Efficacy of a Novel Biphasic Controlled-Release Methylphenidate Formula in Adults With Attention-Deficit/Hyperactivity Disorder: Results of a Double-Blind, Placebo-Controlled Crossover Study

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Objective: To evaluate the efficacy and safety of a new biphasic multilayer-release (MLR) methylphenidate formulation in a double-blind, placebo-controlled crossover study of adults with attention-deficit/hyperactivity disorder (ADHD).

Method: Adults 18 to 60 years of age with a DSM-IV diagnosis of ADHD entered a no-medication baseline week and were then randomly assigned to once-daily MLR methylphenidate or matching placebo. Patients were titrated to optimal effect over 1 to 3 weeks followed by 2 weeks of treatment on a stable dose. The same titration protocol was repeated with the alternate treatment. Clinical Global Impressions scale (CGI) and Conners' Adult ADHD Rating Scales (Self-rated, CAARS-S, and Observer-rated, CAARS-O) were collected at weekly clinic visits. The study was conducted between October 2003 and April 2004.

Results: Fifty patients were randomly assigned to treatment, and 39 were analyzed in a per-protocol population (23 men, 16 women; mean age = 37.9 years). CGI-Improvement scores of subjects taking MLR methylphenidate were significantly improved compared with placebo (Global Improvement: 2.6 vs. 3.7; p = .0015). MLR methylphenidate produced improvements over placebo on the ADHD Index T scores of the CAARS-S (12.2 vs. 5.4 [change from baseline score]; p = .0083) and the CAARS-O (10.9 vs. 6.6 [change from baseline score]; p = .1404). The most frequent adverse events for MLR methylphenidate and placebo were headache (26% and 24%, respectively), anorexia (22% and 6%), insomnia (22% and 8%), nervousness (20% and 4%), and nausea (16% and 8%). There were no serious adverse events.

Conclusions: Once-daily MLR methylphenidate produces significant improvements in ADHD symptoms and situational behavior in adult patients with ADHD, with a prolonged duration of effect and minimal side effects, thus having the potential to improve compliance and, therefore, treatment outcomes in routine clinical use.

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Attention-deficit/hyperactivity disorder (ADHD) was once considered a condition of childhood, but over the past 20 years, it has been accepted as affecting a significant number of adults. Studies have estimated that anywhere from 4% to 80% of children with ADHD display symptoms into their mid-20s,[1–4] while a recent survey of adults in the United States found that 4.4% of adults meet the criteria for ADHD.[5] The DSM-IV defines ADHD as a persistent pattern of inattention/hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development.[6] In adulthood, ADHD has implications for academic performance, work performance, and social and emotional functioning,[7] as well as driving safety.[8–12] There are a number of psychiatric comorbidities

common to adults with ADHD, such as antisocial personality disorder, major depressive disorder, and anxiety disorder.[5,13] In a study of functional impairments, adults with ADHD had significantly lower levels of education and income and higher levels of substance abuse than age- and gender-matched controls.[14]

In order for an adult patient to be diagnosed with ADHD, the patient must also be diagnosed, retroactively if necessary, with childhood-onset ADHD.[15] While diagnostic criteria, such as the Utah Criteria and Wender Utah Rating Scales, have examined adaptations of the DSM-IV criteria for childhood ADHD to adults, a consensus on the inclusion of refinements to the criteria has not emerged.[16–18] Observer reports of patient behavior can enhance the clinical impressions and outcome of treatment in adults with ADHD.[19,20]

A number of stimulant and nonstimulant medications have been used to treat adult ADHD. The efficacy of methylphenidate in improving attention and behavioral symptoms has been supported by many studies in both children and adults, although the optimal dose in adults has not yet been determined.[21–23] Recent reviews suggest that, in the treatment of adult ADHD, methylphenidate should be prescribed from a starting dose of 10 mg/day and titrated to a target range of 40 to 90 mg/day[2,18,24] and *d*-methylphenidate to a range of 20 to 40 mg/day.[25] In one of the earliest adult ADHD studies, by Wender et al.,[21] the average dose after titration was 43.2 mg/day with a range of 10 to 80 mg/day. In a subsequent article,[22] in which adults were titrated from a dose of 0.5 mg/kg to a maximum of 1.0 mg/kg, the average dose after titration was 0.92 mg/kg. Using the same study design but titrating the dose up to a maximum of 1.3 mg/kg per day, the same group later demonstrated the efficacy of both immediate-release and once-daily methylphenidate in adults.[23,26]

Due to its short half-life, methylphenidate is usually given 2 or 3 times per day, once after breakfast, once around midday, and often once in the late afternoon. A medicated patient with ADHD will therefore be maximally affected only for relatively brief periods during the day. The requirement of multiple doses per day results in poor compliance with prescribed regimens.[27,28] These limitations of immediate-release methylphenidate led to interest in products with longer effective periods of action.

