Is Response to OROS-Methylphenidate Treatment Moderated by Treatment with Antidepressants or Psychiatric Comorbidity? A Secondary Analysis from a Large Randomized Double Blind Study of Adults with ADHD

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SUMMARY

Aims: The main aim of this *post hoc* analysis was to evaluate whether response to osmotic release oral system (OROS) methylphenidate (OROS-MPH) was moderated by the concomitant use of antidepressants in attention-deficit/hyperactivity disorder (ADHD) adults stabilized on these medicines for the treatment of depression or anxiety disorders, or a history of mood, anxiety, or substance use disorders. **Methods:** Two hundred and ninety-six subjects were screened for participation; 227 were randomized (112 to OROS-MPH and 115 to placebo), and 223 were analyzed ($N = 109$ and $N = 114$ for OROS-MPH and placebo, respectively). Subjects with anxiety disorders and depression treated with a stable medication regimen of non-MAOI antidepressants or benzodiazepines for at least 3 months could be enrolled in the study. Subjects currently receiving pharmacotherapy for anxiety disorders or depression were required to have Hamilton-Depression and Hamilton-Anxiety rating scales below 15 (mild range). **Results:** Concomitant antidepressant use at baseline was not associated with ADHD response, OROS-MPH dose, study completion rate, adverse effects, or exacerbation of anxiety/depression. We did find nominally significant evidence that a lifetime history of mood ($P = 0.09$) or anxiety ($P = 0.04$) disorders was a moderator of ADHD symptoms and that a lifetime history of substance use disorder ($P = 0.02$) was a potential moderator of dose at endpoint. **Discussion and Conclusions:** We found few moderating effects in this large clinical trial of OROS-MPH in adults with ADHD, which supports the robustness of the clinical response to OROS-MPH in adult ADHD despite variable clinical pictures.

Introduction

A large body of literature provides evidence that attention-deficit/hyperactivity disorder (ADHD) is a valid clinical entity in adults [1–4]. Epidemiological data estimate that close to 5% of adults suffer from ADHD and its presence is associated with a wide range of emotional and functional impairments, impacting all aspects of their lives [1,5–8]. Although its etiology remains unknown, there is mounting evidence for genetic transmission [3,5,6,9], and abnormalities in brain structure and function [10,11].

The extant literature also documents the efficacy of stimulant medications (methylphenidate, and amphetamine compounds) in the treatment of adults with ADHD, particularly when employing equipotent doses to those used in children with ADHD

[12,13]. Acute efficacy, tolerability, and safety have been demonstrated for immediate release (IR) methylphenidate (MPH) administered t.i.d. [14], for long-acting MPH delivered via an osmotic release oral system (OROS) [15,16], for IR dextroamphetamine, for dexamethylphenidate extended release [17], and for lisdexamfetamine dimesylate [18].

We recently completed a large-scale ($N = 223$) single site, 6-week, double blind, randomized, placebo-controlled, parallel study design of OROS-MPH in adults (19–60 years of age) with DSM-IV ADHD. OROS-MPH was formulated to provide day-long clinical effects delivering 22% of the MPH dose immediately and the remaining 78% in an ascending fashion over the next several hours. The mean daily dose was 78.4 ± 31.7 mg (0.97 ± 0.32 mg/kg) OROS-MPH and 96.6 ± 26.5 mg (1.16 ± 0.19 mg/kg) placebo ($P < 0.0001$). Clinical response at the 6-week endpoint

was significantly greater in the OROS-MPH group (62% [$N = 67$] vs. 37% [$N = 41$], $P < 0.001$). While these results indicate that robust daily doses of OROS-MPH are effective and generally well tolerated in the treatment of adults with ADHD, uncertainties remain as to their efficacy on other key aspects of the clinical picture of ADHD.

