

Multisite Controlled Study of OROS Methylphenidate in the Treatment of Adolescents With Attention-Deficit/Hyperactivity Disorder

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Background: Despite the persistence of attention-deficit/hyperactivity disorder (ADHD) into adolescence, little is known about the efficacy and tolerability of stimulant medications in this age group.

Objective: To report the results of a multisite controlled study among adolescents with ADHD evaluating the efficacy and tolerability of osmotic-release oral system (OROS) methylphenidate.

Design: Adolescents (N=220) having a confirmed *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnosis of ADHD underwent dose titration to identify dosages of OROS methylphenidate that improved symptoms to predefined criteria. Subjects successfully completing the dose titration phase (n=177) (ie, tolerated and responded to treatment and adhered to the protocol) were randomized to receive 2 weeks' treatment with their individualized dosage of OROS methylphenidate (18, 36, 54, or 72 mg once daily) or placebo. Treatment effectiveness was mea-

sured using investigator, parent, and adolescent assessments of ADHD.

Results: A significant reduction from baseline in the investigator-rated ADHD Rating Scale, the primary efficacy measure, was found with OROS methylphenidate treatment compared with placebo. Similar findings were noted with parent- and adolescent-report measures. Based on a Clinical Global Impression improvement subscale score of much or very much improved, 52% of subjects in the OROS methylphenidate group improved compared with 31% receiving placebo. Thirty-seven percent of subjects required the maximum dosage of 72 mg/d. The incidence of drug-related adverse events was similar between the 2 study groups.

Conclusion: In adolescents, once-daily OROS methylphenidate significantly reduced ADHD symptoms and was well tolerated using dosages up to 72 mg/d.

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ATENTION-DEFICIT/HYPER-activity disorder (ADHD) is among the most commonly diagnosed and treated neurobehavioral disorders in children and adolescents. Studies indicate that ADHD affects approximately 8% to 10% of school-aged children,¹ and it persists into adolescence in approximately 70% of patients.² Children and adolescents with ADHD share many of the phenotypic characteristics of the disorder,^{2,3} although adolescents may manifest more symptoms of inattention relative to hyperactivity or impulsivity.^{4,5}

Stimulant medications are widely recommended among first-line therapies for ADHD,⁶⁻⁸ and their safety and efficacy are well established in children with ADHD.^{7,9-12} Approximately 70% of school-

aged children treated with a stimulant have a positive response,^{7,13,14} and this percentage increased in a trial instituted with another class of stimulant.¹⁵ However, as noted by Smith et al¹⁶ and by Stein and Baren,¹⁷ few studies have investigated the use of stimulant medications or other agents in adolescents with ADHD.

This study investigates the efficacy and safety of an extended-release formulation of methylphenidate, osmotic-release oral system (OROS) methylphenidate (Concerta; ALZA Corporation, Mountain View, Calif). Osmotic-release oral system methylphenidate has been shown in short-term investigations to manage symptoms of ADHD for up to 12 hours after each single daily dose in children 6 to 12 years old,¹⁸ with efficacy that is comparable to that of 3-times-daily methylphenidate.¹⁸⁻²⁰ In a longer-term trial, OROS methylphenidate (≤ 54 mg/d) showed sustained efficacy for up to 2 years without

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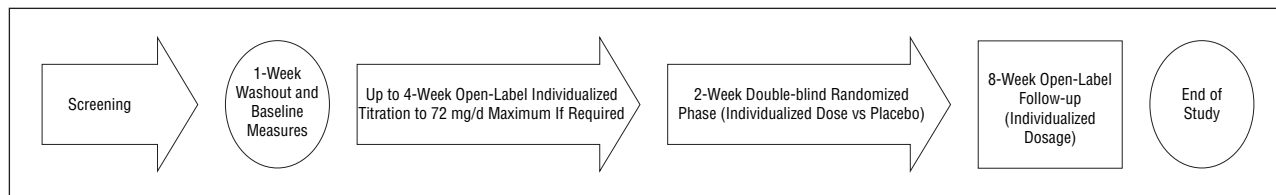


Figure 1. Study design.

undue adverse events.^{21,22} However, anecdotal reports indicate that higher dosages of stimulants may be necessary in some adolescents.¹⁴ In this study, a multi-informant assessment battery was used to assess responses to treatment with OROS methylphenidate (≤ 72 mg once daily) as reported by investigators, parents, and the adolescents. We hypothesized that OROS methylphenidate would be more efficacious than placebo in the treatment of ADHD based on investigator, parent, and adolescent rating scales.

