Combined Treatment With Methylphenidate and Citalopram for Accelerated Response in the Elderly: An Open Trial

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Background: Accelerated antidepressant treatment response may be particularly beneficial for older patients, yet there are few data to inform clinical practice. We evaluated the potential of methylphenidate to accelerate antidepressant response to citalopram and the safety and tolerability of the combined treatment in patients with geriatric major depressive disorder.

Method: We studied 11 elderly outpatients aged 70 years and older who were diagnosed with DSM-IV major depressive disorder in a 10-week, open-label, structured trial (July 2001–July 2002). Methylphenidate was tapered and discontinued during weeks 9 and 10. Response was defined as a Hamilton Rating Scale for Depression (HAM-D) score of less than 10. The daily dose of citalopram ranged between 20 and 40 mg, and the daily dose of methylphenidate ranged between 5 and 20 mg.

Results: Nine patients completed the study. Six patients met criteria for accelerated response (HAM-D score < 10 and Clinical Global Impressions-Improvement scale score of 1 or 2 by treatment day 14), and 2 more patients responded by week 3. One patient was a nonresponder. The mean (SD) citalopram dose for all subjects was 27.5 (10.3) mg and the mean (SD) methylphenidate dose was 12.2 (4.9) mg. The observed side effects were mild to moderate in severity and included sedation, nausea, anxiety, polyuria, dry mouth, and hypersalivation.

Conclusion: Methylphenidate augmentation of citalopram may be a safe and viable strategy for accelerating antidepressant response in elderly depressed patients. The results of this open-label trial need to be confirmed in a placebo-controlled trial.

(J Clin Psychiatry 2003;64:1410–1414)

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This work was supported by grants K23-MH01948 from the National Institute of Mental Health and M01-RR00865 from the National Institutes of Health, Bethesda, Md. (Dr. Lavretsky) and grants R25-MH60473, R-01 MH37869, and P30-MH52247 from the National Institute of Mental Health, Bethesda, Md. (Dr. Reynolds).

Dr. Reynolds has received grant/research support from and has served on the speakers or advisory boards for Forest and GlaxoSmithKline and has received honoraria from Forest, Eli Lilly, and GlaxoSmithKline.

The authors thank Jim Mintz, Ph.D., for statistical advice.

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Depression in later life is associated with increased mortality related to suicide and medical illness.[1] The existing evidence indicates that antidepressant response is less adequate in patients aged 70 years and older compared with that in younger patients.[2] The number of controlled studies of antidepressant response in patients over 70 years of age is limited,[3,4] especially trials involving the use of augmentation techniques.[5–9] Accelerated treatment response may be particularly beneficial for older patients.

Augmentation with a rapidly acting agent may help to accelerate antidepressant response.[3,4] Dopaminergic agents and psychostimulants that act on mesolimbic dopaminergic projections have been suggested as potential candidates to promote acceleration of response.[5,6] Methylphenidate (MPH) has been most commonly used in the elderly due to its shorter response latency compared with pemoline and improved safety features compared with dextroamphetamine.[7–9]

Some earlier studies have pointed out the possible efficacy of stimulants in treating patients with severe medical illnesses and elderly patients suffering from concurrent depression.[8–14] Psychostimulants used in combination with antidepressant drugs provide an enhanced response to antidepressants in patients previously unresponsive to treatment and appear to be a rapid, safe, and efficacious augmentation strategy.[8,15,16] Stimulants may not only augment selective serotonin reuptake in-

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hibitors (SSRIs) but also shorten the response latency to SSRIs if coadministered early in treatment. We previously reported the results of a naturalistic treatment study in a different group of elderly patients who received MPH augmentation of citalopram to enhance antidepressant response in treatment-resistant patients and to accelerate treatment response in severely ill patients.[17] A single brief report on 9 mixed-age (24–66 years) patients using early augmentation of sertraline (50–100 mg) with 5 mg of MPH administered twice a day in a randomized double-blind trial indicated that no patients taking MPH and sertraline had accelerated response within a week.[18]

This article summarizes the results of a structured open-label trial that evaluated the potential of methylphenidate to accelerate antidepressant response to citalopram and evaluated the safety and tolerability of the combined treatment in 11 patients with geriatric major depressive disorder.

