Osmotic-Release Oral System Methylphenidate Augmentation of Antidepressant Monotherapy in Major Depressive Disorder: Results of a Double-Blind, Randomized, Placebo-Controlled Trial

Arun V. Ravindran, M.B., Ph.D., F.R.C.P.C., F.R.C.Psych.; Sidney H. Kennedy, M.D., F.R.C.P.C.; M. Claire O'Donovan, M.D., F.R.C.P.C.; Angelo Fallu, M.D., F.R.C.P.C.; Fernando Camacho, Ph.D.; and Carin E. Binder, M.B.A.

Objective: To evaluate the efficacy, safety, and tolerability of adjunctive osmotic-release oral system (OROS) methylphenidate in outpatients with major depressive disorder (MDD) receiving a stable oral antidepressant regimen.

Method: This multicenter, double-blind, randomized, placebo-controlled, parallel-group, 5-week trial enrolled 145 subjects who met DSM-IV-TR criteria for MDD and who had failed 1 to 3 previous antidepressant monotherapies (including current antidepressant) of adequate dose and duration. Augmentation therapy was initiated with 18 mg of OROS methylphenidate and increased to a maximum dose of 54 mg of OROS methylphenidate until an optimal dose was achieved. Efficacy scales included the Montgomery-Asberg Depression Rating Scale (MADRS), 7 atypical items from the 31-item Hamilton Rating Scale for Depression, the Clinical Global Impressions-Severity of Illness (CGI-S) scale, the CGI-Improvement scale (CGI-I), the Sex Effects scale, the Multidimensional Assessment of Fatigue (MAF) scale, and the Apathy Evaluation Scale (AES). Subjects were recruited at 17 community and academic centers across Canada. The study was conducted from June 8, 2005, to April 18, 2006.

Results: There was no statistically significant difference between the groups at endpoint on the MADRS. OROS methylphenidate was superior to placebo in improving apathy and fatigue as measured by the AES and the MAF. Statistically significant differences using mixed-model analysis were observed on the AES at all visits and at endpoint ($p = .01$) and on the MAF ($p < .01$). No differences were observed on other secondary measures, including the CGI-I and CGI-S. There were no clinically significant findings on electrocardiogram.

Conclusions: OROS methylphenidate did not demonstrate statistical significance on the MADRS at endpoint. Apathy and fatigue were significantly improved with OROS methylphenidate treatment, which was well tolerated with minimal side effects.

Clinical Trials Registration: ClinicalTrials.gov identifier NCT00246233.

(J Clin Psychiatry 2008;69:87–94)

Received Nov. 10, 2006; accepted April 6, 2007. From the Department of Psychiatry, University of Toronto, Toronto, Ontario (Drs. Ravindran and Kennedy); the Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia (Dr. O'Donovan); Clinique Woodward, Sherbrooke, Quebec (Dr. Fallu); Damos Inc., Toronto, Ontario (Dr. Camacho); and Medical Affairs, Janssen-Ortho Inc., Toronto, Ontario (Ms. Binder), Canada.

This trial was funded by Janssen-Ortho Inc., Toronto, Ontario, Canada.

We gratefully acknowledge medical writing support by Jean C. Twiner, B.A., who is a consultant to Janssen-Ortho Inc. as well as to other companies/institutions.

Financial disclosure appears at the end of this article.

Corresponding author and reprints: Arun V. Ravindran, M.B., Ph.D., University of Toronto, Mood and Anxiety Disorders Program, Centre for Addiction and Mental Health (Clarke site), 250 College St., Toronto, ON, Canada M5T 1R8 (e-mail: arun_ravindran@camh.net).

The rates of response and remission to antidepressant therapy are consistently lower than patients and clinicians would desire; 50% to 60% of depressed patients have an inadequate response to antidepressant therapy and only 30% to 45% achieve remission.[1] Incomplete recovery from major depressive disorder (MDD) may lead to recurrence and is burdensome in terms of morbidity, mortality, and health care expenditure.[1]

A potential role for methylphenidate to accelerate antidepressant response has been examined in the past, and the first controlled study using methylphenidate to treat depression successfully occurred almost fifty years ago.[2] Methylphenidate, a piperidine derivative structurally related to amphetamines, is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.[3]

Several open trials and 1 randomized, placebo-controlled study suggest an adjunctive role for methylphenidate in the treatment of depression. In a small, open trial in 1994, Gwirtsman and colleagues[4] added methylphenidate, 5 to 15 mg/day, to standard tricyclic antidepressant treatment for a period of 2 weeks in 20 patients with major depressive episode. The positive results achieved with this combination treatment led the authors to conclude that adjunctive methylphenidate accelerated

tricyclic antidepressant response with tolerable side effects. In 1996, Stoll et al.[5] prescribed methylphenidate in doses of 10 to 40 mg/day to 5 patients treated with selective serotonin reuptake inhibitors (SSRIs), each with a history of chronic depression only partly alleviated by treatment with SSRIs, and achieved rapid and sustained success. Masand et al.[6] in 1998, reproduced these positive results in a case series of 7 patients with MDD whose response to SSRIs had been deemed inadequate.