This study examined the efficacy in adult patients of a novel, once-daily, multilayer-release (MLR) methylphenidate bead formulation. This formulation was designed to provide both a rapid, initial release of methylphenidate (40% of the total methylphenidate, in contrast to 22% reported for the other controlled-release formulation available in Canada)[29] and a more prolonged release resulting in a biphasic concentration-time profile. In a single-dose, fed/fast pharmacokinetic study[30] of healthy adult volunteers, this controlled-release formulation was fully bioavailable, relative to the immediate-release formulation, with a relative area under the plasma-concentration/time curve of 106% and 111% under fasted and fed conditions, respectively. The rate of increase in plasma methylphenidate concentrations during the first 4 hours postdose with the controlled-release formulation was similar to that with the immediate-release formulation, and the maximum concentration during the same time period was 75.6% to 84.4% of that of the immediate-release formulation. These observations suggest that adequate plasma methylphenidate concentrations are achieved, coincident with early morning activities such as preparing breakfast or driving to work. The second peak occurs between approximately 6 and 8 hours following administration, coinciding with late afternoon activities, such as driving home from work, preparing dinner, or parenting children.[30]

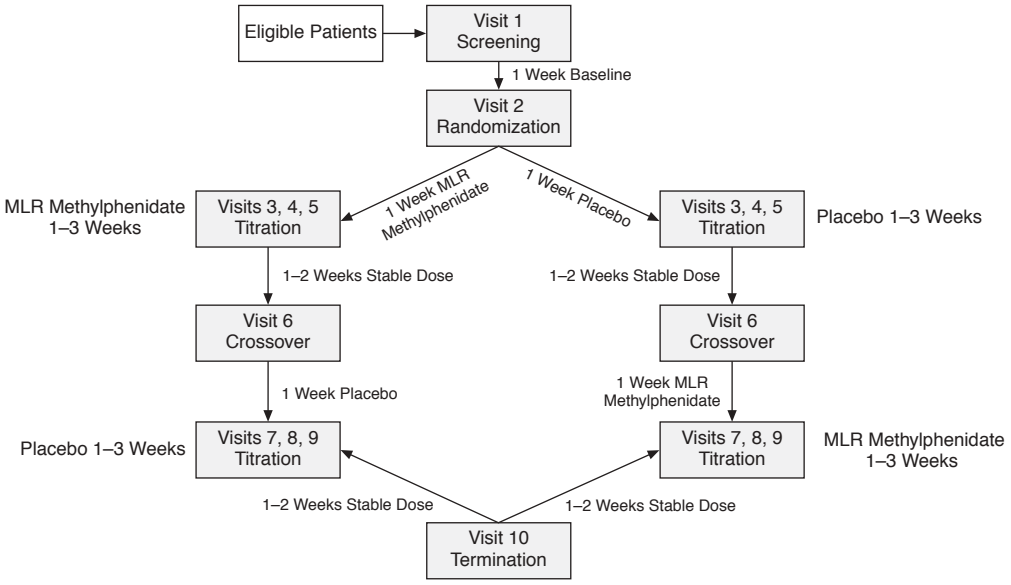
METHOD

Subjects

Fifty-four adults 18 to 60 years of age with a childhood history consistent with ADHD and meeting the DSM-IV diagnosis of ADHD were screened for study entry. Subjects were diagnosed with ADHD using the DSM-IV criteria[6] for ADHD, inattentive or combined, adapted for adults as the Wender Utah Criteria for ADHD, by displaying either motor hyperactivity persisting from childhood or attentional deficits persisting from childhood, plus 2 of the following: (1) affective lability, (2) inability to complete tasks, (3) hot or explosive temper, (4) impaired interpersonal relationships or inability to sustain relationships over time, (5) impulsivity, or (6) stress intolerance.[20] Patients were eligible to participate in the study if they had a T score greater than or equal to 65 on the ADHD Index of 1 of the 2 Conners' Adult ADHD Rating Scales–Self-rated (CAARS-S) forms completed during the baseline week and 1 of the 2 Conners' Adult ADHD Rating Scales–Observer-rated (CAARS-O)[31] forms completed during the baseline week; if they weighed between 50 and 90 kg at baseline assessment; if they had an IQ greater than or equal to 80 as assessed using the Wechsler Adult Intelligence Scale-III (WAIS-III)[32] at visit 1 or during the prior 5 years; and if they were otherwise able to comply with the study protocol.

Patients were excluded from the study if they had a true allergy to methylphenidate or amphetamines; a history of serious adverse reactions to methylphenidate or were known to be methylphenidate nonresponders; serious or unstable medical illness; serious hypertension, defined as any values above 100 mm Hg diastolic and 170 mm Hg systolic; anxiety of sufficient severity to warrant treatment, based upon the Hamilton Rating Scale for Anxiety (HAM-A); depression of sufficient severity to warrant treatment, based upon the Hamilton Rating Scale for Depression (HAM-D); a history of drug or alcohol abuse;

Figure 1. Study Design Flow Chart of Double-Blind, Placebo-Controlled, Crossover Study of Multilayer-Release (MLR) Methylphenidate in Adults With Attention-Deficit/Hyperactivity Disorder



disorders of the sensory organs; autism; or psychosis or any other unstable psychiatric conditions requiring treatment. Patients treated with the following medications were excluded from the study: guanethidine, pressor agents, monoamine oxidase inhibitors, coumarin anticoagulants, anticonvulsants, phenylbutazone, tricyclic antidepressants, selective serotonin reuptake inhibitors, or herbal remedies.