One of these key issues pertains to the efficacy and safety of stimulants in the context of concomitant use of antidepressants. A key methodological feature in our study was that while acute depression and anxiety were exclusionary, subjects on stable doses of non-MAOI antidepressants without prominent symptoms of depression or anxiety, as measured with syndrome congruent scales, were allowed to enter the study allowing us the opportunity to systematically examine this issue. A related and equally important issue is the examination of whether histories of depression or anxiety could moderate response to stimulant treatment in adults with ADHD. This is so considering the potential of stimulants to worsen symptoms of depression and anxiety, and that these risks could be increased in subjects with histories of these disorders. Finally, considering the high comorbidity between ADHD and substance use disorders (SUDs) [19–21], questions remain whether prior history of SUDs moderates the response to OROS-MPH.

Clarifying the effects of potential moderators to stimulant treatment in adults with ADHD has important clinical implications. Considering that ADHD is frequently comorbid with depression and anxiety, many patients with ADHD need treatments for these disorders, thereby requiring the concomitant use of both antidepressants and stimulants. Equally important is the examination of whether a history of mood and anxiety disorders worsens symptoms of anxiety and depression with stimulant treatment. Similarly, whether treatment with stimulants is moderated by prior history of SUDs can reassure clinicians about their safety when treating subjects with such histories. Thus, results from this study can inform clinical practice and guide clinicians on the safety and efficacy of stimulant medicines when coadministered with antidepressants, as well as when they are used in patients with complex psychiatric histories of depression, anxiety, or SUDs.

The main aim of this *post hoc* analysis was to evaluate whether response to OROS-MPH was moderated by the concomitant use of antidepressants in ADHD adults stabilized on these medicines for the treatment of depression or anxiety disorders, or a history of mood and anxiety disorders or SUDs. We hypothesized that OROS-MPH would be safe and effective in adults with ADHD receiving coadministration of antidepressants, and in those with a history of depression, anxiety, or SUDs. To the best of our knowledge these issues have not been adequately addressed in the extant literature.

Methods

This was a three-phase double-blind, placebo-controlled, parallel study design of OROS-MPH in adults (19–60 years of age) with DSM-IV ADHD. Phase I of the study was a 6-week acute efficacy trial ($N = 223$), Phase II was a 24-week double-blind continuation study of responders ($N = 96$), and Phase III was a double-blind, placebo-controlled, 4-week discontinuation study ($N = 23$). The current study evaluating potential moderators of acute treat-

ment response was conducted with only the Phase I double-blind, randomized, 6-week, placebo-controlled, parallel design study of OROS-MPH. Patients were randomized to OROS-MPH or placebo at a ratio of 1:1. Medication was titrated to optimal response (a maximum daily dose of 1.3 mg/kg; initial dose of 36 mg). During titration to optimal response, dose was increased by 36 mg at weekly intervals, but only for subjects who failed to attain an *a priori* definition of improvement (Clinical Global Impression [CGI]–Improvement of 1 or 2 or a reduction in the Adult ADHD Investigator Symptom Report Scale [AISRS] score of larger than 30%) and who did not experience adverse effects. Study clinicians were free to reduce a subject's dose if subjects experienced adverse effects during or after dose titration. The human research committee approved this study and all subjects completed a written informed consent.

Subjects

Subjects were outpatient adults with ADHD between 19 and 60 years of age who satisfied full diagnostic criteria for DSM-IV ADHD with childhood-onset and persistent symptoms based on clinical assessment and confirmed by structured diagnostic interview and a score ≥ 24 on the AISRS. We excluded potential subjects if they had clinically significant chronic medical conditions, abnormal baseline laboratory values, IQ < 80 , delirium, dementia, or amnesic disorders, other clinically unstable psychiatric conditions (i.e., bipolar disorder, psychosis, suicidality), drug or alcohol abuse or dependence within the six months preceding the study, or a previous adequate trial of MPH. We also excluded pregnant or nursing females.

Subjects with anxiety disorders and depression treated with a stable medication regimen of non-MAOI antidepressants or benzodiazepines for at least 3 months could be enrolled in the study. Subjects currently receiving pharmacotherapy for anxiety disorders or depression were required to have Hamilton-Depression and Hamilton-Anxiety rating scales below 15 (mild range) to be randomized to OROS-MPH or placebo.

