A Double-Blind, Placebo-Controlled, Crossover Study of Osmotic Release Oral System Methylphenidate in Adults With ADHD With Assessment of Oppositional and Emotional Dimensions of the Disorder

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Background: The realization that attention-deficit/hyperactivity disorder (ADHD) often persists into adulthood has led to increased frequency of diagnosis and treatment in adults. Osmotic release oral system (OROS) methylphenidate is a long-acting stimulant demonstrated to be effective in the treatment of children and adolescents with ADHD.

Method: Forty-seven adults entered and 41 completed this double-blind, placebo-controlled, crossover trial of OROS methylphenidate. Each double-blind arm lasted 4 weeks; data were collected from August 2004 through December 2005. Subjects met both DSM-IV-TR and Utah Criteria for ADHD in adults. Outcome measures included the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS), the adult ADHD-Rating Scale (ADHD-RS), and the Clinical Global Impressions-Improvement scale (CGI-I). At baseline, subjects were categorized as having significant emotional symptoms with the WRAADDS and/or significant oppositional-defiant symptoms using a self-report scale assessing the DSM-IV criteria for oppositional defiant disorder.

Results: 17% of the sample (N = 8) had ADHD alone, 38% (N = 18) had ADHD plus significant emotional symptoms, and 40% (N = 19) had ADHD with both significant emotional and oppositional symptoms. At a mean ± SD dose of 64.0 ± 23.3 (0.75 mg/kg), OROS methylphenidate proved superior to placebo for all clinical measures: total WRAADDS score decrease of 42% versus 13%, respectively, $p < .001$ and total ADHD-RS score decrease of 41% versus 14%, respectively, $p = .003$, plus the subscales addressing inattention, hyperactivity/impulsivity, and emotional dysregulation.

Conclusions: OROS methylphenidate proved effective in treating adult ADHD. ADHD alone was relatively uncommon. Over 80% of our patients had ADHD with a combination of emotional and/or oppositional symptoms.

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Attention-deficit/hyperactivity disorder (ADHD) is a common childhood illness, which often continues into adulthood.[1,2] Several medications have proven effective; however, stimulants continue to be the most common treatment for children and adults with ADHD. Among the stimulants, methylphenidate was the first medication demonstrated to be effective for adults with ADHD,[3] and it remains at least as effective as other treatments.

Unfortunately, the very short half-life of immediate-release methylphenidate requires that, for an optimum response, it should be administered at least 3 times a day or even more often, particularly in adults. Such frequent administration causes major difficulties in treatment compliance and has produced efforts to develop sustained-release formulations of methylphenidate such as osmotic release oral system (OROS) methylphenidate.

OROS methylphenidate is an extended-release form of racemic methylphenidate. It is designed to provide efficacy for 12 hours with once-a-day administration. Because of its unique drug delivery mechanism, OROS methylphenidate produces an initial release of methylphenidate, followed by increasing plasma methylphenidate concentration across the day, after which, a gradual decrease begins. It has been proposed that the increasing plasma concentrations overcome tolerance or tachyphylaxis to the medication that might actually develop over periods as short as 1 day. Also, this gradually rising

pharmacokinetic profile might produce superior efficacy versus other sustained-release stimulant formulations.[4]

Studies have documented that ADHD is associated with a confusingly wide array of other disorders, including oppositional defiant disorder (ODD); conduct disorder[5]; specific learning disabilities (e.g., dyslexia); substance abuse[6]; various anxiety disorders, including obsessive-compulsive disorder; major depression; dysthymia; and bipolar disorder.[7,8] This assortment of conditions raises a multiplicity of questions regarding proper assessment, treatment, etiology, and prognosis.

One approach in thinking about this diversity was published by Jensen et al.[9] who presented data from the Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder (MTA), a National Institute of Mental Health–funded multicenter study. They reported that childhood ADHD could be viewed as most frequently having dimensions of associated anxiety, ODD, or conduct disorder. Jensen et al.[9] analyzed the impact that these comorbid externalizing and internalizing disorders had upon the clinical correlates, etiology, course, and outcome of childhood ADHD. They then proposed that patients with ADHD could be divided into 4 major groups: ADHD alone, ADHD combined with an anxiety disorder, ADHD combined with ODD and/or conduct disorder, and ADHD combined with both comorbid conditions.[9]

While improvement in symptoms of inattention and hyperactivity remain critical and the most frequently reported outcome measures in ADHD, problems in these other dimensions may actually precipitate the need for treatment. Compared with the symptoms of inattention and hyperactivity, treatment of these other dimensions is needed equally across all waking hours, not primarily during work or school. Some studies have shown that childhood ODD responds to treatment in parallel to the attentional and hyperactive symptoms of childhood ADHD.[9,10] Clinical experience suggests that this is also true in adults. At times, these changes are dramatic, as documented in the personal accounts reported by Wender.[11]