Informed consent was obtained from all patients prior to entry into the study. The study protocol and consent form were approved by the research ethics boards at each site, and the study was conducted according to the Declaration of Helsinki (revised, Washington, D.C., 2002).

Study Design

This randomized, multicenter, double-blind, placebo-controlled, crossover study was designed to evaluate both the efficacy and the side effect profile of MLR methylphenidate over a period of 5 to 11 weeks in adults with ADHD in outpatient settings. Data were collected between October 2003 and April 2004.

Patients who met the entry criteria were entered into a 1-week washout/baseline period. Following the washout/baseline period, patients were randomly assigned, in a blinded fashion, to either MLR methylphenidate given once daily (10-, 15-, 20-, 30-, 40-, 50-, 60- or 80-mg capsules, administered orally) or matching placebo given once daily. Patients received 1 of the 2 study medications and were titrated to optimal effect during a period of 1 to 3 weeks. At the end of the dose titration period, patients were crossed over to the alternate treatment group, and were titrated to optimal effect during a period of 1 to 3 weeks. Medication compliance was monitored by capsule count of returns in the pharmacy and by direct questioning of the patient. Patients who were less than 80%, or more than 120%, compliant were to be withdrawn from the study.

The study consisted of a screening visit, a randomization visit, 3 phase 1 dose-titration visits separated by intervals of 1 week, a crossover visit separated by an interval of 2 weeks from the last dose-titration visit, 3 phase 2 dose-titration visits, and a final termination visit at the end of the second treatment phase separated by an interval of 2 weeks from the last dose-titration visit (Figure 1).

At each site, the principal investigator rated the effectiveness of the treatment regimens with the Clinical Global Impressions scale (CGI) each week to determine the need for dose titration and at the end of each treatment phase to provide an overall assessment of clinical effect at the optimum dose. Those rated "minimal improvement" or worse were titrated to the next dose level and returned in 1 week for a further assessment. Those rated "very much improved" or "much improved" were entered into a second week of stable dose and were then crossed over to the next assigned treatment.

During each 1-week period, including baseline and titration periods, patients were assessed 4 times prior to the next scheduled clinic visit, twice by themselves and twice by an observer with the CAARS-S and the CAARS-O, respectively. Observers included spouses, peers, cowork-

ers, siblings, and offspring. Side effects were assessed by self-rating on a daily basis and were assessed verbally by telephone and in the clinic with the question, "Have you experienced any adverse events?"

At baseline, crossover, and termination visits, the HAM-D, HAM-A, and the Longitudinal Interval Follow-up Evaluation (LIFE) questionnaire[33] were administered to rate the patients' depressive symptoms, anxiety, and quality of life during that phase. At the end of the stable-dose treatment periods, patients rated the acceptability of each of the 2 treatment regimens using the Patient Satisfaction Survey (PSS) (unpublished, available from the authors upon request). Upon completion of the double-blind phase of the study, patients continued to receive MLR methylphenidate, if they chose, during a 6-month open-label treatment period.

Outcome Variables

The principle outcomes were the stable-dose results of the CGI-Global Improvement scale and the CAARS, specifically the E Scale (Conners' ADHD Index). Secondary endpoints included the remaining scales of the CAARS, the PSS, the HAM-A, the HAM-D, and the LIFE questionnaire.

The CGI, originally developed by the National Institute of Mental Health, is a standard measurement tool that records an investigator's assessment of the improvement of a patient's condition or disease with respect to treatment, including therapeutic effect and severity of adverse events.[34] The CGI measures global therapeutic effect, global adverse events, and a global improvement score. The efficacy index is derived as the ratio of therapeutic/adverse effect. The CGI-Global Improvement scale is a 7-point scale that rates the behavioral changes in a patient receiving treatment, ranging from "very much improved" (1) to "very much worse" (7). The investigator scores on the CGI-Global Improvement scale were used to evaluate the overall efficacy of the treatment and to determine the need for dose titration. The CGI-Severity of Illness scale was not collected.