METHODS

SUBJECTS

Adolescent outpatients aged 13 to 18 years having a diagnosis of ADHD (any subtype) were eligible for the study. Diagnosis of ADHD was based on a clinical evaluation using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*²³ criteria, confirmed by structured interview (using the behavior module of the Kiddie Schedule for Affective Disorders and Schizophrenia)²⁴ and by a Children's Global Assessment Scale²⁵ score of 41 to 70. Eligible subjects could be taking no medications for ADHD at the time of enrollment. Subjects using a behavioral modification program at the time of enrollment had to agree not to change the program or initiate a new program during the study period. Participants had to comply with the study visit schedule, and their parents or caregivers had to be willing to complete all assessments.

Excluded subjects included any adolescents with a history of nonresponse to methylphenidate treatment, hypersensitivity or significant intolerance to methylphenidate, clinically significant gastrointestinal tract problems, clinically important electrocardiographic or blood pressure measurement abnormalities, or coexisting medical conditions or concurrent medications likely to interfere with the safe administration of methylphenidate. Subjects requiring any of the following medications were excluded: clonidine or other α_2 -adrenergic receptor agonists, tricyclic antidepressants, selective serotonin reuptake inhibitors, theophylline, warfarin sodium, and anticonvulsant agents. Participants with psychiatric comorbidities were eligible for inclusion, except for those with Tourette syndrome or a family history of Tourette syndrome, an ongoing seizure disorder, bipolar disorder, psychotic disorder, a mood or anxiety disorder requiring drug therapy, alcohol or other drug abuse within the 6 months before study enrollment, an eating disorder, or marked anxiety, tension, or agitation.

Written approval of the study design was obtained from the institutional review boards for all participating centers before initiation of the study. For centers in California, approval was obtained from the California Research Advisory Panel. The study was conducted in accord with the Declaration of Helsinki and its amendments.

STUDY DESIGN

This was a multisite study (15 sites) consisting of 4 phases. These included a 1-week washout phase, an open-label dose titra-

tion phase lasting up to 4 weeks, a 2-week double-blind phase consisting of a randomized comparison of an individualized once-daily dosage of OROS methylphenidate vs placebo, and an 8-week open-label follow-up safety phase assessing treatment with OROS methylphenidate at individualized dosages (data not shown) (Figure 1).

After a 1-week washout period during which all previous pharmacotherapies for ADHD were discontinued, eligible subjects underwent a series of baseline assessments of ADHD symptoms. Subjects then entered the open-label dose titration phase, during which an individualized dosage of OROS methylphenidate was determined for each subject based on operationalized criteria of response, defined as at least 30% improvement from baseline in the investigator-scored ADHD Rating Scale (ADHD RS)²⁶ and a rating of good or excellent on the global assessment of effectiveness. The ADHD RS criterion was based on the use of an ADHD RS score of at least 30% as a definition of response in several studies²⁷⁻³¹ of stimulant and nonstimulant therapy in adults, its approximation with a Clinical Global Impression (CGI) improvement subscale score of much or very much improved,²⁷⁻³¹ and its exceeding the recent inclusion and validated use of 25% reduction in ADHD symptoms as a response criterion in children.^{26,32}

All subjects received OROS methylphenidate, 18 mg once daily, for a mean \pm SD of 7 ± 2 days. At the end of this period, ADHD symptoms were assessed by a site investigator using the ADHD RS and the global assessment of effectiveness based on interviews with the subject and parent. If the change in ADHD symptoms from baseline met the criteria for improvement, the 18-mg/d dosage of OROS methylphenidate was defined as the individualized dosage for the subject, who then immediately entered the double-blind phase of the study. If the criteria for improvement were not met and the medication was well tolerated with no safety concerns, the subject received OROS methylphenidate, 36 mg/d, for the next mean \pm SD of 7 ± 2 days. A similar procedure was followed weekly to a maximum dosage of 72 mg/d. If the criteria were not met at 72 mg/d, the subject was not permitted to continue in the study.

Subjects who successfully completed the open-label dose titration phase were assigned a randomization number within their individualized dosage level for the double-blind phase. On completion of the dose titration phase, subjects were randomized to receive placebo or their individualized dosage of OROS methylphenidate established in the dose titration phase. Investigators were supplied with packages containing the medication for each subject, identified by randomization number. Therefore, investigators and subjects were blinded as to whether a subject was receiving active medication or placebo. During the double-blind phase, ADHD symptoms, safety, and adherence were assessed at the end of each week during clinic visits, and the Child Conflict Index (CCI) was administered twice weekly by telephone interview.

Subjects were eligible to enter an 8-week open-label follow-up phase of the study and receive their individualized dosage of OROS methylphenidate after they completed the double-blind phase or discontinued the double-blind phase prematurely because of a lack of efficacy.