METHOD

Subjects

We studied 11 outpatients aged 70 years and older (mean age = 78.1 years; women, N = 6; white, N = 10) diagnosed with major depressive disorder. After completely describing the study to the subjects, written informed consent was obtained in accordance with the procedures set by the University of California (Los Angeles) Institutional Review Board (IRB). Study protocol was also approved by the IRB.

All subjects met the inclusion criteria: (1) current major depressive episode, (2) 21-item Hamilton Rating Scale for Depression (HAM-D)[19] score of 20 or higher at baseline (mean score = 22.4), and (3) Mini-Mental State Exam (MMSE)[20] score of 24 or higher. The subjects were excluded if they had (1) a history of other psychiatric illness or alcohol or substance abuse/dependence, (2) severe or acute medical illness, (3) acute suicidal or violent behavior, or (4) any other central nervous system diseases or dementia. Subjects with preexisting anxiety (N = 3) were not excluded if the anxiety was considered to be a part of mixed anxiety and depression.

Nine subjects had chronic major depressive disorder with a duration of at least 24 months for the current episode, and 8 subjects had recurrent major depressive disorder. Eight subjects had prior unsuccessful trials with antidepressant medications, and 4 subjects met the criteria for treatment resistance after 2 adequate trials with antidepressants of 2 different classes. Patients were free of psychotropic medications for at least 2 weeks prior to initiation of the trial. All patients were taking between 2 and 16 additional medications for coexisting medical conditions.

Procedures

All subjects underwent the Structured Clinical Interview for DSM-IV[21] administered by 1 rater (H.L.) to estprovement scale (CGI-I)[22] score of 1 ("very much improved") or 2 ("much improved"); (2) accelerated or rapid response was defined as achieving criteria for response by day 14 of treatment according to weekly HAM-D and CGI assessments that were maintained throughout the study, (3) remission was defined as a HAM-D score of 6 or less, (4) relapse after discontinuation of MPH was defined as a HAM-D score greater than 10 after response was achieved and maintained through the first 8 weeks of the trial.

All subjects received an initial assessment including complete physical and neuropsychiatric examinations, electrocardiogram, and laboratory testing at baseline to rule out new-onset medical illnesses that could account for behavioral symptoms.

Study Medications and Treatment Procedures

Patients were seen weekly for 10 weeks from July 2001 to July 2002. Treatment with both drugs was initiated simultaneously after the baseline assessment. The starting dose for MPH was 2.5 mg twice a day and for citalopram was 20 mg daily. The titration schedule included doubling the MPH dose every 3 days until patients reached a 10-mg daily dose by the end of week 1. If patients had a CGI-I score of 3 or greater by the end of week 1, the MPH dose was further increased to 20 mg a day by the end of the second week of treatment and continued until the end of week 8, if tolerated. During the last 2 weeks of the trial, MPH was tapered in 2.5-mg twice-daily decrements every 3 days to observe symptoms of withdrawal or emerging depression. Citalopram was continued in the daily dose of 20 mg throughout the trial if subjects had a CGI-I score of 1 or 2. However, the daily dose was increased to 40 mg at the end of week 4 in patients with a CGI-I score of 3 or greater. In case of intolerable adverse effects, dose reduction was allowed to a minimum of 5 mg a day of MPH and 10 mg a day of citalopram. The use of concomitant medications was restricted to lorazepam up to 1 mg a day. At the end of the trial, the decision was made to continue the prescribed medication(s) or switch to another antidepressant based on treatment response and tolerability.

Assessment Instruments

The HAM-D[19] was used to quantify mood symptoms. The CGI-I[22] served as a measure of overall clinical improvement. The secondary efficacy evaluation included the Montgomery-Asberg Depression Rating Scale (MADRS),[23] a 10-item depression scale sensitive to change over time. Cognitive performance was measured by the MMSE.[20] Medical comorbidity was measured by the Stroke Risk Factor Prediction Chart (SRF)[24] of the

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Table 1. Individual Hamilton Rating Scale for Depression (HAM-D) Scores at Baseline and Weeks 1, 2, 3, 8, and 9 of Active Treatment With Methylphenidate and Citalopram