The Conners' Adult ADHD Rating Scales are standard measurement tools for assessment of the severity of ADHD symptoms in adults and were recently adapted by the authors from child-applicable versions.[31,35] This study used both the Self and Observer forms. The CAARS-S (short) and CAARS-O (short) consist of 26 questions relating to ADHD behavior and rated on a scale of 0 = "not at all"; 1 = "just a little"; 2 = "pretty much true"; and 3 = "very much true." For both scales, scores from specific, predetermined questions are summed to create 5 subscales: the A scale, "Inattention/Memory Problems"; the B scale, "Hyperactivity/Restlessness"; the C scale, "Impulsivity/Emotional Lability"; the D scale, "Problems with Self-Concept"; and the E scale, "ADHD Index." Scores from these scales, referred to as "raw scores," are converted to T scores that correct for gender and age and provide a method of assessing the impairment of patients on each of the 5 subscales relative to a normal population.[35] A "normalized" patient can be defined as one for whom the severity of impairment of ADHD has diminished to subclinical levels. T scores of 65 and above are usually taken to indicate a clinically significant problem.[36] The use of the CGI and Conners' ADHD Rating Scales in the measurement of treatment-related efficacy (cognitive function and behavior) in patients with ADHD is well established.[31,34,35]

The LIFE questionnaire was designed to examine psychosocial functioning and quality of life and consists of 16 items. Only the mean scores were analyzed statistically. Zero values (for "no information" or "not applicable") were not included in the calculation of mean scores. On the PSS, the patients rated 3 items—effectiveness, side effects, and overall satisfaction—as (1) unacceptable, (2) not satisfied, (3) satisfied, and (4) very satisfied. Safety evaluations were based on spontaneous reports of side effects and the adverse effects subscale of the PSS. Other safety evaluations included vital signs and findings on physical examination.

Statistical Analyses

Sample-size calculations were based on the requirement to detect a clinically significant difference of at least 5 T units on the ADHD Index of the CAARS during the stable-dose phase between MLR methylphenidate and placebo. Using variance estimates of the T units and raw scores from previous studies[22,37–42] and assuming type 1 and type 2 error rates of 5% and 20%, respectively, a minimum sample size of approximately 40 patients was estimated to be needed to detect a difference of 8 T units using a 2-tailed test. All patients with efficacy data from a primary endpoint on a stable dose in both phases and without significant protocol violations were evaluated for efficacy in the per-protocol population. All patients with any efficacy data from both phases were evaluated for efficacy in the intent-to-treat (ITT) population. Efficacy data presented are from the per-protocol population, supplemented by confirmatory analyses of primary variables using the ITT population. All patients receiving test medication were evaluated for safety.

For the analysis of data from the per-protocol population, the mean scores during stable-dose periods from the CGI-Global Improvement scale and the CAARS were compared between the active treatment group and placebo, using 2-way analysis of variance. The effects of treatment, phase, and sequence (first order carryover) were determined. The patient-within-sequence variance was used as the error term for testing sequence. Pairwise contrasts were constructed to compare treatments, using a within-patient variance structure. For confirmatory analysis on data from the ITT population, only data from the

last completed visit in each phase were used, as the dose was titrated during each treatment period. The PSS and the LIFE questionnaire were compared by treatment using the Wilcoxon rank sum test. Missing values for major endpoint variables were not replaced. Primary statistical comparisons were selected a priori, while the secondary endpoints were considered exploratory and therefore no adjustment for multiple testing was necessary.

All adverse events were coded with the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART IV) using preferred terms in order to standardize the terminology. McNemar test was used to determine the significance of differences in overall frequency of side effects between the treatments. Statistical significance was defined as $p < .05$ for a 2-tailed hypothesis. Descriptive statistics were calculated for physical examination values and vital signs.

RESULTS

Patients

Of the 54 patients who were screened, 4 were not eligible to participate: 1 due to drug use, 1 due to clinically significant depression, 1 due to a baseline CAARS T score less than 65, and 1 who was lost to follow-up.

Of the 50 patients randomly assigned to treatment in the study, 6 patients withdrew after randomization: 1 due to inadequate efficacy, 1 due to withdrawn consent, 2 due to noncompliance, and 2 who were lost to follow-up. Study completion was defined as completion of stable-dose treatment with both MLR methylphenidate and placebo. Of the 44 patients who completed the double-blind phase, 5 were excluded from the per-protocol (N = 39) population analysis due to protocol violations. These included patients for whom completed CAARS-O and CAARS-S data were not available from the stable-dose period in both phases. Of the 50 patients who were randomly assigned to treatment, 2 were excluded from the ITT population (N = 48) due to absence of efficacy data from both phases. All 50 patients were evaluated for safety. No patients were withdrawn due to medication compliance issues.

The mean age of the patients at baseline was 37.9 years (range, 18.8 to 57.1) and included 23 men and 16 women (Table 1). There were no statistically significant period or carryover effects.

Table 1. Baseline Characteristics of Adult Outpatients With Attention-Deficit/Hyperactivity Disorder (ADHD)

	Analysis Population	
Characteristic	Intent-to-Treat (N = 48)	Per-Protocol (N = 39)
Age, mean ± SD (range), y	37.2 ± 11.2 (18.8–57.1)	37.9 ± 11.1 (18.8–57.1)
Gender, N (%)		
Male	30 (62.5)	23 (59.0)
Female	18 (37.5)	16 (41.0)
Ethnicity, N (%)		
White	42 (87.5)	36 (92.3)
Black	1 (2.1)	1 (2.6)
Asian	3 (6.3)	1 (2.6)
Other	2 (4.2)	1 (2.6)
CAARS-Self, ADHD Index, T score, mean ± SD	72.8 ± 8.4	72.3 ± 8.2
CAARS-Observer, ADHD Index, T score, mean ± SD	73.5 ± 7.0	73.4 ± 6.8

Abbreviation: CAARS = Conners' Adult ADHD Rating Scale.