We recently reported that, in a large, multicenter atomoxetine study of adults with ADHD, a significant subgroup displayed a high level of nonspecific emotional symptoms that we called "emotional dysregulation."[12] These patients had mood lability, mild periods of depression, irritability, problems with temper control, overreaction to stress, and frequent feelings of frustration. These symptoms have been described as part of the Utah Criteria for ADHD in adults.[11] Such symptoms were previously noted in early descriptions of minimal brain dysfunction and are rated by the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS).[11] In this clinical trial, these nonspecific emotional symptoms responded to treatment (atomoxetine vs. placebo) in parallel with the attentional and hyperactive symptoms.[12] Data from the MTA also documented improvement in externalizing and internalizing symptoms coincident with effective treatment for overall ADHD symptoms.[9]

Conversely, most studies of ADHD do not adequately assess these common, additional dimensions either at baseline or endpoint. Consequently, in this study, we have attempted to explore the efficacy of OROS methylphenidate and also to evaluate the presence of associated emotional dysregulation and ODD symptoms in adults with ADHD.

The primary purpose of this study was to assess the efficacy of OROS methylphenidate upon adult ADHD as measured by the WRAADDS, the adult ADHD-Rating Scale (ADHD-RS),[13] and the Clinical Global Impressions-Improvement scale (CGI-I).[14]

The secondary goals of this study were to explore emotional dysregulation and oppositional impairment in adults with ADHD by addressing the following: (1) what percent of these adults with ADHD showed significant oppositional-defiant symptoms and/or emotional dysregulation and (2) was OROS methylphenidate associated with improvement in subjects with these associated difficulties?

METHOD

The University of Utah Institutional Review Board reviewed and approved the study. This was a placebo-controlled trial of OROS methylphenidate containing a screening/baseline phase followed by a double-blind, crossover phase with two 4-week arms. Data were collected from August 2004 through December 2005. During the double-blind, crossover phase, subjects were randomly assigned to 1 of 2 groups in a double-blind manner: placebo or OROS methylphenidate. At the end of 4 weeks, subjects were crossed to the other treatment arm for an additional 4 weeks. Subjects were seen weekly. Subjects were given 2 bottles of study medication (labeled bottle A or B). Bottle A contained 18 mg of OROS methylphenidate or placebo. Bottle B contained 27 mg of OROS methylphenidate or placebo. The use of these bottles allowed subjects to be started at 18 mg per day and to have the dose increased every 2 to 3 days by 9 mg on the basis of response and tolerance up to a maximum dose of 90 mg per day. Once a patient was rated as much improved or better on the CGI-I or improved 50% on the WRAADDS, the dose remained constant for the remainder of that treatment arm. Generally, a stable dose was obtained in 2 weeks and held constant the last 2 weeks.

Study Population

We planned to enroll sufficient subjects to have 40 complete both phases. The subjects were required to have

a current diagnosis of adult ADHD using DSM-IV-TR criteria for current ADHD based on the Conners Adult ADHD Diagnostic Interview for DSM-IV[15] with at least moderate ADHD symptoms and the Utah Criteria for ADHD in adults. Subjects were between 18 and 65 years of age. Female subjects were eligible to enter and participate in this study if they were of non–childbearing potential or agreed to use an approved form of contraception. The following DSM-IV Axis I diagnoses were exclusionary: current diagnosis of major depressive disorder, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, bipolar disorder, schizophrenia, or other psychotic disorder. Subjects with a seizure disorder were also excluded. Subjects with hyperthyroidism or hypothyroidism were excluded. Finally, subjects with significant medical conditions likely to become unstable during the trial or likely to be destabilized by treatment with methylphenidate (e.g., cardiovascular disease) were excluded.

Measures

The Parent Rating Scale (PRS)[11] and the Wender Utah Rating Scale (WURS)[11] were used to verify childhood symptoms of ADHD in the subjects before randomization. Retrospective determination of childhood ADHD for adults is a challenge for the clinician. Sometimes, it is approached by querying adults about their childhood symptoms. However, the accuracy or recall of specific diagnostic signs from such an early age has proven problematic. In contrast, the PRS requires that the patient's mother or other parenting figure rate the patient as he or she had been between the ages of 6 and 10. The use of norms indicates that a score of 12 or greater places the patient in the 95th percentile, making it likely that he or she met criteria for and is likely to have suffered from childhood ADHD. The second rating scale, the WURS, is a self-rating instrument of 61 items on which the adult rates his or her own childhood behavior and symptoms. The scale has proven useful when there is no parent to query using the PRS. Like the PRS, scores in the 95th percentile of the WURS have proven useful in the retrospective identification of childhood ADHD.

The WRAADDS, the ADHD-RS, and the CGI-I were used to assess the efficacy of OROS methylphenidate on ADHD symptoms.

The self-report ADHD scale reported in this article mirrors items from both the WRAADDS and the WURS. The scale is being developed as an adult-oriented questionnaire that assesses the 7 symptom areas of the WRAADDS as well as symptoms in 3 other areas: oppositional-defiant symptoms, academic impairment, and social functioning. The questionnaire uses a 5-point scale ranging from 0 = none to 4 = very much. Copies of this scale are available from the corresponding author (F.W.R.).