EFFICACY ASSESSMENTS

Six different rating scales were used to assess the efficacy of treatment during the double-blind phase of the study. The selection of scales was partly based on scales used in previous trials of OROS methylphenidate to allow comparison with studies in children,¹⁴⁻²⁰ while a scale specific to adolescents was also included. Assessments were completed at baseline and weekly during the double-blind phase of the study. Before the start of the study, all study sites participated in an investigators' meeting at which each scale was reviewed and discussed.

ADHD RS

The ADHD RS^{26,33} is a validated instrument that has been shown to be medication sensitive among adolescents with ADHD in recent clinical trials.^{34,35} It consists of an 18-item list of core ADHD symptoms corresponding to the *DSM-IV* diagnostic criteria.³³ Items are scored on a 4-point scale (from 0, never or rarely, to 3, very often). Investigator-rated and parent-rated versions of the ADHD RS were used, with changes in the investigator-rated score serving as the primary efficacy variable. Response to treatment was defined a posteriori as a decrease of at least 30% in the investigator ADHD RS score.

Conners-Wells Adolescent Self-report of Symptoms Scale

The Conners-Wells Adolescent Self-report of Symptoms Scale^{36,37} is a validated 87-item self-report assessment containing the following 9 subscales: family problems, emotional problems, conduct problems, anger control problems, hyperactivity, ADHD index, *DSM-IV* ADHD total score, *DSM-IV* ADHD inattention, and *DSM-IV* ADHD hyperactivity-impulsivity.^{36,37} Items are scored on a 4-point scale (from 0, not true, to 3, very much true).

Child Conflict Index

The CCI³⁸ is a validated measure of family conflicts in the home and is completed by parents. It consists of 42 items (for boys) or 36 items (for girls) reflecting attention-seeking and conflictual behavior, as well as negativity and withdrawal. Items are scored as yes (1 point) or no (0 points). The CCI has been validated in children³⁸ and has demonstrated clinical usefulness in detecting the effects of methylphenidate use in children.³⁹ The CCI was administered during telephone interviews.

Global Assessment of Effectiveness

The investigator-rated global assessment of effectiveness uses a 4-point scale (0, poor; 1, fair; 2, good; and 3, excellent) to respond to the question: "How effective do you feel the current treatment is at the present time?" The question is answered by the investigator.

CGI Improvement Subscale

The investigator-rated CGI improvement subscale⁴⁰ uses a 7-point scale (from 7, very much worse, to 1, very much improved) to evaluate the response of the subject to the current treatment compared with baseline. The CGI improvement subscale has been shown to be sensitive to medication effects in children⁴¹ and in adults.³¹ Based on previous studies in children,^{26,32,42} the primary efficacy measure was defined as the change in the total investigator-rated ADHD RS score from baseline to the end of the 2-week double-blind period.

SAFETY ASSESSMENT

Subjects' heart rate and blood pressure were recorded at weekly visits throughout the study. Subjects with persistent (2 consecutive visits) systolic or diastolic blood pressure at the 95th percentile or higher for age, sex, and height were discontinued from the study. In addition, each subject underwent electrocardiography at screening and at the end of the double-blind phase of the study. Spontaneous reports to the investigator of adverse events were recorded at weekly visits.

STATISTICAL ANALYSIS

The study aimed to enroll approximately 200 subjects. Allowing for an expected 20% rate of attrition, this would ensure that the study retained at least 90% power to detect a mean difference of 7 units in the total ADHD RS score between the OROS methylphenidate-treated and placebo groups. This was based on a 2-sample, 2-sided *t* test with $\alpha = .05$ and an SD of 12.

Changes in the total scores for the ADHD RS, Conners-Wells Adolescent Self-report of Symptoms Scale, and CCI, as well as changes in heart rate and systolic and diastolic blood pressure from baseline to the end of the double-blind phase of the study, were analyzed using analysis of covariance models with treatment status (drug or placebo) and study site as factors and the corresponding baseline total score as the covariate. Possible treatment \times site interactions were examined at a significance level of $\alpha = .10$. The last observation carried forward technique was used for all assessments in the double-blind phase (except for the CGI improvement subscale, which was assessed only once, at the end of the double-blind phase). Unplanned analyses of response rates at the end of the double-blind phase were conducted using the Cochran-Mantel-Haenszel correlation statistic and were stratified by study site.

