A Randomized, Double-blind, Placebo-controlled Trial of Augmentation With an Extended Release Formulation of Methylphenidate in Outpatients With Treatment-Resistant Depression

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Abstract: We examined the efficacy and tolerability of augmentation with an extended release formulation of methylphenidate (OROS MPH, Concerta) in patients with major depression who were nonresponders or partial responders to antidepressants. Sixty subjects with treatment-resistant depression (TRD) participated in a 4-week, randomized, double-blind, placebo-controlled study of augmentation with methylphenidate (18–54 mg/d). The preexisting antidepressant dose was unchanged. The primary efficacy measure was change in the 21-item Hamilton Depression Rating Scale from randomization to end of treatment. Data were analyzed with intent-to-treat with last observation carried forward approach. There were no statistically significant differences between the methylphenidate (n = 30) and placebo (n = 30) groups in reduction in 21-item Hamilton Depression Rating Scale scores (drug, −6.9; placebo, −4.7) from baseline to end of treatment ($F_{1,47}$ = 1.24, P = 0.22), although responders were numerically higher in the extended-release methylphenidate group (40.0%) than in the placebo group (23.3%). On the secondary efficacy measures of changes in Clinical Global Impression–Improvement and Severity scores and Beck Depression Inventory–Second Edition, the drug failed to separate from placebo, although the proportion of responders in the drug group were numerically higher than placebo. There were no significant differences in weight, heart rate, and blood pressure changes between the 2 groups. The common adverse events were loss of appetite, nausea, headache, and anxiety. The mean dose of drug was 34.2 mg/d. The study did not demonstrate a statistically significant benefit for augmentation with methylphenidate in TRD. Combination of methylphenidate with antidepressants was well tolerated. Adequately powered, randomized, controlled trials are necessary to fully evaluate the efficacy of extended-release methylphenidate in TRD.

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Only 25% to 35% of all patients treated for major depression achieve symptom remission with antidepressant monotherapy.[1] Patients who experience partial or no response to antidepressant treatment are considered to have treatment-resistant depression (TRD)[2] and are candidates for treatment options such as augmenting with another agent or switching to a different class of antidepressant. Open-label studies have suggested that psychostimulants may be an effective augmentation strategy for TRD.[3,4] An extended release formulation of methylphenidate (OROS MPH, Concerta) has been approved for attention deficit disorder. Although open-label studies have found immediate release methylphenidate to be effective as an augmenting agent,[5] controlled studies are lacking. The aims of the present study were to evaluate the efficacy and safety of an augmentation with extended-release methylphenidate for patients with TRD.

METHODS

Design

This was a 4-week, 2-site, randomized, flexible dose, double-blind, placebo-controlled study.

Subjects

After screening 104 individuals, 60 participants were enrolled. Eligible participants were men and women aged 18 to 65 years with TRD. The TRD individuals were defined as those who (1) met *Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition* criteria for major depressive disorder (MDD) without psychotic features on the Mini International Neuropsychiatric Interview,[6] (2) had an entry score of 15 or more on the 21-item Hamilton Depression Rating Scale (HAM-D-21), and (3) had an adequate trial of at least 1 antidepressant at study entry, defined as a 6-week or longer trial of an antidepressant at an acceptable therapeutic dose (a daily dose of ≥40 mg of fluoxetine, paroxetine, or citalopram, 37.5 mg of paroxetine CR, 150 mg of sertraline, 20 mg of escitalopram, 225 mg of venlafaxine XR, 30 mg of mirtazapine, 300 mg of bupropion or bupropion XR, 400 mg

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of nefazodone, 100 mg of nortriptyline, 150 mg of amitriptyline or imipramine). Exclusion criteria were the following: any *Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition* psychotic disorder; serious suicide risk; substance abuse in the previous 12 months; history of hypersensitivity to methylphenidate; treatment with antipsychotics, monoamine oxidase inhibitors, or anticonvulsants in the previous 4 weeks; patients with unstable medical disorders, history of Tourette disorder; and pregnancy.