Subject	Sex	Age, y	HAM-D Score						Lorazepam Use
			Baseline	Week 1	Week 2	Week 3	Week 8	Week 9	
1	M	70	23	12	4	4	6	0	No
2	M	86	20	13	9	5	2	1	No
3	M	81	21	1	9	3	0	0	No
4	F	74	25	15	3	4	4	3	No
5	F	73	20	5	11	7	5	12	No
6	F	75	21	13	8	0	8	17	Yes
7	M	79	20	6	0	3	0	0	No
8[a]	F	73	20	20	N/A	N/A	N/A	N/A	No
9	F	77	20	13	12	6	7	7	No
10	F	92	32	20	18	15	14	19	Yes
11[b]	M	80	24	20	12	14	N/A	N/A	Yes

[a]Subject dropped out due to side effects after 1 week of treatment.
[b]Subject dropped out due to lack of response at week 3.
Abbreviations: F = female, M = male, N/A = not available.

American Heart Association for rating cerebrovascular risk factors, including age, systolic blood pressure, antihypertensive medication use, history of diabetes, smoking, previous strokes, atrial fibrillation, and left ventricular hypertrophy. The Cumulative Illness Rating Scale-Geriatric (CIRS-G)[25] was used for rating global chronic medical illness burden.

Vital signs and weight were measured during each visit. Side effects were assessed by the UKU side effect rating scale (UKU).[26] Plasma drug levels of citalopram and MPH and their active metabolites desmethylcitalopram and ritalinic acid were determined at weeks 2 and 8 using high performance liquid chromatography/mass spectrometry method with fluorescent detection.[27]

Statistical Analysis

All data were entered into the database at the time of collection. Descriptive statistics to assess outcomes were computed. Safety analyses were performed using descriptive statistics and frequency distribution of dropouts. The response of the entire sample according to HAM-D scores was analyzed by using the repeated-measures analysis of variance. Patients who demonstrated accelerated response were compared with those who did not on all clinical and demographic measures using the t test. The level of significance was set at the alpha level of $p < .05$.

RESULTS

Nine patients completed the study. The entire group of completers experienced improvement in HAM-D scores at week 2 (N = 10) ($F = 56.4$, df = 2,8; $p < .0001$) and at week 8 (N = 9) ($F = 278.8$, df = 7,2; $p < .0001$) of active treatment. The mean (SD) daily dose of citalopram used in all subjects was 27.5 (10.3) mg and the mean daily MPH dose was 12.2 (4.9) mg.

Six patients met criteria for accelerated response (HAM-D score < 10 and CGI-I score of 1 or 2 by treatment day 14). Patients who achieved accelerated response (N = 6) differed from those who did not (N = 4) in the lower HAM-D scores (mean [SD] score = 5.5 [3.7] vs. 13.0 [3.5]; $t = 3.2$, df = 8, $p = .01$) supported by the lower MADRS scores (mean [SD] score = 13.8 [5.7] vs. 22.5 [11.7]; $t = 3.2$, df = 8, $p = .01$) at week 2. Three patients achieved remission and had HAM-D scores below 7 at week 2. The rapid responders (N = 6) and nonrapid responders (N = 4) did not differ on baseline HAM-D scores (mean [SD] score = 21.7 [2.0] vs. 24.0 [5.7]; $t = 0.95$, df = 8, $p = .37$), baseline SRF scores (mean [SD] score = 12.3 [5.4] vs. 15.8 [9.7]; $t = 1.7$, df = 8, $p = .5$), or CIRS-G scores (mean [SD] score = 6.5 [2.4] vs. 7.8 [1.5]; $t = 0.9$, df = 8, $p = .4$), respectively. The 2 groups did not differ on other clinical and demographic characteristics.

An additional 2 patients (or 8 of 9 completers) responded by week 3. Time to response for the majority of the completer sample (N = 8 of 9 [85%]) was 3 weeks. Table 1 characterizes the course of HAM-D score changes for all subjects.

The subjects with rapid response required mean (SD) daily doses of 26.67 (11.55) mg of citalopram and 9.17 (1.44) mg of MPH, while subjects without rapid response received a mean (SD) daily dose of 28.57 (10.69) mg of citalopram and 14.29 (4.50) mg of MPH.