The Weissman Social Adjustment Scale-Self Report (SAS-SR)[16] was used to assess social adjustment. This scale consists of 54 questions addressing work, social and leisure, marital, parental, extended family, and economic variables. Although there is minor variability, most ratings range from 1 to 5. A score of 1 always indicates no impairment, and higher ratings indicate more impairment. In general, a score of 3 or greater indicates impairment that is clinically significant, and we defined scores equal to 3 or greater as impaired in our categorical descriptions of this scale.

Vital signs (blood pressure, heart rate, and weight) were measured at each visit. The presence of adverse events was assessed at each interview. Spontaneously reported adverse events were also documented.

Subjects were categorized as having significant emotional and/or oppositional-defiant symptoms at baseline in the following manner. Emotional dysregulation was defined using previously published criteria[12] of scores greater than or equal to 7 on the 3 WRAADDS subscales of temper, mood instability, and emotional overreactivity. Classification of oppositional impairment was defined in a 2-step process. First, subjects averaging at least moderate impairment on the 8 symptoms of oppositional impairment on the self-report ADHD scale were identified. Second, the history of these subjects was reviewed by both the treating psychiatrist and the staff to confirm the assessment.

Using these categorizations, 3 subgroups were developed as follows: (1) subjects meeting criteria for adult ADHD but not criteria for emotional dysregulation or oppositional impairment (ADHD alone), (2) subjects meeting criteria for both ADHD and emotional dysregulation but not criteria for oppositional impairment (ADHD + ED), and (3) subjects meeting criteria for ADHD, emotional dysregulation, and oppositional impairment (ADHD + ED + ODD). Two subjects did not fit in any of these 3 subgroups and were not used in the subgroup analyses.

Data Analysis and Statistical Procedures

Baseline differences for the 3 subgroups (ADHD alone, ADHD + ED, and ADHD + ED + ODD) as well as subjects with or without oppositional impairment were calculated using analysis of variance (ANOVA). The relationship between oppositional impairment and the 3 ADHD factors of the WRAADDS (attention, hyperactivity/impulsivity, and emotional dysregulation) was assessed using Pearson's product-moment correlation coefficient.

The primary objective of comparing the efficacy of OROS methylphenidate versus placebo for the treatment of adults with ADHD was accomplished using a mixed-models design with endpoint WRAADDS scores as the outcome variable, treatment as a fixed variable,

Table 1. Clinical and Demographic Characteristics of All Subjects Meeting Criteria for Attention-Deficit/Hyperactivity Disorder (ADHD) at Baseline[a]

Variable	ADHD Alone	ADHD + ED	ADHD + ED + ODD	All Subjects
Subjects, N (%)	8 (17)	18 (38)	19 (40)	47
Age, mean ± SD	29.4 ± 5.5	32.2 ± 14.3	29.6 ± 8.6	30.6 ± 10.8
Gender (female), %	25	39	26	34
Body mass index, mean ± SD	26.1 ± 6.0	28.3 ± 5.2	29.3 ± 6.1	28.5 ± 5.7
Overweight or obese, %	40	69	82	71
WRAADDS total score, mean ± SD	19.6 ± 1.7	22.9 ± 3.4	24.6 ± 2.0	23.0 ± 3.1
Attention + disorganization[b]	3.9 ± 0.2	3.8 ± 0.5	3.7 ± 0.3	3.7 ± 0.4
Hyperactivity + impulsivity[b]	3.1 ± 0.7	3.0 ± 1.0	3.4 ± 0.4	3.2 ± 0.7
Emotional dysregulation[b]	1.7 ± 0.4	3.2 ± 0.5	3.4 ± 0.6	3.0 ± 0.8
ADHD-RS total score, mean ± SD	35.1 ± 9.8	34.8 ± 8.5	37.9 ± 8.6	36.2 ± 8.6
Inattention	21.4 ± 3.1	20.4 ± 4.6	20.4 ± 4.4	20.7 ± 4.2
Hyperactivity/impulsivity	14.6 ± 7.2	13.8 ± 5.9	17.4 ± 5.4	15.7 ± 5.9
WURS score, mean ± SD**	38.6 ± 16.8	52.7 ± 13.7	65.6 ± 13.4	55.5 ± 17.0
PRS score, mean ± SD*	16.1 ± 8.2	19.3 ± 5.5	23.1 ± 4.4	20.1 ± 6.0
HAM-D score, mean ± SD*	6.9 ± 3.3	10.5 ± 5.4	13.2 ± 5.9	10.9 ± 5.7
Self-report ADHD scale score, averaging moderate impairment, %				
Attention*	88	100	100	98
Disorganization	88	80	95	89
Hyperactivity**	88	60	100	84
Impulsivity**	75	40	84	68
Temper**	13	53	74	55
Mood instability**	25	60	100	70
Emotional overreactivity**	38	53	100	70
Oppositional impairment**	0	0	100	45
Academic impairment*	38	20	63	43
SAS-SR score, mean ± SD (% elevated)				
Work	1.4 ± 0.5 (5)	2.2 ± 1.1 (33)	2.5 ± 1.3 (43)	2.2 ± 0.9 (32)
Marital	1.3 ± 0.5 (0)	2.2 ± 1.1 (30)	2.2 ± 1.2 (35)	2.1 ± 0.5 (28)
Conflicts[c]	1.5 ± 0.7 (12)	1.5 ± 0.7 (8)	2.0 ± 1.1 (32)	1.8 ± 0.8 (19)
Emotionality	1.3 ± 0.2 (0)	1.7 ± 0.8 (15)	2.0 ± 0.8 (25)	1.8 ± 0.7 (17)