Assessment

To assess inclusion and exclusion criteria, subjects underwent a comprehensive clinical assessment that included a psychiatric evaluation by a board certified psychiatrist, structured diagnostic interview, medical history, and laboratory assessments (liver function tests, complete blood count, weight, vital signs, and electrocardiogram [ECG]). The structured diagnostic interview used was the Structured Clinical Interview for DSM-IV (SCID) [22], supplemented for childhood disorders by modules (DSM-IV ADHD and conduct disorder) from the Kiddie SADS–E (Epidemiologic Version) [23]. To have been given a full diagnosis of adult ADHD, the subject must have (1) met full DSM–IV–R criteria (at least six of nine symptoms) for inattentive and/or hyperactive/impulsive subtypes by the age of seven as well as within the past month (i.e., ADHD-IA, ADHD-HI, and ADHD-C subjects were enrolled); (2) described a chronic course of ADHD symptomatology from childhood to adulthood; and (3) endorsed a current moderate or severe level of impairment attributed to the ADHD symptoms.

Overall severity and change in severity of ADHD were assessed with the CGI Scale [24]. The CGI includes Global Severity (1 = not ill, to 7 = extremely ill) and Global Improvement (1 = very much improved, to 7 = very much worse) Scales. The AISRS, shown to be sensitive to drug effects in adult populations [25], assesses each of the 18 individual criteria symptoms of ADHD in DSM-IV on a severity grid (0 = not present; 3 = severe; overall minimum score = 0; maximum score = 54). Response was defined *a priori* as being "Much" or "Very Much" improved according to the CGI-I scale (≤ 2) and a reduction in baseline AISRS score greater than 30%.

To assess symptoms of depression and anxiety we used the 17-item Hamilton Depression Scale (HAM-D, minimum = 0; maximum = 52) [26] and the Hamilton Anxiety Scale (HAM-A, minimum = 0; maximum = 56) [27]. A global measure of psychosocial functioning (global assessment of functioning [GAF] scale) was used according to guidelines in DSM-IV [28].

Adverse events were elicited by spontaneous reports through open-ended questions at each visit and concomitant medications were systematically assessed and documented. As in our original report, adverse effects spontaneously reported on ≥ 2 visits were considered present. Here, we report the number of adverse effects that surpassed that threshold. The following adverse effects were considered "psychiatric" adverse effects: Tense/Jittery, Agitated/Irritable, Sad/Down, Anxious/Worried, Self-Harm, and Suicidal Ideation. Weight and vital signs (systolic blood pressure-SBP, diastolic blood pressure-DBP, heart rate-HR) were obtained at each visit and an ECG was performed at baseline and endpoints. Physician raters and subjects were equally blind to treatment assignment.

Statistical Analysis

Analyses were intention to treat (ITT) with the exception that subjects must have been assessed on drug or placebo for at least 1 week. We used mixed-effects models for repeated measures as implemented in STATA [29]. To test the impact of treatment over time, models are specified with main effects of treatment (OROS-MPH vs. placebo) and time (baseline vs. endpoint) and the interaction of treatment by time. The interaction term is a test of whether the difference from baseline to endpoint was different in the OROS-MPH and the placebo groups. In order to test for moderation of response to OROS-MPH, we included additional main effects of each moderator, two-way interactions for each moderator with both treatment (OROS-MPH vs. placebo) and time (baseline vs. endpoint), and finally three-way interaction terms for each moderator (moderator by treatment by time). The three-way interaction term is a test of whether the treatment effect (estimated by the treatment by time two interaction) was different within the strata of each moderator. Any statistically significant (i.e., $P < 0.05$) three-way interaction terms, then, suggested moderation of OROS-MPH response.

For any response variables that were only measured at endpoint, we did not include any terms associated with time in regression models and fitted either ordinary least squares or logistic regression models (for continuous and binary data, respectively) at endpoint only. Here treatment response was tested with the

main effect of treatment and moderation of treatment effect was tested with a two-way interaction between treatment status and each moderator.