Additional open, naturalistic trials[7,8] and a double-blind trial[9] using methylphenidate augmentation of citalopram concluded that the combination strategy was effective in accelerating the antidepressant response in elderly depressed patients. It was also noted that patients felt less fatigued and developed more energy with methylphenidate augmentation.

Masand et al.[10] conducted a randomized, placebo-controlled trial to determine whether augmentation of standard antidepressant therapy with osmotic-release oral system (OROS) methylphenidate in patients with treatment-resistant depression might be an effective combination strategy. The study (N = 66; average age = 48.9 years) failed to show an overall difference between the active and placebo groups in reduction of Hamilton Rating Scale for Depression (HAM-D) scores from baseline to the end of the 4-week treatment period. The authors suggested that the small sample size (50 subjects completed the trial), suboptimal dosing, and the short trial period (4 weeks) may have contributed to the negative findings. It may also have been the case that the inclusion criteria were overly general, and our own clinical experience indicates that a 50% reduction in HAM-D scores in truly refractory patients is difficult to achieve. It was noted the antidepressant/OROS methylphenidate combination was well tolerated with few adverse effects.

We decided to perform a randomized, placebo-controlled study to expand current clinical knowledge of the effects of adjunctive OROS methylphenidate or placebo in outpatients with MDD.

METHOD

Institutional Review Board approval of the protocol and consent form was received by all sites involved, and all subjects signed informed consent following explanations of study procedures and possible side effects. The first patient entered the study on June 8, 2005, and the last patient completed the study on April 18, 2006.

Subjects

Male and female outpatients (N = 155) aged 18 to 65 years, meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) diagnostic criteria for MDD (without psychotic features), confirmed by the Mini-International Neuropsychiatric Interview,[11] were recruited at 17 community and academic centers across Canada. A training session was held for all raters to ensure interrater reliability on the clinician-rated primary efficacy measure.

Table 1. List of Minimum Adequate Dosage of Antidepressants for Major Depressive Disorder

Drug	Adequate Therapeutic Dose, mg/d
SSRI	
Citalopram	40
Escitalopram	10
Fluoxetine	40
Fluvoxamine	200
Paroxetine	40
Paroxetine CR	50
Sertraline	150
Dual action agent	
Mirtazapine	30
Venlafaxine	150

Abbreviations: CR = controlled release, SSRI = selective serotonin reuptake inhibitor.

Subjects eligible for enrollment had failed at least 1, but not more than 3, previous antidepressant monotherapies and at entry were taking an adequate dose of an antidepressant during the current depressive episode for at least 4 weeks duration (Table 1 shows definitions of adequate dose). A consensus decision regarding "adequate" antidepressant doses was arrived at a priori by the authors and investigators based on the product label, literature, and their own clinical experience. At screening, subjects were evaluated using the Montgomery-Asberg Depression Rating Scale (MADRS)[12] and were required to have a minimum total score of 20, a score ≥ 2 on the lassitude item (item 7), and a score of 3 or less on the suicidal thought item (item 10) to be eligible to enter the study. In addition, subjects needed a Clinical Global Impressions-Severity of Illness (CGI-S)[13] scale score of ≥ 4 at screening and were otherwise healthy as confirmed by physical examination, electrocardiogram (ECG), and blood and urine testing.

Subjects were excluded from the trial if they met criteria for any other current Axis I or II diagnoses according to DSM-IV-TR criteria other than social phobia or generalized anxiety disorder. In particular, no subjects with either current or past history of attention-deficit/hyperactivity disorder, agitation, chronic fatigue syndrome, psychotic disorders, or an eating disorder were included. Disallowed medications covered a broad spectrum of drugs ranging from tricyclic antidepressants and monoamine oxidase inhibitors through anticonvulsants and antipsychotics. Patients already on a stable dose of hypnotics were included, but initiation of new hypnotics or benzodiazepines was not permitted during the study.

Study Design

Subjects entered the 5-week double-blind phase and were randomly assigned to a starting oral dose of 18 mg/day OROS methylphenidate or 1 identically packaged

Table 2. Patient Characteristics at Baseline (intent-to-treat population)