[a]Group differences were evaluated using 1-way analysis of variance.
[b]The 3 WRAADDS factors are expressed as "item means" to facilitate comparisons.
[c]Subjects in the ADHD + ED + ODD sample differed from the other 2 subgroups (p = .009).
*p = .05.
**p = .001.
Abbreviations: ADHD-RS = ADHD-Rating Scale, ED = emotional dysregulation, HAM-D = Hamilton Rating Scale for Depression, ODD = oppositional defiant disorder, PRS = Parent Rating Scale, SAS-SR = Weissman Social Adjustment Scale-Self Report, WRAADDS = Wender-Reimherr Adult Attention Deficit Disorder Scale, WURS = Wender Utah Rating Scale.

and subject as a random variable. The impact of treatment upon the ADHD-RS was similarly evaluated, as was the impact of treatment upon each of the subscales/factors of the WRAADDS and the ADHD-RS. Correlations regarding improvement in each of the 3 ADHD factors were assessed using Pearson's product-moment correlation coefficient.

Improvement for categorical variables was accomplished using both the McNemar test and Fisher exact test. Improvement was defined as follows: (1) scores less than or equal to 2 on the CGI-I and (2) improvement of greater than or equal to 50% on the WRAADDS. The impact of treatment on areas of the self-report ADHD scale was analyzed using paired t tests.

Subjects who received at least 1 dose of double-blind medication (N = 43) were included in the analysis of safety. Continuous variables were analyzed using paired t tests while categorical variables were compared using the χ^2 test.

All analyses were done using the SPSS 13.0 statistical package (SPSS, Inc., Chicago, Ill.). All statistics were 2-tailed with a significance level of $p < .05$.

RESULTS

Baseline

Forty-seven subjects met admission criteria and signed consent agreements for entry into the study. Four subjects were eliminated during the baseline phase after meeting criteria for randomization but before entering the first double-blind phase. One patient dropped out during each treatment arm without contributing usable efficacy data. Forty-one subjects completed the double-blind trial.

Demographic characteristics at baseline are shown in Table 1. Eight subjects (17%) were experiencing ADHD without either emotional dysregulation or oppositional impairment. Eighteen subjects (38%) met criteria for ADHD plus emotional dysregulation. Nineteen subjects (40%) were categorized as having ADHD plus significant

Table 2. Outcome for Attention-Deficit/Hyperactivity Disorder (ADHD) Clinical Scales as a Function of Treatment (OROS methylphenidate or placebo)

Scale	Placebo	OROS Methylphenidate	p Value[a]	Cohen's d
WRAADDS total score, mean ± SD	20.0 ± 7.3	13.5 ± 8.4	< .001	.83
Attention + disorganization	6.6 ± 2.3	4.5 ± 2.8	< .001	.82
Hyperactivity + impulsivity	5.8 ± 2.1	3.8 ± 2.2	< .001	.93
Emotional dysregulation	7.7 ± 3.5	5.1 ± 3.9	.002	.70
ADHD-RS total score, mean ± SD	31.3 ± 14.8	21.4 ± 14.1	.003	.69
Inattention	17.8 ± 7.6	12.0 ± 8.1	.001	.73
Hyperactivity/impulsivity	14.1 ± 7.4	9.5 ± 6.7	.005	.75
CGI-I, no. of responders (%)	9 (22)	23 (56)	.018	NA

[a]p Values result from mixed-models analysis except for the CGI-I, which resulted from χ^2 analysis.
Abbreviations: ADHD-RS = ADHD-Rating Scale, CGI-I = Clinical Global Impressions-Improvement scale, NA = not applicable, OROS = osmotic release oral system, WRAADDS = Wender-Reimherr Adult Attention Deficit Disorder Scale.

oppositional-defiant symptoms plus symptoms of emotional dysregulation. All but 2 subjects who were experiencing at least moderate oppositional impairment also met criteria for emotional dysregulation. A majority of subjects (N = 39, 83%) had substantial symptoms in 1 or both of these areas.