RESULTS

SUBJECTS

The disposition of subjects in the study is shown in **Figure 2**. Two hundred twenty subjects were enrolled in the study between April 1, 2002, and October 15, 2002. Twenty-seven subjects (12%) withdrew from the dose titration phase for the following reasons: adverse events (8 subjects), withdrawal of consent (7 subjects), protocol violations (6 subjects), administrative reasons (3 subjects), lost to follow-up (2 subjects), and unable to swallow medication (1 subject). Eleven subjects (5%) did not meet defined criteria for improvement at 72 mg/d of OROS methylphenidate and were ineligible to continue in the double-blind phase. Of the 182 subjects (83%) who successfully achieved the criteria for improvement at the dose titration phase, 177 subjects were randomized into the double-blind phase; 5 subjects reached the criteria after the double-blind phase was closed and were not randomized. Of the 177 randomized subjects, one subject did not enter the double-blind phase and efficacy data were not collected for another subject. Therefore, 175 subjects were included in the efficacy analysis of the double-blind phase, but 177 subjects were included in the dosage and safety analyses.

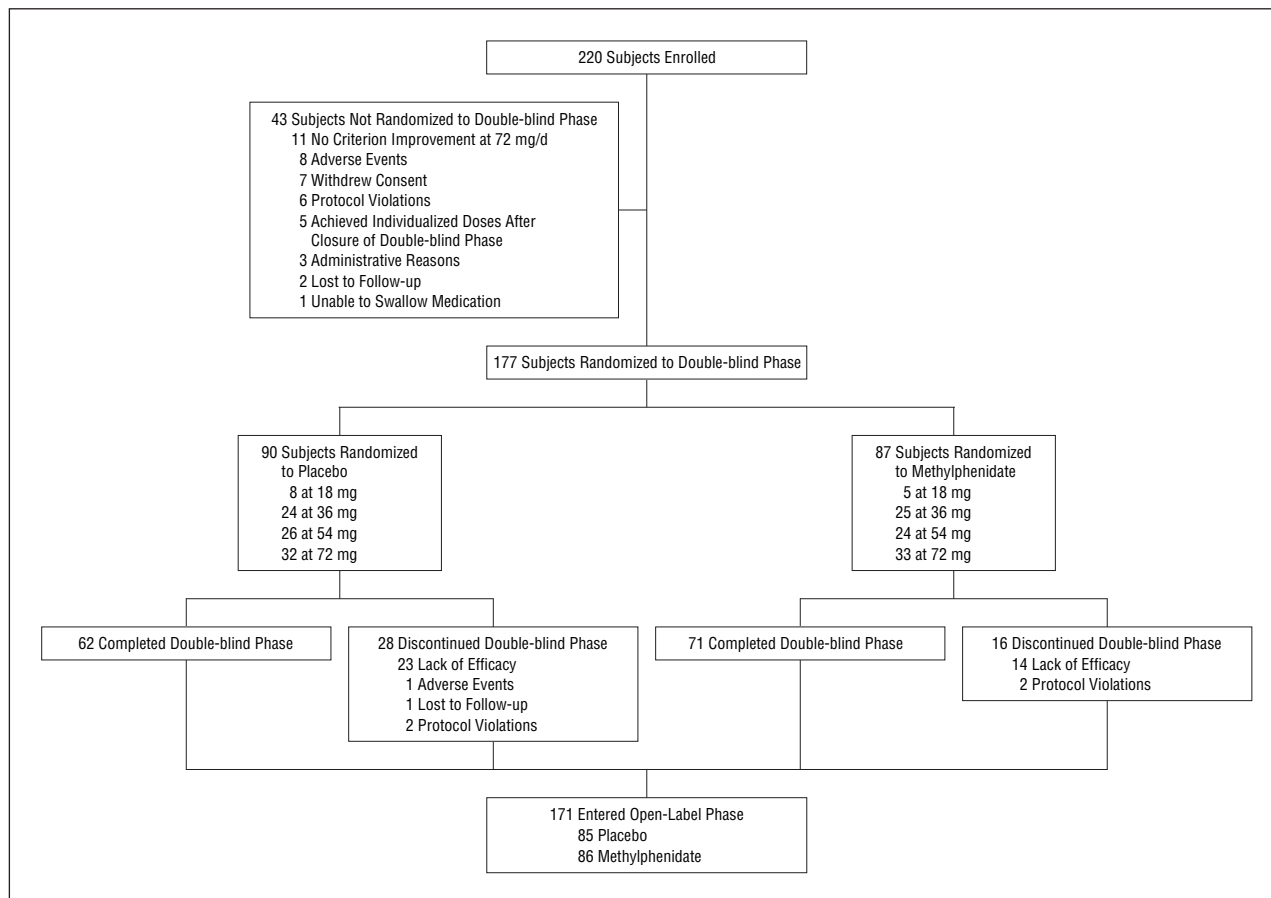


Figure 2. Disposition of subjects.