Characteristic	OROS Methylphenidate (N = 73)	Placebo (N = 72)	All (N = 145)
Gender, N (%)			
Male	26 (35.6)	25 (34.7)	51 (35.2)
Female	47 (64.4)	47 (65.3)	94 (64.8)
Age, mean (SD), y	45.6 (10.8)	41.9 (10.9)	43.8 (11.0)
Race, N (%)			
White	71 (97.3)	71 (98.6)	142 (97.9)
Black	0 (0)	1 (1.4)	1 (0.7)
Asian	1 (1.4)	0 (0)	1 (0.7)
Other	1 (1.4)	0 (0)	1 (0.7)
Depressive episode type, N (%)			
Single	16 (21.9)	14 (19.4)	30 (20.7)
Recurrent	57 (78.1)	58 (80.6)	115 (79.3)
Time in current episode (N = 144), mean (SD), mo	24.1 (56.4)	19.5 (36.3)	21.8 (47.5)
Time since first episode (N = 115), mean (SD), y	12.3 (9.5)	10.1 (7.7)	11.2 (8.7)

Abbreviation: OROS = osmotic-release oral system.

placebo tablet. If well tolerated, the dose was titrated up to 36 mg/day OROS methylphenidate or 2 placebo tablets on day 5. Titration continued on a weekly basis by one 18-mg tablet to a maximum dose of 54 mg/day OROS methylphenidate or 3 placebo tablets until an optimal dose (per clinician judgment) was achieved.

Efficacy scales administered at baseline were the MADRS (the primary efficacy measure), the 7 atypical items that measure atypical depressive symptoms from the 31-item HAM-D,[14] the CGI-S,[13] the Sex Effects (SEX-FX) scale,[15] the Multi-dimensional Assessment of Fatigue (MAF) scale,[16] and the Apathy Evaluation Scale (AES).[17]

Five weekly visits were conducted, with all efficacy scales administered at each visit except for the SEX-FX, which was administered at the baseline and final visits only. Safety and tolerability were monitored through the weekly collection of self-reported adverse events.

Statistical Methods

The sample size was determined using a minimum of 65 subjects per group to ensure a 95% confidence interval for the detection of a treatment difference based on the change from baseline in total MADRS score. Analysis of the efficacy variables is based on the intent-to-treat (ITT) population, defined as all subjects who received at least 1 dose of medication and who had at least 1 postbaseline efficacy assessment. The per-protocol evaluable population is defined as the intent-to-treat population who met all protocol inclusion and exclusion criteria. The safety population is defined as all subjects with at least 1 postrandomization intake of blinded study medication. For each continuous efficacy variable with a baseline value, the change from baseline score at each visit and at endpoint was summarized by group and for between-group differences, with descriptive statistics. Intergroup differences are presented with 95% confidence intervals. The frequency distribution for each visit is presented for each of the categorical efficacy variables. For binary response variables, intergroup differences are presented with 95% confidence intervals. A mixed model analysis was employed to confirm the results of the analysis.

For the safety population, the type and incidence of adverse events over the entire treatment period is summarized. Data were summarized and descriptive statistics calculated to show the changes from baseline to endpoint for vital signs and clinical laboratory variables.

RESULTS

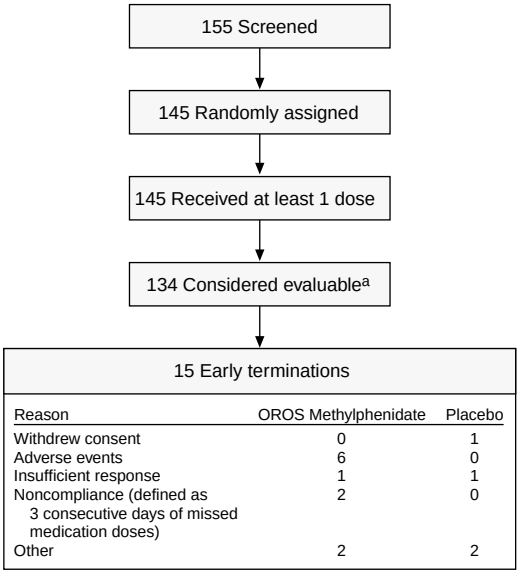
There was no overall difference in results between the ITT group (N = 145) and the per-protocol evaluable population (N = 134); hence the results shown are for the ITT population. Patient characteristics at baseline (Table 2) were similar between the active and placebo groups, although females outnumbered males, and the placebo group was slightly younger. Each group showed a similar distribution of comorbid illness and similar numbers of patients with atypical features and with single or recurrent episodes. The OROS methylphenidate group displayed a somewhat greater degree of chronic illness. The mean body mass index (BMI) of the active and placebo groups was similar and tended towards obesity (mean BMI = 29.7). Other vital signs were also similar in both groups.

Fifteen patients did not complete the study and patient flow is described in Figure 1. Baseline scores are shown in Table 3. The final doses of OROS methylphenidate and placebo are reported in Table 4. The mean dose of OROS methylphenidate was 36.4 mg (SD = 9.15). In patients who discontinued the trial, the mean dose was 22.4 mg (SD = 10.0), and in completers, it was 38.9 mg (SD = 6.39).