In this study we evaluated lifetime history of psychiatric comorbidity (mood, anxiety, or SUDs) and concomitant pharmacotherapy (antidepressants or benzodiazepines) as potential mediators of clinical response. Several features of clinical response were tested for potential moderation: change in ADHD symptoms (AISRS total score) from baseline to endpoint, change in symptoms of depression and anxiety (HAM-A and HAM-D) from baseline to endpoint, dose of study drug (OROS-MPH or placebo) at endpoint, the rate of clinical improvement (CGI-I ≤ 2) at endpoint, the rate of study completion (6 weeks) for subjects entered into the trial, the total number of adverse effects reported on ≥ 2 visits, and the rate of any psychiatric adverse effect reported on ≥ 2 visits. All moderators were tested simultaneously for each dependent measure while also correcting for age and sex in eight models (one for each measure of response). Statistical significance was determined at $P < 0.05$.

Results

As described in the primary report [30], 296 subjects were screened for participation, 227 were randomized (112 to OROS-MPH and 115 to placebo), and 223 were analyzed ($N = 109$ and $N = 114$ for OROS-MPH and placebo, respectively). In the OROS-MPH ($N = 109$) and placebo groups ($N = 114$), respectively, there was no difference in age (34.7 ± 9.2 vs. 36.4 ± 8.6 , $P = 0.2$) or sex (60% [$N = 66$] vs. 52% [$N = 59$] male, $P = 0.2$). As shown in Table 1, OROS-MPH was associated with a statistically and clinically significant ADHD response according to both symptom measures and clinically assessed improvement on the CGI. The dose of OROS-MPH was statistically significantly lower than that of placebo at study endpoint. OROS-MPH was associated with increased reports of adverse effects and a greater incidence of psychiatric adverse effects relative to placebo (Table 1, see original report for full accounting of specific adverse effects). There was no difference in symptoms of depression/anxiety between the groups from baseline to endpoint, or in the rate of study completion at 6 weeks (Table 1).

Potential moderators of treatment response examined in this analysis are presented in Table 2. There were no differences in the lifetime history of psychiatric comorbidity between the OROS-MPH and the placebo groups; subjects with currently active psychiatric comorbidity were excluded from the study. At baseline, 29 subjects (15% [$N = 16$] of OROS-MPH vs. 11% [$N = 13$] of placebo, $P = 0.5$) were receiving concomitant treatment with a non-MAOI antidepressant: amitriptyline ($N = 1$, 25 mg), bupropion ($N = 5$, 75–300 mg), citalopram ($N = 5$, 20–40 mg), fluoxetine ($N = 2$, 20 mg), paroxetine ($N = 1$, 30 mg), sertraline ($N = 8$, 50–200 mg), and venlafaxine ($N = 2$, 75 mg). Owing to the small number of subjects treated with benzodiazepines (Table 2) and the overlap of their use with antidepressants (all of the placebo subjects treated with benzodiazepines were also treated with antidepressants), we did not assess benzodiazepines in any further statistical analyses.

Table 1 Response to treatment

	OROS-MPH N = 109	Placebo N = 114	
Dose (mg/kg) (Mean $\pm$ SD)	0.97 $\pm$ 0.33	1.16 $\pm$ 0.19	<0.001
Completed 6 weeks (N [%])	86 (79)	98 (86)	0.2
Number of adverse effects (Mean $\pm$ SD) ^a	1.97 $\pm$ 1.85	1.02 $\pm$ 1.15	<0.001
Psychiatric adverse effects (N [%]) ^b	26 (24)	5(4)	<0.001
CGI-I $\leq$ 2 (N [%])	69 (63)	42 (36)	<0.001
AISRS (Mean $\pm$ SD)			
Baseline	29.7 $\pm$ 5.9	30.0 $\pm$ 6.2	0.0003 ^c
End point	15.19 $\pm$ 10.1	20.7 $\pm$ 10.6	
HAM-A (Mean $\pm$ SD)			
Baseline	4.0 $\pm$ 3.5	3.3 $\pm$ 3.1	0.99 ^c
Endpoint	3.2 $\pm$ 4.1	2.5 $\pm$ 2.7	
HAM-D (Mean $\pm$ SD)			
Baseline	4.4 $\pm$ 4.2	4.0 $\pm$ 3.9	0.89 ^c
Endpoint	3.4 $\pm$ 4.3	3.0 $\pm$ 3.3	

^aAs in our original report adverse effects spontaneously reported on ≥ 2 visits were considered present. Here, we report the number of adverse effects that surpassed that threshold.