Dosing

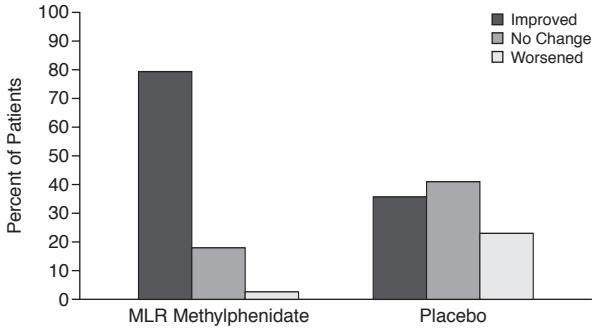
The mean ± SD daily dose for the 2 groups was 57.8 ± 20.1 mg/day for MLR methylphenidate and 64.9 ± 17.5 mg/day for placebo. Patients were titrated to a maximum of 1.0 mg/kg or 80 mg/day, whichever was the lower dose. Of patients on active medication who were eligible to titrate up to 80 mg, 65% (15/23) did so. The stable dose of MLR methylphenidate ranged from 0.2 mg/kg to 1.0 mg/kg, with a mean ± SD of 0.7 ± 0.2 mg/kg per day, and for placebo, the mean was 0.8 ± 0.2 mg/kg per day.

Efficacy

On the primary outcome measure (investigator ratings on the CGI), there was significant improvement on MLR methylphenidate compared with placebo on each of the subscales: global improvement ($p = .0015$) and therapeutic effect ($p = .0033$), with higher adverse event severity ($p = .0066$). These results were confirmed by ITT analysis ($p = .0005$, $p = .0006$, and $p = .0014$, respectively). Among patients on MLR methylphenidate, 48.7% (19/39) were rated as "much improved" or "very much improved" compared with 23.1% (9/39) on placebo ($p = .0158$; Figure 2). The magnitude of the effect of MLR methylphenidate compared with placebo, as measured by the effect size (95% CI) for global improvement, was 0.90 (0.43 to 1.36).

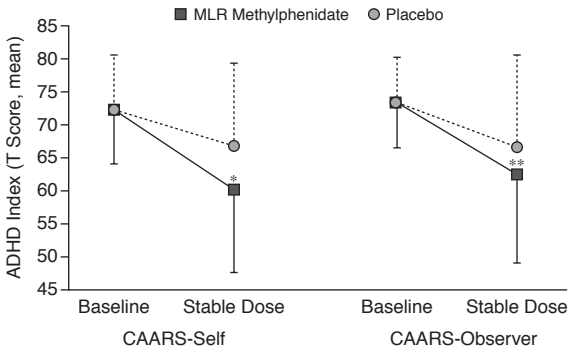
MLR methylphenidate produced improvements over placebo on the stable-dose ADHD Index T scores of the CAARS-S ($p = .0083$; Figure 3). This result was confirmed by ITT analysis ($p = .0033$). The CAARS-S was completed at a mean time of 5:17 p.m. Normalization rates in this study (a T score of less than 65) were 73.7% (28/38) on MLR methylphenidate and 33.3% (13/39) on placebo using the CAARS-S ADHD Index ($p = .0001$). The magnitude of the effect of MLR methylphenidate compared with placebo, as measured by the effect size (95% CI) for the CAARS-S ADHD Index, was 0.53 (0.08 to 0.99). Statistically significant improvements were also observed with MLR methylphenidate over placebo on the Inattention/Memory Problems subscale of the CAARS-S ($p = .0037$; Table 2). Borderline statistically significant improvements were observed with MLR methylphenidate

Figure 2. Proportion of Patients Improved From Baseline on the Clinical Global Impressions-Global Improvement Scale by Treatment Group



Abbreviation: MLR = multilayer-release.

Figure 3. Patient Response on Conners' Adult ADHD Rating Scales (CAARS) Self-Rated and Observer-Rated ADHD Index (mean T score) on MLR Methylphenidate and Placebo



*p = .0083.
**p = .1404.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, MLR = multilayer-release.

over placebo on the Problems with Self-Concept and Impulsivity/Emotional Lability subscales of the CAARS-S (p = .0601 and p = .0899, respectively; Table 2). MLR methylphenidate produced lower scores than baseline on the ADHD Index of the CAARS-O, but the difference from placebo did not reach statistical significance (p = .1404; Figure 3). This result was confirmed by ITT analysis (p = .0967). The CAARS-O was completed at a mean time of 4:08 p.m. Using the CAARS-O ADHD Index, normalization rates were 65.8% (25/38) on MLR methylphenidate and 45.9% (17/37) on placebo (p = .0707). Statistically significant improvements were also observed with MLR methylphenidate over placebo on the Hyperactivity/Restlessness subscale of the CAARS-O (p = .0284; Table 2). Significant differences from placebo were not found with other subscales (Table 2).