Efficacy and Safety Measures

The primary efficacy measure was defined as a change in HAM-D-21 scores from baseline to end of treatment. Secondary efficacy measures were defined as changes in Clinical Global Impression–Improvement and Severity (CGI-I and CGI-S, respectively) scores and Beck Depression Inventory–Second Edition (BDI-II)[7] scores. Response was defined as 50% or more reduction in HAM-D-21 score. Remission was defined as HAM-D-21 score of 7 or less at end point. Adverse effects were determined by the Systematic Assessment for Treatment Emergent Events–General Inquiry.[8]

Procedures

The study protocol was approved by the Institutional Review Board and written informed consent was obtained. After the Mini International Neuropsychiatric Interview, physical examination, and laboratory testing, eligible participants were randomly assigned to drug or placebo. The dose of preexisting antidepressant remained unchanged during the trial. Drug was dosed using a forced titration strategy starting at 18 mg/d and increased weekly in 18-mg/d increments, the maximum dose being 54 mg/d based on tolerability. No other psychotropic medications were permitted during the study except nonbenzodiazepine hypnotics for insomnia. Weekly efficacy and safety evaluations were performed.

Data Analyses

The group differences on efficacy variables were compared using intent-to-treat (ITT) analysis, with the last observation carried forward (LOCF) approach employing analysis of variance (ANOVA) with repeated measures. Fisher exact tests compared proportion of responders in each group.

RESULTS

Subjects

Fifty (83%) participants completed the study. The duration of current episode of MDD was 19.4 ± 23.4 months. The age of onset of MDD was 27.8 ± 14.5 years. About 63% of subjects were women, 60% were white, and the mean age was 48.5 years. The baseline scores for HAM-D-21, CGI-S, and BDI-II were comparable between the 2 groups.

All patients had failed to respond to an antidepressant trial for longer than the minimum defined duration to enroll, about 40% had doses higher than the necessary doses to enroll and 70% had failed multiple antidepressant trials for the current MDD episode. Ten of subjects (17%) were dropouts. The mean dose of extended-release methylphenidate was 34.2 ± 6.3 mg/d. Forty of participants (80%) who completed the study reached the final maximum dose of 54 mg/d.

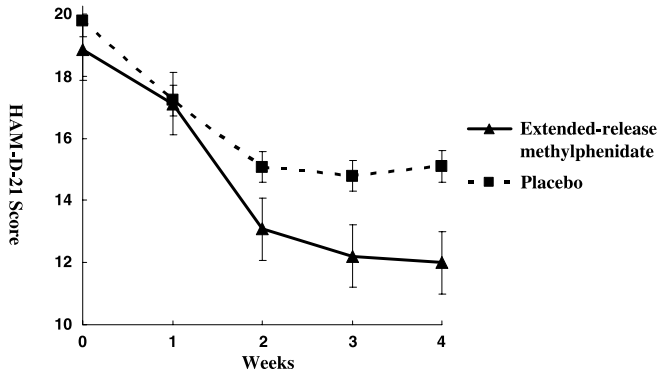

FIGURE 1. Changes in HAM-D-21 scores during the study period in patients receiving extended-release methylphenidate or placebo. Data were analyzed with ITT, with LOCF approach (between-group effect: repeated measure ANOVA, $F_{1,47}$ = 1.24, P = 0.22). The number of subjects at each week are as follows: week 0, drug = 30, placebo = 30; week 1, drug = 29, placebo = 27; week 2, drug = 29, placebo = 26; week 3, drug = 28, placebo = 24; week 4, drug = 27, placebo = 23.

Primary Efficacy Measure

There were no significant differences in reduction of mean HAM-D-21 scores from baseline to end point between the methylphenidate (−6.9) and placebo (−4.7) groups in ITT with LOCF analyses (extended-release methylphenidate, week 0 = 18.9, week 1 = 17.1, week 2 = 13.1, week 3 = 12.2, week 4 = 12.0; placebo, week 0 = 19.8, week 1 = 17.2, week 2 = 15.1, week 3 = 14.8, week 4 = 15.1; $F_{1,47}$ = 1.24, P = 0.22) (Fig. 1).