^bThe following adverse effects were determined considered "psychiatric adverse effects: Tense/Jittery, Agitated/Irritable, Sad/Down, Anxious/Worried, Self-Harm, and Suicidal Ideation.

^cTesting drug effect from baseline to endpoint with interaction term between drug status and endpoint in mixed regression model.

The statistical significance of the three-way interaction (moderator by treatment group by time) tests for moderation of clinical response to OROS-MPH. We fitted eight models (one for each measure of treatment response) simultaneously testing for all potential moderators (all main effects, two-way interactions, and three-way interactions). In addition to the statistical significance of the three-way interaction terms, Table 3 presents the beta-coefficients (for continuous outcomes) or odds ratios (for binary outcomes) to indicate the direction and magnitude of effect. Concomitant antidepressant use at baseline was not associated with ADHD response, OROS-MPH dose, study completion rate, adverse effects, or exacerbation of anxiety/depression (Table 3). We did find nominally significant evidence that a lifetime history of mood

Table 2 Potential moderators of treatment response

	OROS-MPH N = 109 N (%)	Placebo N = 114 N (%)	P-value
Psychiatric history (lifetime)			
Mood disorder	45 (42)	44 (40)	0.8
Multiple (≥ 2) anxiety disorders	19 (18)	15 (14)	0.4
Substance use disorder	66 (61)	70 (64)	0.7
Existing concomitant pharmacotherapy			
Antidepressants	16 (15)	13 (11)	0.5
Benzodiazepines	1 (1)	3 (3)	0.3

or anxiety disorders was a moderator of ADHD symptoms and that a lifetime history of SUDs was a potential moderator of dose at endpoint.

The nominally significant findings in Table 3 are illustrated in Figures 1 and 2. The endpoint dose of OROS-MPH, but not placebo, was statistically significantly higher in ADHD adults with a lifetime history of SUD (Figure 1). Histories of depression and anxiety disorders were associated with divergent patterns of placebo response but did not moderate response to OROS-MPH (Figure 2): a history of comorbid anxiety disorders was associated with an increased placebo response, while history of comorbid major depressive disorder was associated with a decreased placebo response.

Discussion

This study sought to evaluate whether concomitant pharmacotherapy and history of mood, anxiety, or SUDs moderated response to OROS-MPH treatment in adults with ADHD. An insufficient number of subjects received concomitant benzodiazepines, but we found that concomitant antidepressant use did not interfere with OROS-MPH efficacy or tolerability. However, the endpoint dose of OROS-MPH, but not placebo, was significantly higher in ADHD adults with a history of SUD whereas histories of mood and anxiety disorders were associated with divergent patterns of placebo response.

It is reassuring that concomitant antidepressant use was not associated with ADHD response, OROS-MPH dose, study completion rate, adverse effects, or exacerbation of anxiety or depression ratings. Considering the high comorbidity between ADHD and major depression as well as anxiety disorders in clinical and community samples [6,31], many adults with ADHD with these comorbid disorders may need treatment with antidepressants. Since antidepressants (with the exception of bupropion) do not treat ADHD and stimulants do not treat depression or anxiety disorders, patients with active symptoms of both disorders may require the coadministration of both stimulants and antidepressants.

Our finding that histories of depression and anxiety disorders did not moderate response to OROS-MPH in our sample of adults with ADHD is consistent with similar findings in pediatric samples. For example Gadow *et al.* [32] reported that MPH was effective for the management of ADHD behaviors in children with mild-to-moderate anxiety or depression symptoms.

However, histories of depression and anxiety disorders were associated with divergent patterns of placebo response. A history of comorbid anxiety disorders was associated with an increased placebo response while a history of comorbid major depressive disorder was associated with a decreased placebo response. While high placebo responses are well documented in clinical trials with patients with anxiety disorders, the increased placebo response in an ADHD trial is a novel finding. Equally novel is the marked decrease in placebo response observed in ADHD subjects with a history of depression. Because these intriguing findings could be due to chance and their mechanisms of action remain unknown, they need to be confirmed in future clinical trials before firmer conclusions can be drawn.