Efficacy

The depressive symptoms as measured by the mean MADRS scores (the primary efficacy variable) demonstrated a lack of effect for OROS methylphenidate and did not show a significant difference between the groups

Figure 1. Patient Flow



[a]Reasons for nonevaluable status (N = 11): 4 patients received an inadequate antidepressant dose, and 7 patients had a change of antidepressant medication.
Abbreviation: OROS = osmotic-release oral system.

Table 3. Mean Efficacy Scores at Baseline (intent-to-treat population)

	OROS Methylphenidate			Placebo		
Scale	N	Mean	SD	N	Mean	SD
MADRS	73	26.4	4.6	72	27.0	5.3
CGI-S	74	4.4	0.5	72	4.4	0.5
HAM-D-7[a]	73	3.1	2.7	72	4.1	3.3
SEX-FX	70	2.7	3.0	71	2.5	3.2
AES	73	25.7	9.9	72	27.1	9.1
MAF	72	30.9	5.5	72	30.6	6.4

[a]HAM-D-7 = the 7 atypical items that measure atypical depressive symptoms from the 31-item Hamilton Rating Scale for Depression (HAM-D).
Abbreviations: AES = Apathy Evaluation Scale, CGI-S = Clinical Global Impressions-Severity of Illness, MADRS = Montgomery-Asberg Depression Rating Scale, MAF = Multidimensional Assessment of Fatigue, OROS = osmotic-release oral system, SEX-FX = Sex Effects scale.

Table 4. Number of Patients Taking Specific Dose Amounts at Endpoint

Dose	OROS Methylphenidate (N = 73), N (%)	Placebo (N = 72), N (%)
18 mg/d	9 (12.3)	2 (2.8)
36 mg/d	16 (21.9)	7 (9.7)
54 mg/d	48 (65.8)	63 (87.5)

Abbreviation: OROS = osmotic-release oral system.

Table 5. Mean MADRS Score Change From Baseline (intent-to-treat population)

Visit	Group	N	Mean	SD	Difference	95% CI	p Value
Day 5	OROS methylphenidate	72	–3.78	4.20	–1.28	–2.57 to 0.02	.05
	Placebo	72	–2.50	3.63			
Day 14	OROS methylphenidate	66	–7.53	6.57	–2.00	–3.99 to –0.00	.05
	Placebo	71	–5.54	5.18			
Day 21	OROS methylphenidate	64	–9.11	6.90	–0.78	–3.17 to 1.62	.52
	Placebo	69	–8.33	7.06			
Day 28	OROS methylphenidate	62	–10.32	7.60	–0.01	–2.66 to 2.63	.99
	Placebo	68	–10.31	7.64			
Day 35 (final visit)	OROS methylphenidate	72	–10.38	8.13	0.46	–2.22 to 3.14	.74
	Placebo	72	–10.83	8.12			

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, OROS = osmotic-release oral system.

at endpoint (–10.38 for OROS methylphenidate, –10.83 for placebo; p = .74) (Table 5).

None of the secondary efficacy variables (Tables 6–8) demonstrated a difference at endpoint between the active and placebo groups except for the AES (Figure 2, Table 9). Baseline values of the AES indicated that neither group demonstrated severe symptoms of apathy (OROS methylphenidate, mean = 25.7 [SD = 9.0]; placebo, mean = 27.1 [SD = 9.12]), and although change from baseline over time showed a statistically significant improvement for the OROS methylphenidate group at days 5, 14, and 28, at day 35 (endpoint) the difference was not significant (–3.10, 95% CI = –6.36 to 0.16). A mixed model analysis indicated an overall significant treatment difference in favor of OROS methylphenidate (p = .01).

The MAF demonstrated statistically significant differences at all visits (p < .05) except endpoint (p < .27). When the mixed model analysis was performed for the MAF scale, a statistically significant difference was found in favor of OROS methylphenidate (F = 6.82, df = 1, p < .01).

The mean CGI-I score was statistically significant at day 14 in favor of OROS methylphenidate (2.8 vs. 3.3 for placebo, p < .01; not corrected for multiple comparisons) but not at endpoint.

The SEX-FX (function) for patients sexually active at baseline demonstrated a mean change at endpoint for placebo of 0.9 and for OROS methylphenidate of 3.9 (in favor of OROS methylphenidate, p < .03). Mean change in SEX-FX (global sexual impression [GSI]) did not show any differences between the groups (–0.1 for placebo and 0.4 for OROS methylphenidate, p = .45). The SEX-FX

Table 6. Mean HAM-D-7[a] Score Change From Baseline (intent-to-treat population)

Visit	Group	N	Mean	SD	Difference	95% CI	p Value
Day 5	OROS methylphenidate	72	–0.94	1.95	0.17	–0.55 to 0.88	.65
	Placebo	72	–1.11	2.38			
Day 14	OROS methylphenidate	66	–1.48	2.11	0.18	–0.63 to 0.98	.66
	Placebo	71	–1.66	2.59			
Day 21	OROS methylphenidate	64	–1.80	2.40	0.10	–0.76 to 0.97	.82
	Placebo	69	–1.90	2.64			
Day 28	OROS methylphenidate	62	–1.87	2.64	0.35	–0.61 to 1.31	.47
	Placebo	68	–2.22	2.85			
Day 35 (final visit)	OROS methylphenidate	72	–1.53	2.49	0.63	–0.27 to 1.52	.17
	Placebo	72	–2.15	2.92			

[a]HAM-D-7 = the 7 atypical items that measure atypical depressive symptoms from the 31-item Hamilton Rating Scale for Depression (HAM-D).
Abbreviation: OROS = osmotic-release oral system.