On the PSS, patients found MLR methylphenidate more effective than placebo (p = .0018) and did not find a difference in side effects between treatments (p = .1484; Table 2). Among patients taking MLR methylphenidate, 70.6% (24/34) of patients were "somewhat satisfied," "satisfied," or "very satisfied" with side effects compared with 82.9% (29/35) of patients on placebo (p = .2482). Patients were also more satisfied with MLR methylphenidate treatment than with placebo (p = .0054); 76.5% (26/34) of patients were "somewhat satisfied," "satisfied," or "very satisfied" with MLR methylphenidate treatment compared with 34.3% (12/35) of patients with placebo (p = .0046).

There was no difference between mean scores for anxiety on the HAM-A between treatments (p = .5312; Table 2). During both phases of the study, all patients either had "none to mild" anxiety on the HAM-A or did not complete the questionnaire. There was no difference between mean scores for depression on the HAM-D between treatments (p = .1724; Table 2). "No depression" was rated in 38, 36, and 37 patients in baseline, placebo, and MLR methylphenidate phases, respectively. "Mild to moderate depression" was rated in 0, 1, and 1 patient in baseline, placebo, and MLR methylphenidate phases, respectively. "Moderate to severe depression" was rated in 0, 1, and 1 patient in baseline, placebo, and MLR methylphenidate phases, respectively. One patient did not complete the scale during the baseline and MLR methylphenidate phases.

No statistically significant differences were observed between treatments on any question in the LIFE questionnaire (Table 2). Level of patient functioning was minimally improved with MLR methylphenidate over baseline and placebo in work activities, household duties, and student work, but the differences were not statistically significant (p = .2177, p = .3580, and p = .5500, respectively). The level of overall patient satisfaction with quality of life was minimally improved with MLR methylphenidate over baseline and placebo, but the difference was not statistically significant (p = .2498). The patient's level of social adjustment was minimally improved with MLR methylphenidate over baseline and placebo, but the difference was not statistically significant (p = .0950).

Safety and Vital Signs

Compared with baseline values, there was a statistically significant mean ± SD weight loss during treatment with MLR methylphenidate (1.1 ± 0.9 kg; p = .0001), but not placebo (0.1 ± 1.6 kg; p = .5982), and change from baseline was significantly different between treatments (p = .0001). Mean ± SD change in systolic and diastolic blood pressure was not significantly different from baseline during MLR methylphenidate treatment (0.6 ± 10.4 mm Hg systolic increase and 0.0 ± 6.7 mm Hg diastolic increase; p = .7055 and p = 1.0000, respectively) or placebo treatment (0.9 ± 10.6 mm Hg systolic increase

Table 2. Results of Efficacy Measures in Adult Attention-Deficit/Hyperactivity Disorder (ADHD) Patients

Efficacy Measure	Baseline	MLR Methylphenidate	Placebo
CGI score, mean ± SD			
Global improvement[a]	NA	2.6 ± 1.0***	3.7 ± 1.4
Therapeutic effect[b]	NA	2.6 ± 1.0***	1.7 ± 1.1
Adverse effects[c]	NA	1.8 ± 0.8**	1.3 ± 0.7
CAARS-Self, T score, mean ± SD			
Inattention/memory problems	75.7 ± 8.1	64.9 ±12.3**	71.1 ± 11.6
Hyperactivity/restlessness	62.6 ± 10.9	53.1 ± 9.0	56.9 ± 11.4
Impulsivity/emotional lability	60.7 ± 11.7	52.5 ± 12.9	56.6 ± 13.0
Problems with self-concept	64.1 ± 9.2	55.7 ± 12.4	59.9 ± 10.9
ADHD Index	72.3 ± 8.2	60.1 ± 12.7**	66.9 ± 12.5
CAARS-Observer, T score, mean ± SD			
Inattention/memory problems	70.4 ± 8.3	62.5 ± 11.9	66.0 ± 12.5
Hyperactivity/restlessness	63.0 ± 10.8	54.8 ± 10.2*	59.7 ± 13.4
Impulsivity/emotional lability	64.5 ± 9.3	55.3 ± 12.8	58.2 ± 13.4
Problems with self-concept	63.9 ± 11.0	56.8 ± 12.5	58.1 ± 12.5
ADHD Index	73.4 ± 6.8	62.5 ± 13.4	66.8 ± 13.7
LIFE Questionnaire (selected questions)			
Level of functioning score, mean ± SD[d]			
Work activities	2.9 ± 1.2	2.3 ± 1.2	2.8 ± 1.0
Household duties	3.3 ± 1.0	2.6 ± 1.2	2.8 ± 0.9
Student work	3.4 ± 0.7	2.6 ± 1.3	3.0 ± 1.1
Relationship level score, mean ± SD[e]			
Spouse/mate	2.6 ± 1.1	2.3 ± 1.0	2.5 ± 1.1
Children	2.1 ± 0.8	2.0 ± 1.1	2.1 ± 0.8
Other relative	2.8 ± 1.1	2.1 ± 0.9	2.3 ± 1.0
Friends	2.2 ± 1.0	2.3 ± 1.2	2.0 ± 1.0
Level of satisfaction, mean ± SD	2.7 ± 0.8	2.4 ± 1.0	2.6 ± 0.9
Level of social adjustment, mean ± SD	3.4 ± 1.0	2.7 ± 1.1	3.1 ± 1.0
HAM-A, mean ± SD[f]	4.4 ± 2.8	4.2 ± 5.0	4.5 ± 4.8
HAM-D, mean ± SD[g]	3.2 ± 4.0	3.3 ± 4.6	4.2 ± 4.5
Patient Satisfaction Survey, mean ± SD[h]			
Efficacy		2.5 ± 1.1***	1.5 ± 1.0
Side effects		2.6 ± 1.3	3.1 ± 1.1
Overall satisfaction		2.4 ± 1.1**	1.6 ± 0.9