Equally intriguing is the novel finding that the endpoint dose of OROS-MPH, but not placebo, was significantly higher in ADHD

Table 3 Moderator analysis

	Potential moderator							
	Concomitant antidepressant		Mood disorder		Multiple anxiety disorders		Substance use disorder	
	β /OR	P-value	β /OR	P-value	β /OR	P-value	β /OR	P-value
Treatment response								
Study drug dose (mg/kg)	−0.09	0.4	−0.01	0.9	−0.06	0.6	0.18	0.02
Completed 6 weeks ^a	-		1.1	0.9	3.9	0.2	0.8	0.7
Number of adverse effects	0.4	0.5	0.6	0.2	0.9	0.1	−0.03	0.9
Psychiatric Adverse Effects ^a	0.7	0.8	6.4	0.1	-		1.6	0.7
CGI-I $\leq 2^a$	3.1	0.3	2.1	0.3	0.5	0.4	0.8	0.8
AISRS	−4.3	0.3	−5.4	0.09	8.5	0.04	0.8	0.8
HAMA	−1.2	0.5	1.1	0.4	−0.2	0.9	1.1	0.4
HAMD	−0.6	0.7	−0.3	0.8	−1	0.6	0.4	0.8

^aAnalyzed with logistic regression and odds ratios (OR) are included in the table. Bold face indicates statistically significant at $P < 0.05$.

adults with a history of SUD. Although this could be a chance finding considering the many statistical tests conducted, it could suggest that the neurobiological underpinnings of substance use or prior exposure to alcohol and drugs may result in a lower sensitivity to MPH treatment requiring higher daily doses. More work is needed to test this intriguing finding.

Our findings should be considered in light of methodological limitations. The assessment of ADHD symptoms relied on self-report and the assessment of adverse effects relied on spontaneous report by subjects. However, there is evidence that self-reports of adults with ADHD correspond very well to corroborating histories provided by parents and spouses [33]. It is also possible that our flexible titration to optimal response and clear exit criteria, prevented a full spectrum of adverse effects to emerge as they might in other settings. For example, we did not find any appreciable change in symptoms of anxiety or depression, but this may have occurred if perhaps subjects left the study before any psychiatric adverse effects became serious enough to affect the HAM-A or HAM-D ratings. The number of subjects taking antidepressants was small, which limited our statistical power to fully examine their moderating effects. Since the majority of our subjects were Caucasians, our results may not generalize to other ethnic groups.

Despite these limitations, our results suggest that concomitant antidepressant use in adults with ADHD does not interfere with the safety and efficacy of OROS-MPH for the management of ADHD. While we observed some small moderating effects of histories of SUD (affecting dose), anxiety disorder (increasing placebo response), and major depression (decreasing placebo response), the benefits of treatment with OROS-MPH were minimally moderated by the variables assessed. It is overall quite remarkable

Figure 1 Lifetime history of substance use disorder moderates OROS-MPH dose.

Stratified analyses following up interactions observed in Table 3. Models predicting endpoint dose from age, sex and all moderators were conducted separately for OROS-MPH and placebo groups.

Figure 2 Lifetime history of mood and anxiety disorders moderate placebo response in adults with ADHD.

that there were so few moderating effects in this large clinical trial, which suggests a relatively homogenous clinical response to OROS-MPH in adult ADHD despite variable clinical pictures.

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Conflict of Interest

The authors have no conflict of interest.

Author Contributions

Dr Joseph Biederman was the principal investigator of the study and wrote the manuscript. Dr. Eric Mick was involved in the statistical analysis. Dr. Thomas Spencer was involved in study design,

data acquisition, writing and editing of the manuscript. Dr. Craig Surman was involved in study design, analyzing results, and writing/editing the manuscript. Dr. Stephen Faraone helped to plan the approach to statistical analyses and helped to write and edit the manuscript.

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