Five of 6 rapid responders maintained response until week 8. Five of 8 responders continued to maintain antidepressant response even after MPH was discontinued at weeks 9 and 10. Three patients experienced worsening of their symptoms and required reinstatement of MPH. One female subject, who initially responded rapidly, experienced worsening in symptoms at week 5, then improved with the increase in methylphenidate dose to 20 mg a day. The only completer who failed to respond was the oldest subject in the group, a 92-year-old woman.

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Two subjects dropped out, 1 due to side-effects after 1 week and 1 due to lack of response at week 3.

All subjects reported between 1 and 4 side effects. However, all subjects but 1 were able to tolerate them and complete the trial. The observed side effects were mild to moderate in severity, rated 1 or 2 on the UKU, and included sedation (N = 1 [1%]), impaired concentration (N = 1 [1%]), nightmares (N = 1 [1%]), nausea (N = 1 [1%]), anxiety (N = 2 [2%]), muscle twitching (N = 1 [1%]), polyuria (N = 3 [3%]), diarrhea (N = 1 [1%]), dry mouth (N = 1 [1%]), and hypersalivation (N = 1 [1%]). Two patients required dose reduction of MPH due to nausea and anxiety. One male patient experienced an improvement in sexual functioning. None of the patients experienced any significant changes in blood pressure, heart rate, or weight. The fluctuation of systolic and diastolic blood pressure and pulse did not exceed 10% in any patient throughout the trial. No patient developed tolerance to MPH.

Three patients used lorazepam as an adjunct medication, but they had a history of preexisting anxiety and prior benzodiazepine use. Despite the use of lorazepam during the trial, all 3 had unfavorable outcomes. One was a nonrapid responder, 1 dropped out at week 3, and the third had fluctuations in HAM-D scores throughout the trial and relapsed after MPH discontinuation.

Although the rapid responders required smaller doses of MPH than did nonrapid responders (mean [SD] dose = 9.2 [2.0] mg vs. 11.9 [3.8] mg at week 2 and 10 mg [2.7] vs. 13.3 mg [5.8] at week 8), the differences between the groups in the dose and the achieved plasma levels of MPH and ritalinic acid (not shown) were not statistically significant. This can be explained by the relatively narrow range of the MPH dose used in the trial (i.e., 7.5–20 mg daily). We observed the same trend in relation to the citalopram dose and plasma levels.

DISCUSSION

This is the first report of a structured open-label trial of MPH augmentation of citalopram used to accelerate antidepressant response in elderly depressed patients aged 70 years and older. The observed reduction in time to response relative to that usually reported is dramatic given the existing observations of prolonged onset of antidepressant action in the elderly.[28] There are no reports of accelerated response to SSRIs in the elderly. Waugh and Goa[29] claimed rapid onset of symptom improvement with escitalopram within 1 to 2 weeks in younger adults. However, the criteria for response or onset of symptom improvement were less stringent compared with those used in this trial. This is even more impressive considering the characteristics of our group of patients, with 9 subjects suffering from chronic major depressive disorder and showing lack of response to other antidepressants. Our results support our previous encouraging findings from a different group of patients with treatment-resistant depression.[17]

Our preliminary observations suggest that a combination of MPH and citalopram is relatively well tolerated by elderly patients and may induce a rapid response even among treatment-refractory patients. The observed interindividual differences in response may occur due to differences in drug metabolism. Methylphenidate is known to inhibit cytochrome P450 2D6 enzymes, which are also involved in the metabolism of citalopram.[17] However, in our sample, we did not detect any clear relationship between plasma drug levels and drug response.

We cannot consider our results conclusive due to the small number of subjects, the relatively short duration of the trial, and the lack of a control group. Although our group of patients was able to tolerate the combined treatment relatively well, caution should be used in combining pharmacotherapy in frail older patients to avoid potentially serious adverse events such as cardiovascular side effects. Based on our limited experience, patients with preexisting anxiety may have no or only limited benefit from the use of the combination of citalopram and MPH, even with the concomitant use of lorazepam. Our preliminary findings warrant further investigation in a randomized, double-blind, placebo-controlled trial.

Drug names: citalopram (Celexa), dextroamphetamine (Dexedrine, Dextrostat, and others), escitalopram (Lexapro), lorazepam (Ativan and others), methylphenidate (Ritalin, Concerta, and others), pemoline (Cylert and others), sertraline (Zoloft).

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