DOSE TITRATION PHASE

One hundred seventy-seven subjects were assigned an individualized dosage of OROS methylphenidate (13 subjects [7.4%] at 18 mg/d; 49 subjects [28%] at 36 mg/d; 50 subjects [28%] at 54 mg/d; and 65 subjects [37%] at 72 mg/d). The mean investigator ADHD RS score for these subjects at the end of the dose titration phase was 10.64 compared with 31.26 at baseline (a change of -66%) ($t_{174}=34.6$, $P<.001$, paired t test).

DOUBLE-BLIND PHASE

The demographic and baseline characteristics of subjects for the double-blind phase are given in **Table 1**. The mean age of subjects was 14.6 years, and most subjects were white and male. Eighty-seven subjects were randomized to receive OROS methylphenidate, and 90 were randomized to receive placebo. Both groups were similarly matched for demographic characteristics and severity of ADHD at baseline, although there were significantly more male subjects in the placebo group compared with the OROS methylphenidate-treated group ($P<.04$).

Eighty-two percent (71/87) of subjects in the OROS methylphenidate-treated group completed the 2-week double-blind phase. The main reason for withdrawal was lack of efficacy (14 subjects); 8 of these subjects were receiving the highest permitted OROS methylphenidate dos-

age. In the placebo group, 69% (62/90) of subjects completed the double-blind phase; the main reason for withdrawal was lack of efficacy (23 subjects). Other reasons for withdrawal in the placebo group were adverse events (1 subject, lost to follow-up (2 subjects), and protocol violations (2 subjects). The difference in retention rate between treatment groups was marginally significant ($P=.05$). Of the 37 subjects who discontinued the double-blind phase early because of a lack of efficacy, all elected to enter the open-label follow-up phase, receiving their unblinded, individualized dosage of OROS methylphenidate. Of the 171 subjects who entered the open-label follow-up phase, only 3 withdrew because of a lack of efficacy.

EFFICACY DURING THE DOUBLE-BLIND PHASE

Treatment with OROS methylphenidate was associated with clinically and statistically significant improvement from baseline compared with placebo ($F_{1,158}=11.21$, $P=.001$) for the primary efficacy variable of mean change from baseline in investigator ADHD RS score (**Table 2**). Statistically significant differences between the OROS methylphenidate-treated and placebo groups ($P<.05$) were observed for all other efficacy measures. There were no significant site \times treatment interactions for the ADHD outcome measures. Post hoc responder analyses indicated that the percentages of subjects responding to treatment were significantly greater for OROS methylpheni-

Table 1. Demographic and Baseline Characteristics of the Cohort*

Characteristic	All Subjects (N = 177)	Methylphenidate Group (n = 87)	Placebo Group (n = 90)	P Value
Sex				
Male	142 (80.2)	64 (73.6)	78 (86.7)	.03†
Female	35 (19.8)	23 (26.4)	12 (13.3)	
Age, y	14.6 ± 1.5	14.8 ± 1.6	14.5 ± 1.4	.16‡
Race				
White	133 (75.1)	65 (74.7)	68 (75.6)	.19†
Black	24 (13.6)	9 (10.3)	15 (16.7)	
Other	20 (11.3)	13 (14.9)	7 (7.8)	
Height, mean, cm	168.1	168.5	167.7	.64‡
Weight, mean, kg	66.0	66.2	65.7	.96‡
ADHD RS score§				
Investigator	31.26	31.55	30.99	.70
Parent	30.82	30.65	30.99	.93
Parent Child Conflict Index	0.272	0.286	0.259	.30
Subject Conners-Wells Adolescent Self-report of Symptoms Scale score	91.96	89.81	94.02	.58

Abbreviation: ADHD RS, Attention-Deficit/Hyperactivity Disorder Rating Scale.

*Data are given as number (percentage) or as mean ± SD unless otherwise indicated.

† χ^2 Test.

‡1-Way analysis of variance.

§Baseline data are for the population in the efficacy analysis of the double-blind phase (n = 175).