Some, but not all, differences between these groups were attributable to how they were defined. As seen in Table 1, there were differences between the 3 subgroups for our 2 measures of childhood ADHD and the Hamilton Rating Scale for Depression (HAM-D).[17] Subjects with ADHD alone were less impaired than subjects with ADHD plus emotional dysregulation. The group impaired in all 3 areas was also more impaired than either of the other 2 groups as measured by the following scales: WURS ($F = 10.94$, $df = 2,42$; $p = .001$), PRS ($F = 3.70$, $df = 2,31$; $p = .04$), and HAM-D ($F = 3.70$, $df = 2,31$; $p = .04$). Although the group with ODD appeared to have more hyperactive/impulsive symptoms, this difference was not significant ($F = 1.82$, $df = 2,41$; $p = .17$). The apparent difference on academic functioning was also not significant ($F = 1.58$, $df = 2,34$; $p = .22$). Finally, the apparent difference between the 2 more severe groups of levels of emotionality was not statistically significant ($p = .17$).

In previous studies,[12,18] the symptoms of ADHD, as measured either by the factors of the WRAADDS or the subscales of the ADHD-RS, have been highly correlated with each other, with correlations of .50 and higher. In contrast, the self-report symptoms of oppositional impairment were correlated with attention ($r = .384$) and disorganization ($r = .288$) at a lower level than hyperactivity ($r = .639$), impulsivity ($r = .547$), temper ($r = .647$), affective lability ($r = .714$), and emotional overreactivity ($r = .696$).

At baseline, subjects averaging at least moderate oppositional impairment had mean ± SD WRAADDS scores of 24.3 ± 2.4 compared with the rest of the subjects who had scores of 22.0 ± 3.4 ($p = .01$). While there was also a difference in scores of the ADHD-RS, the difference failed to achieve significance.

We have limited our report on social functioning to several critical items. We combined the responses of work, housework, and school as appropriate into 1 category called "work." Table 1 displays the percent of responses indicating impairment (scores ≥ 3) for the individual questions within each category. While there was a general relationship between the increasing impairment of our 3 groups and SAS-SR impairment (ADHD alone < ADHD + ED < ADHD + ED + ODD), this difference did not reach statistical significance. Additionally, there was no significant group difference on marital adjustment. Table 1 includes 2 groupings of these questions that have not been previously described. Eight items of the SAS-SR addressed conflicts (often arguing) within various social relationships. We compared mean scores on these items for the ADHD + ED + ODD group with the other 2 groups. The difference was significant ($p = .009$), suggesting that these questions were identifying aspects of oppositional impairment. Similarly, 5 items within the SAS-SR addressed feelings of strong emotion within various social relationships. We compared mean scores on these items for the ADHD-alone group with the 2 groups experiencing emotional dysregulation. The difference only approached significance ($p = .11$); however, this statistic was limited by the low number of ADHD-alone subjects.

A large number of subjects in this study were overweight. At baseline, 19 subjects (42%) were overweight (body mass index of 25–29.9), and an additional 13 (29%) were obese (body mass index ≥ 30). This problem occurred with subjects in all 3 groups, and the use of ANOVA found no statistical differences between the groups.

Efficacy

ADHD symptoms, as measured by mean total WRAADDS scores, decreased 42% on OROS methylphenidate and 13% on placebo ($F = 14.686$, $df = 1,78.3$; $p < .001$). All individual WRAADDS scales also demonstrated positive treatment effects. As seen in Table 2, there was a positive treatment effect when we combined

Table 3. Outcome on Self-Report ADHD Scale Items for 20 Treatment Responders[a] as a Function of Treatment (mean ± SD)

Scale	Placebo	OROS Methylphenidate	p Value[b]	Cohen's d
Attention + distractibility	2.8 ± 0.8	1.4 ± 0.9	.001	1.65
Hyperactivity + impulsivity	2.5 ± 0.9	1.2 ± 0.9	.001	1.44
Emotional dysregulation	2.2 ± 0.9	1.0 ± 0.8	.001	1.41
Oppositional impairment	1.7 ± 0.9	1.0 ± 0.6	.001	.93
Academic impairment	2.5 ± 0.9	1.7 ± 1.0	.001	.84
Social adjustment	1.8 ± 1.0	1.1 ± 0.8	.001	.78

[a]Defined by WRAADDS scores improving 50% or more while taking OROS methylphenidate.
[b]p Values were computed using paired t tests.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, OROS = osmotic release oral system.

attention + distractibility ($F = 13.973$, $df = 1,78.8$; $p < .001$), hyperactivity + impulsivity ($F = 15.847$, $df = 1,76.0$; $p < .001$), and the symptoms of emotional dysregulation ($F = 10.476$, $df = 1,79.5$; $p = .002$). As in previous studies,[12,18] the response of emotional dysregulation to active treatment was significantly correlated with the responses of attention + distractability ($r = .88$) and hyperactivity + impulsivity ($r = .81$). Improvement in attention + distractibility was correlated to improvement in hyperactivity + impulsivity ($r = .84$) at a similar level.