[a]Global improvement: (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, (7) very much worse.
[b]Therapeutic effect: (1) unchanged or worse, (2) minimal, (3) moderate, (4) marked.
[c]Adverse effects: (1) none, (2) mild, (3) moderate, (4) severe-extreme.
[d]Level of functioning scale: (1) high level of functioning, (2) satisfactory level of functioning, (3) mild impairment, (4) moderate impairment, (5) severe impairment.
[e]Relationship, satisfaction, and social adjustment levels: (1) very good, (2) good, (3) fair, (4) poor, (5) very poor.
[f]Hamilton Rating Scale for Anxiety: (0–18) mild, (19–25) moderate, (26–30) severe.
[g]Hamilton Rating Scale for Depression: (0–13) mild, (14–17) moderate, (> 17) severe.
[h]Patient Satisfaction Survey: (1) unacceptable, (2) not satisfied, (3) satisfied, (4) very satisfied.
*$p \leq .05$ (MLR methylphenidate vs. placebo).
**$p \leq .01$ (MLR methylphenidate vs. placebo).
***$p \leq .005$ (MLR methylphenidate vs. placebo).
Abbreviations: CAARS = Conners' Adult ADHD Rating Scale, CGI = Clinical Global Impressions scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, LIFE = Longitudinal Interval Follow-up Evaluation, MLR = multilayer-release, NA = not applicable.

and 1.4 ± 8.3 mm Hg diastolic decrease; p = .5719 and p = .2498, respectively). Mean ± SD change in heart rate was not significantly different from baseline during MLR methylphenidate treatment (1.8 ± 10.9 beats-per-minute increase; p = .2703) or placebo treatment (0.7 ± 12.8 beats-per-minute decrease; p = .6981). There was no significant difference in between-treatment comparisons of systolic and diastolic blood pressure or heart rate (p = .7942, p = .2122, and p = .4891, respectively).

Treatment with MLR methylphenidate was well tolerated. No patients in either group withdrew due to adverse events. No serious adverse events occurred during the course of the study; however, 84.0% of patients (42/50) experienced at least 1 adverse event on MLR methylphenidate during the double-blind treatment and 58.0% (29/50) during the placebo phase. The most common adverse events (percent incidence) from each group are listed in Table 3. The most frequent adverse events for MLR methylphenidate and placebo were headache, anorexia, insomnia, nervousness, and nausea. Rebound was defined as an occurrence of ADHD symptoms worse than baseline levels occurring either after active treatment was discontinued, or during the evening—after methylphenidate blood plasma levels were expected to diminish—and was only observed in 1 patient during placebo treatment.

Table 3. Incidence Greater Than or Equal to 5% of Related Spontaneous Adverse Events in Adult Attention-Deficit/Hyperactivity Disorder Patients (N = 50) Reported by Phase

Event	MLR Methylphenidate, % (N)	Placebo, % (N)	p Value
Headache	26.0 (13)	24.0 (12)	.8083
Anorexia	22.0 (11)	6.0 (3)	.0325
Insomnia	22.0 (11)	8.0 (4)	.1088
Nervousness	20.0 (10)	4.0 (2)	.0047
Nausea	16.0 (8)	8.0 (4)	.2482
Anxiety	14.0 (7)	0 (0)	.0082
Dry mouth	12.0 (6)	2.0 (1)	.0588
Emotional lability	10.0 (5)	2.0 (1)	.1025
Depression	8.0 (4)	2.0 (1)	.0833
Asthenia	8.0 (4)	8.0 (4)	1.0000
Sweating	6.0 (3)	0 (0)	.0833

Abbreviation: MLR = multilayer-release.

DISCUSSION

In this double-blind, placebo-controlled study, adults on MLR methylphenidate demonstrated significant behavioral improvement compared with placebo and baseline, as measured by patients, observers, and investigators in outpatient situations, such as work, home, or university/college.

