects of single doses of amphetamine with naltrexone pretreatment in 12 healthy volunteers.

The finding that naltrexone diminished IR-MPH–associated euphoria significantly more in the morning than in the afternoon is noteworthy. Considering that naltrexone was administered in the morning, this finding suggests that the euphoria-blocking effect of naltrexone may be maximally beneficial if administered proximally to the stimulant dosing. The mean elimination half-life ($T_{1/2}$) values for naltrexone and 6-β-naltrexol are 4 hours and 13 hours, respectively. However, clinical studies indicate that 50 mg of naltrexone will block the pharmacologic effects of 25 mg of intravenously administered heroin for periods as long as 24 hours.[21,22] More work is needed to confirm this intriguing finding.

The euphoric response to the acute bolus, supratherapeutic dose of IR-MPH was significantly decreased at week 3 regardless of naltrexone. This finding is consistent with the hypothesis that chronic treatment with methylphenidate is associated with some desensitization to IR-MPH–associated

euphoria. Despite the lower euphoric response to IR-MPH at week 3, naltrexone was associated with a *further* decrease in euphoric response.

While subjects reported both euphoria and some degree of dysphoria simultaneously, there was no effect of either IR-MPH or naltrexone on dysphoria. This finding is surprising considering that dysphoria is associated with activation of opiate κ receptors and that naltrexone blocks κ receptors. Additionally, our results do not support the time-lagged association of euphoria and dysphoria, suggesting that dysphoria in the afternoon does not seem to be related to "crashing" after euphoria in the morning. More work is needed to further examine the relationship of euphoria to dysphoria and the effects of naltrexone on dysphoria.

The observed positive effects of naltrexone on IR-MPH–induced euphoria are particularly important when coupled with the previously reported observation that treatment with naltrexone does not interfere with the clinical benefits of SODAS-MPH on ADHD.[4]

Our study has important strengths. Notably, this study translates programmatic work on the relationship of euphoria to stimulant-induced opioid activation from animals to humans. Additionally, this is a double-blind study of both naltrexone and test doses of IR-MPH in an enriched sample of ADHD subjects who register a euphoric response to IR-MPH. However, our findings need also to be seen in light of limitations. Future studies should examine whether naltrexone reduces "liking" and "estimated monetary street value" within populations of non–treatment-seeking poly–substance use disorder volunteers. Because naltrexone was added to open-label treatment with SODAS-MPH, further studies are needed to examine the effect of naltrexone on euphoric response without chronic stimulant treatment. While our results suggest some desensitization to euphoria after open treatment with stimulants, naltrexone was associated with a further decrease in euphoric response, particularly at week 3. Because our study was restricted to referred Caucasian adults, our findings cannot be extrapolated to a younger populations or community samples. Because the sample was largely Caucasian and referred, our findings do not generalize to community samples or other ethnic groups.

Despite these limitations, this double-blind, randomized controlled study showed that treatment with naltrexone diminished the euphoric effect of IR-MPH during the initial methylphenidate titration period of heightened vulnerability. If confirmed, these findings could lead to the development of a nonaddictive form of stimulant treatment for ADHD, which could facilitate access to an effective ADHD treatment.

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