Similarly, the mean ADHD-RS score decreased 41% on OROS methylphenidate and 14% on placebo ($F = 9.59$, $df = 1,78.0$; $p = .003$). Both subscales also showed positive treatment effects: inattention ($F = 10.874$, $df = 1,78.0$; $p = .001$) and hyperactivity ($F = 8.241$, $df = 1,78.0$; $p = .005$).

Categorical measures also showed a significant treatment effect. The percent of subjects experiencing at least a 50% improvement in the total WRAADDS score was 49% (N = 20) taking OROS methylphenidate and 15% (N = 6) taking placebo (Fisher exact test, $p = .007$). Similarly, a CGI-I score of much or very much improved was obtained by 54% of the sample (N = 22) while receiving OROS methylphenidate and 22% (N = 9) while receiving placebo (McNemar test, $\chi^2 = 5.63$, $p = .018$).

Each of the 3 ADHD subgroups presented in Table 1 displayed a numerical advantage with OROS methylphenidate over placebo in improvement in the total WRAADDS score. The 5 subjects who met criteria for ADHD alone improved 49% while taking OROS methylphenidate and 19% while taking placebo ($p = .20$). The 16 subjects who met criteria for ADHD + ED improved 25% while taking OROS methylphenidate and 16% while taking placebo ($p = .36$). The 18 subjects who met criteria for ADHD + ED + ODD improved 50% while taking OROS methylphenidate and 11% while taking placebo ($p < .001$).

In contrast to the investigator-scored WRAADDS, the self-report ADHD scale displayed a treatment effect that seldom reached statistical significance for the total sample (data not shown). However, the reduction in symptoms associated with OROS methylphenidate (compared with placebo) as measured by the self-report ADHD scale was significantly correlated with the reduction in scores of the investigator-rated WRAADDS. As a result, the data from treatment responders were analyzed separately from the nonresponders. For the 20 subjects who responded to treatment (improvement of ≥ 50% on the WRAADDS in the OROS methylphenidate arm), the treatment effect consistently reached significance. As seen in Table 3, this subsample reported substantially fewer problems at the end of the OROS methylphenidate arm than at the end of the placebo arm, with significant p values and large effect sizes.

Medication Administration

There was also a significant difference in dosage levels between those who responded to OROS methylphenidate and those who did not respond. Treatment responders averaged less (57 ± 20 mg/day) medication than nonresponders (75 ± 21 mg/day), at a significant level ($t = 2.3$, $df = 40$, $p = .02$). Most of the treatment nonresponders (N = 14/19, 74%) ended the treatment arm taking doses that were relatively large (63–90 mg/day). In contrast, a majority (N = 14/22, 64%) of the treatment responders ended the treatment arm taking low (N = 10/22, 45% taking 27–36 mg/day) or medium (N = 4/22, 18% taking 45–54 mg/day) doses. The 3 groups received similar doses of OROS methylphenidate (ADHD alone = 64.8 ± 3.3mg, ADHD + ED = 64.1 ± 24.8 mg, ADHD + ED + ODD = 60.5 ± 21.1 mg) at endpoint. In the treatment responders alone, there was a trend toward a difference in final dosage between the 3 groups (ADHD alone = 40.5 ± 6.4 mg, ADHD + ED = 46.8 ± 13.3 mg, ADHD + ED + ODD = 55.5 ± 21.3 mg).

Safety and Adverse Events

OROS methylphenidate was associated with small but statistically significant increases in systolic ($F = 3.67$, $df = 1,37$; $p = .064$) and diastolic ($F = 4.46$, $df = 1,37$; $p = .042$) blood pressure (Table 4). Mean ± SD weight dropped 2.5 ± 3.8 lb while in the OROS methylphenidate arm versus an increase of 1.3 ± 4.3 lb while taking placebo ($t = 3.48$, $df = 36$, $p = .001$). QT interval was the

Table 4. Vital Signs and Adverse Events During Both Treatment Arms

Variable	Placebo	OROS Methylphenidate	p Value[a]
Systolic blood pressure, mean ± SD, mm Hg	119.1 ± 8.6	121.5 ± 10.4	.064
Diastolic blood pressure, mean ± SD, mm Hg	78.2 ± 7.6	80.1 ± 8.8	.042
Heart rate, mean ± SD, bpm	73.6 ± 10.6	75.5 ± 11.7	.10
PR interval, mean ± SD, msec	146.0 ± 20.4	148.9 ± 16.9	.75
QRS interval, mean ± SD, msec	90.0 ± 9.5	90.2 ± 9.4	.23
QT interval, mean ± SD, msec	369.4 ± 29.5	387.3 ± 33.1	.001
QTc interval, mean ± SD, msec	412.9 ± 20.3	409.3 ± 17.6	.73
Weight change, mean ± SD, lb	1.3 ± 4.3	–2.5 ± 3.8	.001
Subjects experiencing specific adverse events, N			
Decreased appetite	0	5	.025
Sleep/insomnia	3	9	.05
Anxiety	0	4	.05
Headache	6	4	NS
Nausea	2	4	NS
Aches/pains	2	3	NS
Urinary problems	2	3	NS
Dry eyes, nose, mouth	1	3	NS
Tension	1	3	NS
Cold hands	1	2	NS
Agitation	0	2	NS
Subjects experiencing at least 1 adverse event, %	39	55	NS
Subjects experiencing at least 1 adverse event at moderate impairment, %	23	39	NS