Table 7. Clinical Impressions-Severity of Illness Scale Scores Over Time (intent-to-treat population)

Visit	Group	N	Mean	SD	p Value
Baseline	OROS methylphenidate	73	4.3	0.5	.50
	Placebo	72	4.4	0.6	
Day 5	OROS methylphenidate	72	4.0	0.8	.02
	Placebo	72	4.3	0.5	
Day 14	OROS methylphenidate	66	3.7	0.9	.10
	Placebo	71	3.9	0.7	
Day 21	OROS methylphenidate	64	3.5	1.1	.44
	Placebo	69	3.6	0.9	
Day 28	OROS methylphenidate	62	3.2	1.1	.21
	Placebo	68	3.4	1.0	
Day 35 (final visit)	OROS methylphenidate	72	3.2	1.2	.43
	Placebo	72	3.3	1.1	

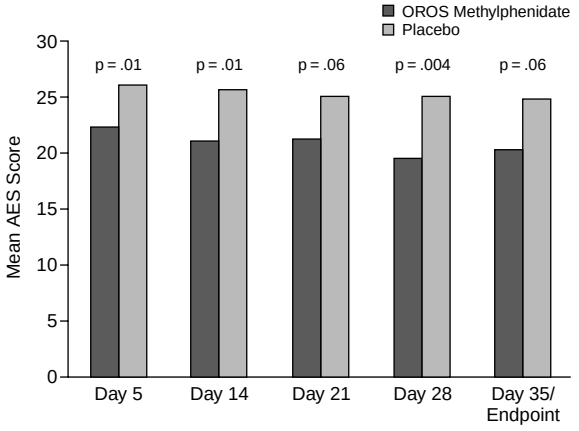
Abbreviation: OROS = osmotic-release oral system.

Table 8. Clinical Global Impressions-Improvement Scores Over Time (intent-to-treat population)

Visit	Group	N	Mean	SD	p Value
Day 5	OROS methylphenidate	72	3.5	0.9	.05
	Placebo	72	3.7	0.6	
Day 14	OROS methylphenidate	66	2.8	1.0	.007
	Placebo	71	3.3	0.9	
Day 21	OROS methylphenidate	64	2.9	1.2	.48
	Placebo	69	3.0	1.1	
Day 28	OROS methylphenidate	62	2.6	1.2	.27
	Placebo	68	2.8	1.1	
Day 35 (final visit)	OROS methylphenidate	72	2.7	1.2	.38
	Placebo	72	2.8	1.1	

Abbreviation: OROS = osmotic-release oral system.

Figure 2. Change in Apathy Evaluation Scale (AES) Mean Score Over Time[a]



[a]p Values in favor of OROS methylphenidate.
Abbreviation: OROS = osmotic-release oral system.

function and GSI for patients not sexually active at baseline demonstrated no statistical difference in terms of function (p = .62) or GSI (p = .36).

Safety

Fifty-one patients (69.9%) in the active group and 43 (59.7%) in the placebo group had at least 1 adverse event. Of these, 6 patients in the active group discontinued due to adverse events. Table 10 lists treatment-emergent adverse events in 3 subjects or more. The OROS methylphenidate group included 1 patient who experienced a serious adverse event (hospitalization due to bone fractures). Five OROS methylphenidate patients and 3 placebo patients reported adverse events at a severity level judged to be severe; 45% of OROS methylphenidate and 39% of placebo patients' adverse events were considered by the physician to be related to study medication.

Heart rate in the OROS methylphenidate group increased by a mean of 1.3 beats per minute at endpoint, in comparison to a mean 1.7 beats per minute decrease in heart rate in the placebo group. Mean systolic blood pressure increased by 1.1 mm Hg in the OROS methylphenidate group compared to a 0.8 mm Hg decrease in the placebo group. A similar effect was seen in diastolic blood pressure. All vital signs are presented in Table 11. Four subjects, all in the placebo group, developed clinically significant laboratory test results (elevated cholesterol and/or triglycerides were common to all) over the course of the study. There were no clinically significant ECG findings in either group. A mean weight decrease of 1.1 kg was noted in the OROS methylphenidate group compared to a mean weight gain of 0.1 kg in the placebo group.