Table 2. Symptoms at Baseline and at the End of the Double-blind Phase*

Assessment	Group	Baseline	End of the Double-blind Phase	Mean Change†	% Change	ANOVA‡
ADHD RS score	Investigator					$F_{1,158} = 11.21, P = .001$
	OROS methylphenidate	31.55 ± 9.42	16.62 ± 11.03	-14.93 ± 10.72	-47	
Placebo	30.99 ± 9.64	21.40 ± 13.44	-9.58 ± 9.73	-31		
Parent	OROS methylphenidate	30.65 ± 9.81	16.65 ± 11.07	-14.00 ± 10.31	-46	$F_{1,158} = 7.29, P = .008$
	Placebo	30.99 ± 11.55	20.84 ± 13.58	-10.14 ± 10.00	-33	
Parent Child Conflict Index	OROS methylphenidate	0.286 ± 0.174	0.188 ± 0.145	-0.098 ± 0.189	-34	$F_{1,157} = 8.05, P = .005$
	Placebo	0.259 ± 0.182	0.247 ± 0.206	-0.016 ± 0.150	-6	
Subject Conners-Wells Adolescent Self-report of Symptoms Scale score	OROS methylphenidate	89.81 ± 41.44	57.57 ± 41.07	-31.70 ± 28.96	-35	$F_{1,157} = 11.00, P = .001$
	Placebo	94.02 ± 49.20	75.32 ± 52.20	-18.70 ± 26.94	-20	

Abbreviations: ADHD RS, Attention-Deficit/Hyperactivity Disorder Rating Scale; ANOVA, analysis of variance.

*Data are given as mean ± SD unless otherwise indicated.

†From baseline to the end of the double-blind phase.

‡Comparing change from baseline for the methylphenidate vs placebo groups.

date compared with placebo for all efficacy outcome measures (**Table 3**).

ADVERSE EVENTS DURING THE DOSE TITRATION AND DOUBLE-BLIND PHASES

The most frequently reported adverse events considered by investigators to be treatment-related during the open-label dose titration phase of the study included headache (25%), decreased appetite (21%), insomnia (15%), and abdominal pain (9%). During the double-blind phase, 16 subjects (18%) receiving OROS methylphenidate and 14 subjects (16%) receiving placebo reported at least 1 adverse event deemed by investigators to be probably or possibly related to study medication. **Table 4** gives all treatment-related

adverse events in the double-blind phase that occurred in at least 2% of subjects in either study group.

Serious adverse events were reported in only 1 subject during the open-label dose titration phase of the study. While being treated with OROS methylphenidate, 18 mg/d, a 16-year-old female subject with a history of depression and suicidal ideation threatened suicide on the third day of medication use after an argument with her mother. A decision was made to discontinue study medication, and the symptoms resolved. The investigator considered the recurrence of depression to be possibly related to treatment and the suicidal ideation unlikely related to study medication. No serious adverse events were reported during the double-blind phase. No subject experienced clinically important effects on electrocardiographic indexes, heart rate, or blood pressure during the study.

Table 3. Response Rates for Efficacy Assessments During the Double-blind Phase

Assessment	Criterion for Response	Response Rate, %		P Value*
		Methylphenidate Group	Placebo Group	
Investigator				
ADHD RS	≥30% Decrease from baseline	73.3	56.2	$\chi^2 = 4.6, P = .03$
Global assessment of effectiveness	Subjects with good or excellent rating	51.2	32.6	$\chi^2 = 8.1, P = .004$
Clinical Global Impression improvement subscale	Subjects with much improved or very much improved rating†	51.8	31.0	$\chi^2 = 6.4, P = .01$
Subject Connors-Wells Adolescent Self-report of Symptoms Scale	≥30% Decrease from baseline	62.8	41.6	$\chi^2 = 7.4, P = .007$

Abbreviation: ADHD RS, Attention-Deficit/Hyperactivity Disorder Rating Scale.

*Cochran-Mantel-Haenszel test comparing the methylphenidate vs placebo groups.

†Based on a 7-point scale (very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse).

COMMENT

The results of this short-term multisite study involving a large group of adolescents titrated to individualized dosages of OROS methylphenidate indicate that OROS methylphenidate is associated with clinically and statistically significant improvement in ADHD compared with placebo, as measured by investigator, parent, and adolescent assessments. A large number of adolescents (37%) required 72 mg/d of OROS methylphenidate. This dosage provided effective treatment without increased risk of adverse events.

The treatment efficacy demonstrated in this trial is consistent with findings from smaller investigations among adolescent populations¹⁶ demonstrating therapeutic benefits of methylphenidate for ADHD. A placebo-controlled crossover study⁴³ involving 45 adolescents with ADHD who received 1 of 3 dosages of methylphenidate 3 times daily for 6 weeks demonstrated that 78% to 91% of subjects achieved beneficial effects from methylphenidate treatment. Similarly, a review¹⁶ of 8 controlled studies of methylphenidate use among adolescents reported a mean effect size for ADHD symptoms of 0.94 (range, 0.13-3.00), which is at the top of the range (0.47-0.96) reported in a meta-analysis⁴⁴ of studies among children. The aggregate literature involving more than 150 adolescents from 9 controlled studies thus indicates a highly significant effect of immediate-release methylphenidate on improving ADHD symptoms and functioning in adolescents. The present study extends the literature by evaluating a once-daily formulation of methylphenidate at dosages of up to 72 mg/d among a large patient population from multiple sites.