Although there were numerically more responders (≥50% reduction in HAM-D-21) in the drug group (n = 12, 40%) compared with placebo (n = 7, 23.3%), this difference did not reach statistical significance (Fisher exact test, 2.34, P = 0.12). Of the subjects who responded at week 3, 83.3% continued to show a significant response at end of the study. Participants achieving remission (HAM-D-21 ≤ 7) were 4 (13.3%) in the drug and 1 (3.3%) in the placebo group. A reanalysis of the data employing random effects regression model also failed to show a significant effect of the drug (F = 7.96, df = 1,209, P = 0.065).

Secondary Efficacy Measures

There were no significant differences between the drug and placebo groups in changes in CGI-I (Fig. 2) in ITT analyses ($F_{1,46}$ = 1.11, P = 0.34), although the proportion of responders in the drug group based on end of treatment CGI-I score of 1 or 2 were numerically higher in the drug group (42.3%) than placebo (26.1%) (Fisher exact test, 1.82, P = 0.44).

Similar to CGI-I analyses, there were no significant differences between the drug and placebo groups in changes in CGI-S scores ($F_{1,46}$ = 1.44, P = 0.18) or proportion of subjects with a reduction of 1 point or more in CGI-S at end of treatment in ITT analyses. There were no significant differences between the drug and placebo groups in changes

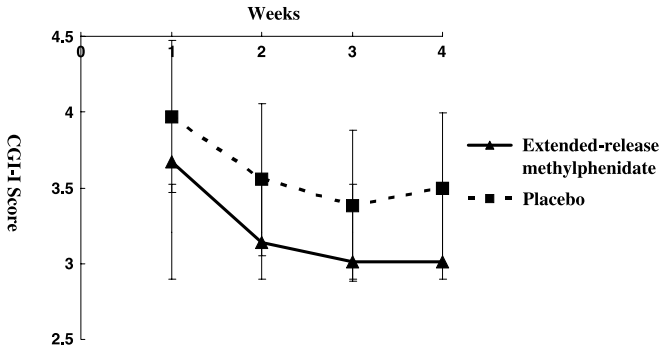

FIGURE 2. Changes in CGI-I score during the study period in patients receiving extended-release methylphenidate or placebo. Data were analyzed with ITT, with LOCF approach (between-group effect: repeated measure ANOVA, $F_{1,46}$ = 1.11, P = 0.34).

in BDI-II from randomization to end of treatment ($F_{1,43}$ = 2.14, P = 0.14).

Results from completer analyses were consistent with ITT analyses for the primary and secondary efficacy measures. There were no between-site differences in outcome.

Comparison of Response by Stages of Treatment Resistance

Because of the variability in terminology and definition of TRD, Thase and Rush[2] proposed a staging system based on prior treatment response. According to this system, TRD is staged from 1 (nonresponse to an adequate trial of 1 antidepressant), 2 (failure to respond to adequate trials of 2 antidepressants with different pharmacological profiles), 3 (stage 2 plus 1 augmentation strategy), 4 (stage 3 plus failure of second augmentation), and 5 (stage 4 plus failure to respond to ECT). We examined the proportion of responders in each stage of treatment resistance. In the drug group, 50% in stage 1, 36% in stage 2, and 25% in stage 3 of participants showed a response compared with 34% in stage 1, 20% in stage 2, and 0% in stage 3 considered as responders in the placebo group. Because of small cell sizes, statistical comparisons are not performed.

Adverse Events

Any treatment-emergent adverse event was reported by 64% of the extended-release methylphenidate– and 58% of the placebo-treated participants. Adverse events were cited as the reason for study discontinuation by 2 individuals in the methylphenidate group (headache and anxiety) and 2 persons in the placebo group (headache and nausea). One participant in the methylphenidate (noncardiac chest pain) experienced a serious adverse event with full recovery. Table 1 shows the treatment emergent adverse events reported by 5% or more of subjects.