[a]p Values were computed using paired t tests for continuous variables and χ^2 test for dichotomous variables.
Abbreviations: NS = not significant, OROS = osmotic release oral system.

only electrocardiographic parameter that showed a drug-placebo difference (mean ± SD = 369.4 ± 29.5 for placebo versus 387.3 ± 33.1 for OROS methylphenidate [t = –3.84, df = 23, p = .001]). However, there was no significant difference in QTc interval. There were no apparent differences between the changes in vital signs at the 3 treatment levels; however, statistical power was limited by the small sample size in the lowest dose group. Finally, there were no clinically significant outliers in QTc interval (> 460 msec), blood pressure (systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg), or heart rate (> 100 bpm).

Subjects were assessed for adverse events at each visit using open-ended questioning. Only 3 symptoms appeared related to treatment. Subjects experienced significantly more sleep disturbance, decreased appetite, and/or anxiety while taking OROS methylphenidate than placebo. There did not seem to be any relationship between dose levels and the frequency of experiencing adverse effects. However, statistical power was limited by the small sample size in the lowest dose group.

DISCUSSION

Our subjects responded positively to OROS methylphenidate across all continuous and categorical outcome measures. While p values for the WRAADDS and the ADHD-RS were similar, effect sizes for the WRAADDS were somewhat larger. OROS methylphenidate was remarkably well tolerated. There were some changes in vital signs and an increase in some side effects (decreased appetite, insomnia, and anxiety). There were no clinically significant outliers in QTc interval, blood pressure, or heart rate. Only 2 subjects left the study following randomization: 1 each in the placebo and OROS methylphenidate arms. Of concern is the fact that most of these study subjects were overweight, and 29% met criteria for obesity. Given the impact of weight on cardiovascular health, past research has probably not given the interaction between weight, treatment, and cardiovascular functioning sufficient emphasis.

The responders in this study averaged 57 mg/day of OROS methylphenidate (mean ± SD = 0.7 ± 0.3 mg/kg) with a range of 27 to 90 mg/day or, based on body weight, 0.2 to 1.3 mg/kg. This mean dose level was lower than has been observed in some other studies. A meta-analysis performed by Faraone et al.[19] indicated that studies in adults taking methylphenidate doses of 0.9 mg/kg generated larger effect sizes than studies using lower doses. A study conducted by Biederman et al.[20] reported a mean dose of 81 mg/day OROS methylphenidate (0.99 mg/kg). Conversely, some of our subjects responded in a very positive manner to doses ranging from 27 to 54 mg/day. These differing results clearly indicate that individualized dosing is paramount when treating patients with ADHD. For instance, some of our subjects were dosed at higher levels than the mean dose noted by Biederman et al.[20] It is important to continue to titrate the dose until significant improvement is achieved with minimal side effects. This titration can best be done with the use of interview forms

like the WRAADDS and the involvement of reliable informants such as a significant other. We have observed increased levels of irritability and mood lability with higher doses of stimulant medication that is not detected by the patient but is noted by family members.

Given that dosing 3, 4, and even 5 times a day of immediate-release formulations of stimulants is common in adults with ADHD, once-a-day dosing represents a significant advantage.

A majority of our subjects had not only the DSM-IV-TR ADHD symptoms but also symptoms of emotional dysregulation and/or oppositional-defiant symptoms. Previous studies[21–23] have pointed to the pivotal definitional aspect of attention and hyperactivity in adult ADHD. Conversely, these symptoms by themselves do not convey the full symptomatic phenotype present in many patients. In this study, 80% of the population had 1 or both of these associated symptoms. While the use of these symptoms to create subsamples is unusual, the pervasiveness of the symptoms led us to analyze these data in this exploratory manner.

Symptoms of emotional dysregulation responded positively to treatment with OROS methylphenidate at a level similar to inattention and hyperactivity/impulsivity. Thirty-eight percent of the subjects had a high level of emotional symptoms defined in a manner previously reported[12] but without significant oppositional symptoms. These subjects had a distinctly higher level of symptoms than those with ADHD alone (WURS: a self-rating of childhood ADHD symptoms; PRS: a parent rating of childhood ADHD symptoms; HAM-D: a clinician rating of current depressive symptoms; self-rated current symptoms of mood instability, temper, and emotional overreactivity; and self-rated problems in work and marital adjustment). While there is some disagreement on whether or not these symptoms are a part of ADHD, they fit comfortably within Barkley's[24] theory of ADHD. He has theorized that ADHD represents a developmental delay in response inhibition processes including self-regulation of affect, motivation, and/or arousal. Symptoms of emotional dysregulation could result from the impaired self-regulation of affect. Further, the Utah description of these symptoms was developed prior to the DSM-III on the basis of empirical observations of adults with ADHD, and they have consistently demonstrated a response to treatment similar to the DSM symptoms. Finally, studies of ADHD that exclude affective and anxiety disorders nevertheless contain many adults who meet our criteria for emotional dysregulation.[12]