The response rate (based on the CGI improvement subscale) of 52% achieved in this study is similar to that reported in a previous multisite study²⁰ of OROS methylphenidate use (response rate, 47%) among school-aged children (6-12 years old),²⁰ as well as in the Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder,⁴⁵ in which most children received immediate-release methylphenidate 2 to 3 times daily. The consistency in response rates of these methylphenidate trials demonstrates comparable effective-

Table 4. Treatment-Related Adverse Events During the Double-blind Phase Reported in at Least 2% of Subjects in Either Study Group*

Event	Methylphenidate Group (n = 87)	Placebo Group (n = 90)
Headache	3 (3.4)	6 (6.7)
Decreased appetite	2 (2.3)	0
Insomnia	4 (4.6)	0
Abdominal pain	1 (1.1)	2 (2.2)
Nausea	1 (1.1)	2 (2.2)
Asthenia	0	2 (2.2)
Diarrhea	2 (2.3)	0

*Data are given as number (percentage).

ness in children and in adolescents. However, a higher placebo response was observed in our study compared with a study²⁰ among children (31% vs 17%). There are several possible explanations for this finding. First, as observed in the Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder,⁴⁵ subjects may have had improved ADHD symptoms or psychosocial carryover effects as a consequence of participation in our study, medication titration, and regular meetings with study personnel. Second, our study was conducted partially during the summer, and this may have resulted in less stress on the adolescents and overall improvement in both study groups. Third, it may be that more sensitive measures of attention are needed for adolescents with ADHD compared with children. Adolescents are generally less likely to display overt hyperactivity, and parents or investigators might consider this reduced hyperactivity in their evaluation of treatment effects.⁴⁶ The placebo response in our study was lower (a change of -20%) for subject-reported ratings, and there was virtually no placebo response to the CCI (a change of -6%). Fourth, in contrast to standard placebo-controlled, parallel-group trials, subjects in our study were transitioned to placebo from their lowest effective dosages, determined during open-label dose titration. It is possible that any decline in function associated with this

transition may not have been readily perceptible to investigators or parents performing the ratings.

As expected, there was a high degree of correspondence between investigator and parent ADHD RS scores because investigator ratings were based on parent ratings and on the results of interviews with parents and subjects. However, changes in parent-rated CCI scores and in subject-rated Conners-Wells Adolescent Self-report of Symptoms Scale scores also showed significant improvement over baseline for OROS methylphenidate treatment compared with placebo. The improvement in adolescent self-report measures suggests that patient self-reports may be useful for assessing treatment outcomes. The changes from baseline reported by adolescent subjects in the OROS methylphenidate – treated and placebo groups seemed lower than those recorded by investigators and parents. The implications of these response differences for the sensitivity and specificity of self-report measures need to be determined, as our results are contrary to the findings of other researchers.⁴⁷⁻⁴⁹ The ability of adolescents to accurately report their symptoms warrants further investigation. If adolescents are able to reliably assess the effectiveness of their ADHD medication, self-reports could provide an important means of evaluating treatment outcomes as patients age and become more independent from teachers.

Teacher ratings were not included because of concerns about privacy and the difficulties of obtaining information from multiple teachers involved in an adolescent's education. Although teacher ratings are essential for assessing ADHD in studies of children up to 12 years old, they may be less critical in the evaluation of older patients because of the reduced amount of daily contact. The availability of a reliable self-report measure³⁷ and recent findings of the sensitivity of parent reporting in evaluating extended-release stimulant medications^{20,32,41,42} suggest that adequate assessment of symptoms could be achieved without teacher ratings.

Although our study did not assess dose-response relationships with randomized dosages of OROS methylphenidate, the results of the dose titration phase of the study indicate that some adolescents benefit from higher absolute doses. This higher dosing is consistent with the greater body weight of adolescents. Bostic et al³⁴ demonstrated robust improvement in ADHD symptoms among adolescents who were using higher absolute doses (but similar weight-corrected doses) of pemoline relative to younger children. However, Evans et al⁴³ found that although some adolescents benefited from higher methylphenidate dosages, for most subjects there was little additional benefit for increasing dosages above 25 mg/d. The scarcity of data among adolescents makes it difficult to determine whether a relationship exists between weight and clinical response, or whether additional factors such as the presence of comorbidities or greater executive functioning affect dosing requirements as patients age. Regardless, the present findings suggest that adolescents may require higher absolute doses than younger children, similar to the dose-dependent variation in response to pharmacotherapy that has been observed among adults with ADHD.⁵⁰