As seen in Table 1, loss of appetite, headache, nausea, and anxiety were reported more frequently with the extended-release methylphenidate group than placebo, whereas tremors were reported more frequently by the placebo group. Most of the treatment emergent adverse events were mild to moderate in severity. In 4 instances, the adverse events were present at the end of the study (insomnia, 2 [both drugs], headache, 1 [placebo], and anxiety, 1 [placebo]). There were no significant changes in blood pressure between the 2 groups during the trial (extended-release methylphenidate, baseline = 110/74 mm Hg, week 4 = 118/74 mm Hg; placebo, baseline = 116/76 mm Hg, week 4 = 112/74 mm Hg; P = 0.69 and 0.76). Similarly, there were no significant differences in heart rate, weight, or laboratory parameters from baseline to end point.

DISCUSSION

Although open-label studies of stimulants in TRD have yielded positive results, to date, there have been no randomized, controlled studies of stimulants as augmentation agents in TRD. There was no statistically significant difference between an extended release formulation of methylphenidate and placebo on the primary or secondary efficacy measures. Although numerically more subjects responded to methylphenidate than to placebo, this failed to reach statistical significance. There could be several reasons to explain why extended-release methylphenidate did not separate from placebo on the efficacy measures. First, the drug had low efficacy in TRD. Second, the placebo response rate was high, and third the study was not sufficiently powered to detect the drug placebo difference. The placebo response rate was lower than that seen in studies of major depression, as expected in a treatment resistant sample. Before concluding that the findings are truly negative, it is important to rule out a type II error. This is relevant because there were noticeable differences in the drug and placebo groups on efficacy measures. For example, there was a 6.9-point reduction in HAM-D-21 in the drug group compared with a 4.7-point drop in the placebo group. Similarly on the BDI-II, the reduction in the drug group was 8.8 compared with 5.8 in the placebo group. There was also a 17% difference in response rate favoring the drug over placebo by both HAM-D-21 and CGI-I measures. Our original power calculations were based on an open-label study of methylphenidate augmentation.[4] A power analyses using the means and standard deviations of change in HAM-D-21 scores from our study showed that a sample size of 170 would be sufficient to power the study at 80% with an α =

TABLE 1. Treatment-emergent Adverse Effects With an Incidence of 5% or More in Subjects During the Study Period (Intention-to-Treat)

	Extended-release Methylphenidate (n = 30)	Placebo (n = 30)
Loss of appetite	3 (10.0)	1 (3.3)
Nausea	3 (10.0)	1 (3.3)
Anxiety	2 (6.6)	1 (3.3)
Headache	3 (10.0)	2 (6.6)
Insomnia	3 (10.0)	3 (10.0)
Tremor	1 (3.3)	2 (6.6)

Data represent n (%).

0.05. The only randomized trials of similar agents in depression showed 8% to 13% difference in favor of modafinil.[9,10] The 17% difference observed in the present study exceeds these differences. A lack of power could be a likely explanation of the findings, although it is possible that the drug is not efficacious in TRD. Clearly adequately powered studies are required to address this issue.

The starting daily dose of extended-release methylphenidate was 18 mg, and the mean dose was about 34 mg. Among the drug group, patients had started responding by week 2. The reductions in HAM-D-21 and BDI from weeks 2 to 4 were not as strong. This indicates that among responders to extended-release methylphenidate augmentation, the response is likely to occur within 2 weeks of treatment. However, the relatively brief study duration does not permit any conclusions to be drawn about delayed response or sustainability of response.

There were no major safety issues of combining extended-release methylphenidate with therapeutic doses of antidepressants. Overall, the dropout rate was low, and dropouts due to adverse event were comparable between the 2 groups. There were no significant changes in heart rate, blood pressure, or weight. It does not appear that combining extended-release methylphenidate with antidepressants increases the side effect profile.

The principal limitation of this study was the small sample size leading to inadequate power. Additional limitations of the study include a retrospective definition of treatment resistance and short trial duration. Also, we did not assess for comorbid adult attention-deficit/hyperactivity disorders, and it is possible that patients with such comorbidity might have shown a more favorable response.[11] Finally, the mean dose of methylphenidate was less than that reported in ADHD studies.[12]

In conclusion, the study failed to show a statistically significant benefit for augmentation with extended-release methylphenidate in patients with MDD without psychotic features who are not responsive to antidepressant therapy. Adequately powered, randomized, double-blind, placebo-controlled trials are necessary to fully evaluate the efficacy of extended-release methylphenidate in TRD.

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