Methylphenidate in Early Poststroke Recovery: A Double-Blind, Placebo-Controlled Study

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ABSTRACT. Grade C, Redford B, Chrostowski J, Toussaint L, Blackwell B. Methylphenidate in early poststroke recovery: a double-blind, placebo-controlled study. Arch Phys Med Rehabil 1998;79:1047-50.

Objective: To determine the efficacy and safety of methylphenidate in acute stroke rehabilitation.

Design: A prospective, randomized, double-blind, placebo-controlled study.

Patients and Setting: Twenty-one stroke patients consecutively admitted to a community-based rehabilitation unit.

Intervention: Three-week treatment of methylphenidate (or placebo) in conjunction with physical therapy. Methylphenidate was started at 5mg and increased gradually to 30mg (15mg at 8:00AM and 15mg at 12:00 noon), and discontinued before discharge.

Main Outcome Measures: Mood measures included the Hamilton Depression Rating Scale (HAM-D) and Zung Self-Rating Depression Scale (ZDS). Cognitive status was evaluated using the Mini-Mental State Exam (MMSE). Motor functioning was assessed using the Fugl-Meyer Scale (FMS) and a modified version of the Functional Independence Measure (M-FIM). All measures were administered pretreatment and weekly thereafter. Side effects were measured after each increase in dosage and weekly.

Results: Patients receiving methylphenidate treatment scored lower on the HAM-D ($F(1,18) = 5.714$, $p = .028$), lower on the ZDS ($F(1,18) = 4.206$, $p = .055$), higher on the M-FIM ($F(1,18) = 5.374$, $p = .032$), and higher on the FMS ($F(1,9) = 4.060$, $p = .075$) than patients receiving placebo.

Conclusion: Methylphenidate appears to be a safe and effective intervention in early poststroke rehabilitation that may expedite recovery.

RECOVERY FROM AN acute cerebrovascular accident is a daunting task that more than 500,000 Americans face each year. Physical rehabilitation is often hampered by fatigue, communication deficits, cognitive impairment, and depression[1] (which affects 30% to 60% of stroke victims[2]). These symptoms directly interfere with the already intimidating process of rehabilitation.

Two double-blind, placebo-controlled studies have shown the utility of antidepressant medications in recovery from poststroke depression.[3,4] Unfortunately, their side effects may complicate acute stroke recovery, especially in the first 2 weeks, often before any antidepressant effect is seen. Because of these complications associated with the use of standard antidepressants in an elderly, acute-stroke population, attention has turned to the use of stimulant medications.[5]

Research into the effect of stimulants on poststroke recovery has progressed using animal and human models. Feeney and associates[6] found that amphetamine hastened recovery of motor function in poststroke rats. A small, double-blind study of humans also showed that amphetamine significantly accelerated recovery during physical therapy.[7] Both animal and human research have indicated potential benefits with the use of stimulants in the acute poststroke setting.

Methylphenidate (Ritalin[a]) is a stimulant that offers the advantage of a mild side-effect profile and immediate onset of action. Thus, it is ideal for use in an acute rehabilitation setting.[8,9] An open-label, uncontrolled study of the effect of methylphenidate on poststroke depression concluded that it was safe and effective.[10] In addition, the incidence of problematic side effects was low, and there were no patient dropouts.

Our study was designed as a double-blind, placebo-controlled investigation of the effect of methylphenidate on poststroke recovery. Methylphenidate was expected to improve mood, cognition, and motor function. In addition, methylphenidate was expected to be well tolerated and produce few major side effects.

DESIGN AND PROCEDURE

Patients

Patients included in this study were able to comprehend and comply with protocol requirements. Informed consent was obtained from all participants or from guardians if necessary. The study was approved by the institutional review board at Sinai Samaritan Medical Center and was not funded by any outside source.

The study group consisted of patients consecutively admitted between November 1993 and June 1994 to the rehabilitation unit at Sinai Samaritan Medical Center, an urban medical center affiliated with the University of Wisconsin Medical Center, who were diagnosed with stroke (all types) based on clinical history, neurologist evaluation, and computed tomography (CT). The criteria for exclusion from the study were as follows: childbearing potential, hypersensitivity to methylphenidate, significant medical conditions, schizophrenia, delusional disorder, atypical psychosis, glaucoma, Tourette disorder, motor tics, uncontrolled epilepsy, malignant hypertension, prominent agitation, and current antidepressant treatment. Patients with aphasia symptoms were retained in the study if their symptoms were judged to be not of sufficient severity to interfere with completion of the test instruments.

Thirty-one patients were admitted after acute stroke, but 10 were not included in the trial. Five patients were excluded because of acute medical problems: 2 with delirium, 1 with

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gastrointestinal bleed, 1 with severe congestive heart failure, and 1 with renal failure who was on dialysis. Five other patients did not give consent, two of whom had severe aphasia. Twenty-one patients were enrolled in the study. Ten received methylphenidate and 11 were given placebo.

In the methylphenidate group, 5 patients completed 3 weeks of the study, 2 completed 2 weeks, and 3 completed 1 week. Four patients completing 1 or 2 weeks had significant clinical improvement leading to early discharge. One patient developed abdominal pain from peptic ulcer disease and was withdrawn from the study.

In the placebo group, 8 patients completed 3 weeks of the study, 2 completed 2 weeks, and 1 completed 1 week. The two patients completing 2 weeks showed significant improvement and were discharged early. One patient was disenrolled after 1 week because of worsening depression.