Table 9. Apathy Evaluation Scale Change From Baseline (intent-to-treat population)

Visit	Group	N	Mean	SD	Difference	95% CI	p Value
Day 5	OROS methylphenidate	72	–3.25	5.69	–2.33	–4.20 to –0.47	.01
	Placebo	72	–0.92	5.63			
Day 14	OROS methylphenidate	66	–4.70	7.27	–3.23	–5.69 to –0.77	.01
	Placebo	71	–1.46	7.29			
Day 21	OROS methylphenidate	64	–4.86	7.28	–2.67	–5.49 to 0.15	.06
	Placebo	69	–2.19	9.01			
Day 28	OROS methylphenidate	62	–6.84	8.29	–4.54	–7.59 to –1.50	.004
	Placebo	68	–2.29	9.20			
Day 35 (final visit)	OROS methylphenidate	72	–5.32	9.15	–3.10	–6.36 to 0.16	.06[a]
	Placebo	72	–2.22	10.60			

[a]A mixed-model analysis indicated an overall significant treatment difference in favor of osmotic-release oral system (OROS) methylphenidate (p = .01).

Table 10. Treatment-Emergent Adverse Events Reported in at Least 3 Subjects

Event	OROS Methylphenidate (N = 73), % (N)	Placebo (N = 72), % (N)
Headache	30.14 (22)	19.44 (14)
Nausea	15.07 (11)	9.72 (7)
Appetite decreased NOS	8.22 (6)	2.78 (2)
Common cold	8.22 (6)	1.39 (1)
Abdominal cramps	5.48 (4)	0 (0)
Dry mouth	5.48 (4)	4.17 (3)
Fatigue aggravated	5.48 (4)	1.39 (1)
Anxiety	5.48 (4)	1.39 (1)
Insomnia	5.48 (4)	6.94 (5)
Diarrhea	4.11 (3)	2.78 (2)
Appetite loss	4.11 (3)	0 (0)
Dizziness	4.11 (3)	1.39 (1)
Migraine	1.37 (1)	4.17 (3)
Irritability	4.11 (3)	2.78 (2)
Sweating	4.11 (3)	1.39 (1)

Abbreviations: NOS = not otherwise specified, OROS = osmotic-release oral system.

Table 11. Mean Vital Signs

	OROS Methylphenidate		Placebo	
Vital Sign/Visit	N	Mean (SD)	N	Mean (SD)
Heart rate, bpm				
Baseline	73	76.2 (10.2)	72	76.7 (12.0)
Day 35 (final visit)	72	77.3 (10.7)	71	74.9 (10.8)
Systolic BP, mm Hg				
Baseline	73	124.0 (14.8)	72	121.1 (14.0)
Day 35 (final visit)	72	124.9 (15.5)	71	120.4 (14.8)
Diastolic BP, mm Hg				
Baseline	73	78.0 (10.5)	72	76.1 (8.5)
Day 35 (final visit)	72	79.6 (10.5)	71	75.9 (9.6)

Abbreviations: BP = blood pressure, bpm = beats per minute, OROS = osmotic-release oral system.

DISCUSSION

In clinical practice, clinicians use methylphenidate as an augmenting agent to antidepressants, but there is limited evidence to support this treatment decision due to a lack of well designed, robust, randomized controlled trials (RCTs). The data available in the literature are comprised mainly of case series and open studies that reported favorably on the efficacy of methylphenidate.[4,6,18–21] A recent abstract of an RCT by Masand et al.[10] found that both OROS methylphenidate and placebo demonstrated improvement in depressive symptoms, but this was not statistically significant at endpoint (a similar finding to this report). The authors attributed the negative result to small sample size, short duration, and suboptimal doses used in the study.

Current literature on antidepressant response confirms multiple latency for the onset of action of these agents.[22,23] The delayed onset of an antidepressant effect has been attributed to adaptive cellular changes that follow a slow time course. The use of high initial pulse loading, dual action agents (e.g., venlafaxine), or augmentation with lithium, pindolol, and psychostimulants may all accelerate antidepressant effects.[4,18,24] In early case series,[4,19] adding methylphenidate was associated with a faster onset of response to tricyclics. More recently, such enhanced antidepressant response was reported in elderly depressed patients who received citalopram and methylphenidate compared to citalopram-placebo combination.[9]