Before this study, the symptoms of ODD had never been examined so closely in a medication trial of adults. To explore this area, we developed 8 adult-oriented items reflecting 8 of the DSM-IV criteria for ODD for inclusion in the self-report ADHD scale we are developing. For example, 2 of the DSM-IV criteria for childhood ODD are "often angry and resentful" and "arguing with adults." They are addressed in the self-report ADHD scale by the following items: "Feeling angry, resentful" and "Get into disagreements, arguments," respectively. The other ODD items are as follows: loses temper, actively defies or refuses to comply with rules, deliberately annoys people, blames others for his mistakes, touchy or easily annoyed, and spiteful or vindictive. Approximately 45% of the subjects (N = 21) met our criteria for oppositional impairment by reporting a moderate level of problems on these 8 items. All but 2 of these subjects also met our criteria for emotional dysregulation. Unlike children, our adults acknowledged the presence of oppositional symptoms. This observation was confirmed by the psychiatrists involved in the assessment of these subjects, as well as our clinic staff who reported that these subjects were very difficult to deal with. These subjects frequently changed appointments at the last minute, forgot to return study medications, did not complete their medication diaries, or failed to come in for appointments. Although the self-report ADHD scale remains in need of further development (normative data, reliability, and validity) and the results are exploratory in nature, we believe that these data were of sufficient import to deserve inclusion in this article.

As in previous studies, the 3 parings of the ADHD factors of inattention + distractibility, hyperactivity + impulsivity, and emotional dysregulation were similarly correlated. Conversely, the symptoms of oppositional impairment were less strongly related to attention/distractibility than to the other 2 ADHD factors. Further, the data in Table 1 seem to suggest a continuum of the illness, in which increased symptoms in 1 area are positively associated with increased symptoms in the other areas. Again, on a number of measures, these subjects had a numerically higher level of symptoms than those in the other 2 groups. These subjects were more symptomatic on the following: WURS: a self-rating of childhood ADHD symptoms; PRS: a parent rating of childhood ADHD symptoms; HAM-D: a clinician rating of current depressive symptoms; self-rated current symptoms of mood instability, temper, and emotional overreactivity; self-rated problems in work and marital adjustment; and conflicts in social relationships. In summary, on a variety of rating instruments, these subjects were more symptomatic.

These data suggest that ODD can be identified in adulthood in a manner of presentation that is similar to childhood. For instance, Murphy et al.[25] found that it is the impulsivity associated with ADHD that predisposes children with ADHD to externalizing behaviors. Similarly, we found that oppositional impairment was correlated more strongly with hyperactivity/impulsivity and emotional dysregulation than inattention. Further, our finding of a positive correlation between symptoms of

oppositional impairment and the symptoms of ADHD replicated Newcorn et al.'s[26] finding that baseline ADHD symptoms were greater in subjects comorbid for ODD or conduct disorder.

Childhood studies suggest that these symptoms often improve as a result of ADHD treatment in parallel with other ADHD symptoms.[10,26] These data partially replicate those positive childhood studies. OROS methylphenidate improved these oppositional symptoms; however, this improvement was limited to ADHD treatment responders. All 3 groups showed at least numerical improvement. Unfortunately, the limited number of subjects in this study limits the reliability of these subgroup findings. Further replication of these findings with larger numbers of subjects is necessary.

These data support the use of OROS methylphenidate in the treatment of adult ADHD. Like the immediate-release formulations of methylphenidate, OROS methylphenidate treats the primary symptoms of ADHD: inattention, hyperactivity/impulsivity, and emotional dysregulation. Additionally, OROS methylphenidate was associated with improvements in our adult-defined symptoms of oppositional impairment, although this depended on a response of the primary ADHD symptoms. The research community has not previously documented improvement in symptoms of oppositional impairment in adult ADHD; however, the extensiveness of these symptoms and response to treatment warrants further study. The findings regarding oppositional impairment were limited by the number of subjects and the use of a nonvalidated instrument. This study showed that 3 distinct groups of adults with ADHD could be identified: ADHD alone, ADHD with significant emotional symptoms, and ADHD with a combination of emotional and oppositional symptoms. While interesting, this division was exploratory in nature, and its ultimate usefulness will be determined by future studies. Unlike the symptoms of hyperactivity and inattention, emotional dysregulation and oppositional impairment seem to be at least as disruptive at home in the evening as they are at work. As a result, extended-release stimulant formulations may be especially useful for patients with significant oppositional and/or emotional symptoms.

Drug names: atomoxetine (Strattera), methylphenidate (Concerta, Focalin, and others).

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