Dosages of OROS methylphenidate up to 72 mg administered once daily were well tolerated during our initial

dose titration and the controlled study, with adverse events similar to those previously reported in controlled trials of OROS methylphenidate use among children aged 6 to 12 years.¹⁸⁻²⁰ Moreover, no subjects taking active drug discontinued treatment during the double-blind phase secondary to adverse events. There were no clinically important effects on electrocardiographic indexes, heart rate, or blood pressure, consistent with studies¹⁸⁻²⁰ of OROS methylphenidate use among children. Although spontaneous reporting may underestimate the incidence of adverse events, the adverse event profile of OROS methylphenidate use in our study is similar to that which has been well established for immediate-release methylphenidate.⁵¹⁻⁵³

The case of suicidal ideation observed in our study was judged not likely to be related to treatment with OROS methylphenidate by an investigator. This patient had a history of depression and suicidal ideation, and it is likely that the patient's actions stemmed from an underlying idiopathic depression. Depression is a common comorbid condition associated with ADHD, with prevalence estimates for depression among patients with ADHD as high as 44%.^{54,55} A modest association between ADHD and increased risk for suicide has also been reported.⁵⁶

The findings in this study should be tempered against the methodological limitations of the study. Adolescents with unstable psychiatric and medical disorders and clinically important concurrent psychiatric comorbidity necessitating treatment were excluded from the study. Also excluded were subjects with a history of nonresponse to methylphenidate, as it was not considered ethical to enroll subjects who were unlikely to respond to treatment. Accordingly, our findings may not be generalizable to clinical practice. Moreover, data on exposure to stimulants before study entry were not collected in this study; thus, the possible effect of medication history on outcome cannot be assessed.

Two features of the study design may have biased the results toward improved efficacy and tolerability in the double-blind phase. First, a positive bias may have resulted from enrollment of only subjects who could tolerate OROS methylphenidate and experienced efficacy during the dose titration phase. However, only 11 (5%) of 220 subjects were discontinued from the study after the dose titration phase because of failure to meet the defined criteria for improvement at 72 mg/d. Second, the fact that subjects were titrated to their individualized dosage before the double-blind phase of the study may have biased the results toward a positive response in the double-blind phase. However, the upward dosing of the medication in the dose titration phase was determined by a threshold for improvement and not dosed to optimal outcome, probably biasing for a less robust outcome. Nevertheless, the substantial placebo effect observed in the double-blind phase of this study suggests that the results may have been positively biased toward improved efficacy. This placebo effect limits our ability to gauge the true extent of improvement with OROS methylphenidate therapy in the present study.

The attrition rate seen in both arms of the double-blind phase, although higher in the placebo group, may have affected the study results. In particular, discontinuation from the double-blind phase because of a per-

ceived or real lack of efficacy, the primary reason for attrition, may have been biased by the knowledge that subjects who discontinued the study early could enter the open-label follow-up phase of the study and receive active study medication. This is supported by the fact that 97% (171/177) of subjects from the double-blind phase entered the open-label follow-up phase of the study and only 3 subjects (1.82%) of 177 withdrew from the open-label follow-up phase because of a lack of efficacy compared with 16% (14/87) of the subjects receiving OROS methylphenidate in the double-blind phase. However, in the dose titration phase, 5% (11/220) of subjects did not achieve an adequate response to OROS methylphenidate at the highest dosage tested, indicating that a small number of subjects experienced a true lack of efficacy.

The conclusions from the open-label follow-up safety analysis of this study are limited by the fact that the study was not powered to detect differences in adverse events between active treatment and placebo. The short duration of the double-blind phase also may have limited the incidence of adverse events reported and may have decreased the likelihood of detecting potential rare adverse events. In addition, the rates of adverse events reported for OROS methylphenidate use during the double-blind phase may have been underestimated, because subjects entering this study phase were already stabilized on an effective and tolerated dosage of medication and 8 subjects who could not tolerate OROS methylphenidate had been discontinued during the open-label dose titration phase.

CONCLUSIONS

The results of this multisite controlled clinical study indicate that OROS methylphenidate treatment produces clinically and statistically significant improvement in ADHD among adolescents, as assessed by multiple raters. The study also demonstrates the efficacy and tolerability of a high OROS methylphenidate dosage, 72 mg/d, in this age group. Longer-term studies on the effectiveness and tolerability of use of stimulant medications among adolescents will increase awareness of the appropriate management of ADHD in this understudied age group.

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There's no exact time when it is important to start solid food. Fifty years ago it was begun when a baby was a year old.
—From the *Pocket Book of Baby and Child Care* by Benjamin Spock, MD, 1947