In our study, there was no significant difference between groups at endpoint on the MADRS. There was symptom improvement noted for OROS methylphenidate at day 14 of treatment (as measured by the MADRS and CGI-I; no correction for multiple comparisons) compared to placebo, but the difference between groups did not continue to day 21 and after. It is also unclear whether the improvement noted with the MADRS on day 14 is explained by the effect on fatigue and apathy. Fatigue and apathy are frequent residual physical symptoms found in depressed patients, often persisting with partial or nonresponse to antidepressant treatment.[25,26] These residual symptoms contribute to poor quality of life and increased vulnerability to relapse.[27] An inclusion criterion for the study was a minimum score of ≥ 2 on the lassitude item of the MADRS at baseline, hence selecting a population that may benefit from the effects of a psychostimulant. OROS methylphenidate was found

to be superior to placebo on 2 measures: the AES and the MAF scales. Previous studies have reported the beneficial effect of other stimulants, including modafinil, in residual fatigue and antidepressant sedation in patients with depression.[28,29] Dopaminergic dysfunction has been proposed to mediate such fatigue and other physical symptoms,[30] hence, the beneficial effect of OROS methylphenidate on fatigue and apathy may be attributed to its enhancement of dopaminergic neurotransmission. Clinically, it has been observed that some patients whose depression ameliorated on SSRI therapy subsequently developed apathy and fatigue while other symptoms remained improved.[31] Although evidence from RCTs are lacking, dopaminergic agents have been reported to alleviate these symptoms.[31] Given the effect on the symptoms of apathy and fatigue, perhaps a patient population with these predominant features may benefit from adjunctive use of OROS methylphenidate.

OROS methylphenidate was well tolerated, with each group reporting only 1 serious adverse effect. This is in keeping with previous investigations both in the adult population[20,21] and in the elderly.[9] Importantly, there were no clinically significant effects on mean heart rate or blood pressure changes. The retention rate of 84.9% (62/73) in our study also speaks to the tolerability of OROS methylphenidate.

Clinical Limitations

This study has several shortcomings. It is a study of relatively short duration and the enrolment of subjects was from multiple sites with small patient numbers from each site. Fewer centers with larger patient numbers from each may have mitigated the 41.7% (30/72) placebo response rate, although placebo response rates in antidepressant studies are usually high. A training session on MADRS and CGI was held for raters based on assessment of one patient. Rater assessments of multiple patients to obtain a group κ may have also mitigated the placebo response rate. There was significant variability on the type, dose, and duration of antidepressant usage between patients. The study also included several heterogeneous subgroups, including recurrent and chronic major depressive subjects. Most placebo responders and many in the active treatment group improved in the last 3 weeks of the study. It is possible that the ongoing effect of previously prescribed antidepressants, spontaneous remissions, and the supportive therapeutic environment may have been contributory factors.

Sample size is another factor. One may speculate that at least 200 patients should have been randomly assigned to mitigate the high placebo response rate. It may have been useful to include criteria to increase study medication dose based on attaining a prespecified level of response on MADRS, since it is possible a higher dose may have been of greater therapeutic benefit.

Summary

There was no benefit of OROS methylphenidate (over placebo) augmentation of antidepressants in improving global symptoms of depression. However, OROS methylphenidate was superior to placebo in improving specific residual symptoms of fatigue and apathy and was well tolerated.

Drug names: citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), methylphenidate (Ritalin, Concerta, and others), mirtazapine (Remeron and others), modafinil (Provigil), paroxetine (Paxil, Pexeva, and others), pindolol (Visken and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Financial disclosure: **Dr. Ravindran** is a consultant for, has received grant/research support and honoraria from, and has participated in speakers/advisory boards for AstraZeneca, Cephalon, Eli Lilly, GlaxoSmithKline, Janssen-Ortho, Pfizer, Roche, Servier, and Wyeth. **Dr. Kennedy** has received research support or speakers honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen-Ortho, Lundbeck, Organon, Servier, and Wyeth. **Dr. O'Donovan** is a consultant to Janssen-Ortho; has received honoraria from Janssen, AstraZeneca, Wyeth, and Biovail; and has participated in speakers/advisory boards for AstraZeneca, Wyeth, and Biovail. **Dr. Fallu** has received research support from Bristol-Myers Squibb, AstraZeneca, Janssen-Ortho, GlaxoSmithKline, Lundbeck, Pfizer, Eli Lilly, Merck-Frosst, and Shire; is a consultant to Shire, AstraZeneca, Janssen-Ortho, GlaxoSmithKline, Eli Lilly, Lundbeck, Biovail, Wyeth, and Pfizer; and has participated in CME activities for Wyeth, AstraZeneca, Janssen-Ortho, GlaxoSmithKline, Lundbeck, Shire, Biovail, and Eli Lilly. **Dr. Camacho** is a consultant for Janssen-Ortho and Ortho Biotech. **Ms. Binder** is an employee of Janssen-Ortho, Inc.