Although the study limited the daily dose of methylphenidate to a maximum of 1.0 mg per kg per day, possibly leading to underdosing of heavier patients, significantly more patients on MLR methylphenidate were rated as "much" or "very much improved" than patients on placebo on the CGI. When completing the CGI for this study, the physician took into account feedback received from the patient and the observer and direct observation in the clinic, as well as his or her own clinical judgment, to provide a comprehensive evaluation of the overall efficacy of the study medication. MLR methylphenidate also produced significant improvement over placebo on the therapeutic effect and global improvement subscales. Addition of the CGI-Severity of Illness subscale to the study would have provided additional information on patient severity levels.

As would be expected in a comparison of an active drug to a placebo, adverse event severity was rated as significantly greater compared with placebo. However, the mean severity of adverse events was between "none" and "mild" for both treatments, indicating that adverse event levels were low and tolerable. The CGI values are comparable to those for methylphenidate and other accepted treatments reported elsewhere in the literature[38,41,43,44] and indicate that a single, daily dose of MLR methylphenidate is effective in the treatment of ADHD, with a treatment success rate similar to that of other accepted treatments.

On the basis of patient and observer ratings of the CAARS,[31] patients in this study had primarily inattentive ADHD characteristics at baseline, with a mean value of 2 to 2.5 standard deviations from the norm, whereas hyperactivity characteristics were approximately 1.5 standard deviations from the norm. Following treatment with MLR methylphenidate, patients obtained statistically significant improvement in inattentive behavior over placebo. Improvements in hyperactive behavior were also noted by observers when comparing MLR methylphenidate with placebo, and there was a trend toward improvement in patient-rated hyperactivity. These observations are consistent with the level of insight patients would be expected to have into their own cognitive performance, while external observers would be expected to be most sensitive to overt hyperactivity or restlessness.

On the CAARS ADHD Index, patients' self ratings showed significant improvement in ADHD behavior with MLR methylphenidate when compared with placebo. A "normalized" patient can be defined as one for whom the severity of impairment of ADHD has diminished to subclinical levels, with T scores of below 65 taken to indicate absence of a clinically significant problem.[31,35] The mean, patient-rated ADHD Index T score after treatment was below 65, with the proportion of patients who were normalized on MLR methylphenidate being approximately twice as large as the proportion normalized on placebo (73.7% on MLR methylphenidate and 33.3% on placebo). This suggests that the response was clinically, as well as statistically, significant.

Normalization rates were lower when based on observer ADHD Index ratings, with a higher placebo effect (65.8% on MLR methylphenidate and 45.9% on placebo), and, although rating of the ADHD Index by patients and observers showed improvement from baseline, significant difference was found between MLR methylphenidate and placebo for patient-rated symptoms only. This may be due to a greater placebo response in adults that could lead to less robust efficacy results in adults.[39,41,45] In a study of self-rating in adult ADHD, De Quiros and Kinsbourne[46] suggest that, unlike children with ADHD, adult ADHD patients are capable of analyzing their behavior on a structured rating scale. These authors concluded that self-rating has primacy over observer ratings since no single observer is likely to have had first-hand experience of the patient in all or most of the diverse settings in which ADHD symptoms may present,[46] although consideration should be given to the problems of rating ego-syntonic symptoms present in most adults with ADHD.[47] In the current study, the observer rating was performed at only 1 time period during the day, and therefore may not have accurately characterized the patient behavior over the course of the day, and use of an additional ADHD rating scale may have allowed for confirmation of study results. In addition, the observers consisted of a heterogeneous mixture of spouses, peers, coworkers, siblings, and offspring, which may also have led to a higher degree of

variability in this rating. When compared with patient and observer ratings in this study, the robust improvements in global functioning noted by clinicians suggest that investigator ADHD ratings are a superior measure to self or observer checklists.

There were small, but nonsignificant improvements in quality-of-life measurements over the course of the 5- to 11-week study, although failure to find an effect may have been due to a lack of sensitivity of the scale over the relatively short duration of the trial. However, patients reported significantly greater satisfaction with MLR methylphenidate treatment than with placebo. Although adverse event levels were greater in frequency and severity with MLR methylphenidate treatment and, of spontaneously reported adverse events, only appetite decrease, nervousness, and anxiety were significantly increased over placebo, there were no significant differences in patient-rated acceptability of adverse events, and investigators rated adverse effects as between "none" and "mild," indicating that active treatment was well tolerated. Recent concerns regarding potential cardiovascular effects have led to recommendations that patients with preexisting cardiovascular conditions should be closely monitored.[48] Vital signs showed a small, but statistically significant weight loss over the course of the study, but heart rate and blood pressure were not significantly different from baseline or placebo. Likewise, measurements of anxiety and depression showed no difference between active and placebo treatment.

This study demonstrated that a once-daily formulation of methylphenidate is an effective and well-tolerated treatment for adult ADHD. In outpatient settings, patients, observers, and investigators rated the efficacy of MLR methylphenidate as superior to placebo. Patient-rated acceptability of adverse events was not significantly different from placebo treatment. These results indicate that once-daily, multilayer-release methylphenidate produces improvements in situational behavior in adult patients with ADHD, with the added benefit of prolonged duration of effect and the potential to improve compliance and, therefore, treatment outcomes in routine clinical use.

Drug name: methylphenidate (Ritalin and others).

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