REFERENCES

1. Kennedy SH, Lam RW. Enhancing outcomes in the management of treatment resistant depression: a focus on atypical antipsychotics. Bipolar Disord 2003;5(suppl 2):36–47
2. Jacobson A. The use of Ritalin in psychotherapy of depressions of the aged. Psychiatr Q 1958;32:474–483
3. Concerta [product monograph]. Fort Washington, Pa: McNeil Pediatrics; July 26, 2005
4. Gwirtsman HE, Szuba MP, Toren L, et al. The antidepressant response to tricyclics in major depressives is accelerated with adjunctive use of methylphenidate. Psychopharmacol Bull 1994;30:157–164
5. Stoll AL, Pillay SS, Diamond L, et al. Methylphenidate augmentation of serotonin selective reuptake inhibitors: a case series. J Clin Psychiatry 1996;57:72–76
6. Masand PS, Anand VS, Tanquary JF. Psychostimulant augmentation of second generation antidepressants: a case series. Depress Anxiety 1998;7:89–91
7. Lavretsy H, Kim M-D, Kumar A, et al. Methylphenidate-enhanced antidepressant response to citalopram for accelerated response in the elderly: an open trial. J Clin Psychiatry 2003;64:1410–1414
8. Lavretsky H, Kumar A. Methylphenidate augmentation of citalopram in elderly depressed patients. Am J Geriatr Psychiatry 2001;9:298–303
9. Lavretsky H, Park S, Siddarth P, et al. Methylphenidate-enhanced antidepressant response to citalopram in the elderly: a double-blind, placebo-controlled pilot trial. Am J Geriatr Psychiatry 2006;14:181–185
10. Masand PS, Peindl K, Hooper-Wood C, et al. A randomized, double-blind, placebo-controlled, flexible dose trial of augmentation with OROS methylphenidate in treatment-resistant depression. Presented at the 46th annual meeting of the New Clinical Drug Evaluation Unit [poster 62]; June 13, 2006; Boca Raton, Fla
11. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The validity of the Mini-International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. Eur Psychiatry 1997;12:232–241

12. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
13. Guy W, Bonato RR, eds. CGI: Clinical Global Impressions. In: Manual for the ECDEU Assessment Battery 2, Revised Edition. Chevy Chase, Md: National Institute of Mental Health; 1970:12.1–12.6
14. Williams JBW, Link MJ, Rosenthal NE, et al. Structured interview guide for the Hamilton Depression Rating Scale, seasonal affective disorders version (SIGH-SAD). New York, NY: New York State Psychiatric Institute; 1992
15. Kennedy SH, Fulton K, Bagby RM, et al. Sexual function during bupropion or paroxetine treatment of major depressive disorder. Can J Psychiatry 2006;51:234–242
16. Bormann J, Shively M, Smith TL, et al. Measurement of fatigue in HIV-positive adults: reliability and validity of the global fatigue index. J Assoc Nurses AIDS Care 2001;12:75–83
17. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. Psychiatr Res 1991;38:143–162
18. Miller FE. Strategies for the rapid treatment of depression. Hum Psychopharmacol 2001;16:125–132
19. Naor S, Talmon Y, Guy N. Combined tricyclic antidepressants and Ritalin in elderly depressives. Harefuah 1992;123:251–252
20. El-Mallakh RS. An open study of methylphenidate in bipolar depression. Bipolar Disord 2000;2:56–59
21. Carlson PJ, Merlock MC, Suppes T. Adjunctive stimulant use in patients with bipolar disorder: treatment of residual depression and sedation. Bipolar Disord 2004;6:416–420
22. George MS, Lydiard RB. Speed of onset of action of the newer antidepressants: fluoxetine and bupropion. Int Clin Psychopharmacol 1991; 6:209–217
23. Bech P. Acute therapy of depression. J Clin Psychiatry 1993;54(suppl): 18–27
24. Leinonen E, Skarstein J, Behnke K, et al. Efficacy and tolerability of mirtazapine versus citalopram: a double-blind, randomized study in patients with major depressive disorder. Nordic Antidepressant Study Group. Int Clin Psychopharmacol 1999;14:329–337
25. Tylee A, Gastpar M, Lepine JP, et al. Identification of depressed patient types in the community and their treatment needs: findings from the DEPRES II (Depression Research in European Society II) survey. DEPRES Steering Committee. Int Clin Psychopharmacol 1999;14: 153–165
26. Maurice-Tison S, Verdoux H, Gay B, et al. How to improve recognition and diagnosis of depressive syndromes using international diagnostic criteria. Br J Gen Pract 1998;48:1245–1246
27. Kapur S, Mann JJ. Role of the dopaminergic system in depression. Biol Psychiatry 1992;32:1–17
28. DeBattista C, Doghramji K, Menza MA, et al. Adjunct modafinil for the short-term treatment of fatigue and sleepiness in patients with major depressive disorder: a preliminary double-blind, placebo-controlled study. J Clin Psychiatry 2003;64:1057–1064
29. Schwartz TL, Azhar N, Cole K et al. An open-label study of adjunctive modafinil in patients with sedation related to serotonergic antidepressant therapy. J Clin Psychiatry 2004;65:1223–1227
30. Roth BL, Meltzer HY. The role of serotonin in schizophrenia. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven; 1995:1215–1227
31. Pies RW, ed. Chapter 2: Antidepressants. In: Handbook of Essential Pharmacology, 2nd edition. Washington, DC: American Psychiatric Publishing Inc; 2005:19–138