Drug Protocol

Using a random numbers table, the pharmacy department randomly assigned all patients to receive either methylphenidate or placebo in identical capsules. All patients and their families, as well as nurses and clinical examiners, were unaware of which participants were receiving methylphenidate. The drug protocol developed for this study was based on that used in previous case studies[10-12] and on guidelines in the Physicians Desk Reference.[13] The starting dosage was one capsule (5mg) given on day 1 at 8:00AM. Patients were closely monitored for any adverse effects over the first 24 hours; if none were present, the dosage was increased to one capsule given twice daily at 8:00AM and 12:00 noon on day 2. While under close observation, the dosage was increased by one capsule every 3 days. The maximum dosage[13] consisted of three capsules (30mg) taken twice daily. Analysis of variance (ANOVA) showed no significant difference between the methylphenidate ($\overline{X}$ = 22.22, SEM = 1.89) and placebo group ($\overline{X}$ = 24.55, SEM = 1.71) in average total dosage achieved, $F(1,18) = .832$, $p = .374$. The use of methylphenidate was confined to the period of acute recovery during hospitalization. The maximum duration of treatment was 3 weeks, after which medication was tapered off over the course of 5 days.

Measures

Neurologic. All patients underwent an initial physical examination, laboratory screening, and CT. To evaluate the equivalence of both groups with regard to neurologic factors, the following data were collected: (1) the number of days since the stroke occurred, (2) which hemisphere was affected, (3) whether the stroke was cortical or subcortical, (4) any history of stroke, and (5) hemispheric dominance. Patients also received neurologic consultation and treatment planning for rehabilitation.

Demographic. Answers to a patient demographics questionnaire provided data on age, gender, race, and marital status. A measure of social functioning was also completed. The social functioning exam[14] (SFE) is a 28-item survey that evaluates satisfaction with one's social and environmental setting.

Outcome. Primary outcome measures assessed mood, cognition, and motor functioning. These measures were administered before treatment and weekly thereafter. As reported above, some patients did not require 3 full weeks of treatment, and thus scores from each week were summed and divided by the number of weeks completed to produce an average improvement score. The Hamilton Depression Rating Scale[15] (HAM-D) and Zung Self-Rating Depression Scale[16] (ZDS) were used to evaluate mood, the Mini-Mental State Exam[17] (MMSE) was used to assess cognitive status, and the Fugl-Meyer Scale[18] (FMS) and a modified version of the Functional Independence Measure[19] (M-FIM) were used to evaluate motor function.

Depression. The HAM-D is a 25-item examiner-rated scale. For each item, patients are rated on a scale of 0 (none) to 4 (extreme). Total scores range from 0 to 100. The ZDS is a 20-item scale. The patient responds to each item on a scale of 1 (none or a little of the time) to 4 (most or all of the time). Total scores range from 20 to 80. Both scales were administered at a consistent time of day (between 3:00 PM and 5:00 PM).

Cognition. The MMSE is an examiner-rated instrument used to determine cognitive status. Five areas of general cognitive functioning are assessed: (1) orientation, (2) registration, (3) attention and calculation, (4) recall, and (5) language. Total scores on the MMSE range from 0 to 30, and a score of less than 24 indicates cognitive impairment.

Motor function. The M-FIM is a 29-item scale. For each item, the examiner rates the patient on a scale from 1 (complete dependence) to 7 (complete independence). Total scores range from 29 to 203. The FMS assesses functioning in the upper and lower extremities. Several aspects of functioning (reflex, coordination, speed) are rated on a scale from 0 (no function) to 2 (full function). Total scores range from 0 to 100.

Side Effects

A side-effect checklist was developed[10] to include all side effects of methylphenidate listed in the 1993 Physicians Desk Reference.[17] The checklist was completed before the study and subsequently at 3-day intervals. Examiners rated side effects on a scale of 0 to 3 based on severity. A rating of 0 indicated the absence of a side effect, and a 3 indicated that a side effect was severe enough to warrant discontinuation of the medication.

Evaluation of the Double Blind

To check the integrity of the double-blind design, a short questionnaire was given after the last rating period. Patients, examiners (psychiatrist, physical therapist, and psychologist), and other study staff (nurses and physiatrist) were asked to indicate whether they believed the patient was given methylphenidate or placebo (respondents could also answer "don't know"). Data from this questionnaire were not compiled or analyzed until the conclusion of the study, after the blind had been broken.

Statistical Analysis

Parametric data were analyzed using ANOVA and analysis of covariance (ANCOVA). Descriptive statistics calculated for these data were means and standard errors. Nonparametric data were analyzed using χ^2 tests. The descriptive statistic calculated for these data was a frequency.

RESULTS

Demographic and Neurologic Variables

Descriptive statistics for demographic and neurologic variables are presented in tables 1 and 2. Values reported in these tables are frequencies unless otherwise noted. ANOVA and χ^2 analyses revealed no difference between the methylphenidate and placebo groups regarding any demographic or neurologic variables (all p values $> .05$).

Outcome Measures

Pretreatment scores for the five outcome measures were analyzed using ANOVA, and no significant between-groups differences were found (mean $p = .52$, range = .20 to .82) (table 3). However, to increase the sensitivity and power of

Table 1: Demographic Characteristics of Patient Sample

Variable	Methylphenidate Patients ($n = 10$)	Placebo Patients ($n = 11$)
Age*	69.80 (3.66)	72.64 (3.49)
Social function*	.65 (.05)	.77 (.05)
Sex		
Male	4	7
Female	6	4
Marital status		
Married	4	5
Divorced	3	1
Widowed	2	5
Race		
Black	9	8
White	1	2
Hispanic	0	1

* Reported values are means (standard errors).

subsequent analyses, pretreatment scores were used as covariates to control even minimal preexisting differences. ANCOVA analyses on average improvement scores revealed that patients receiving methylphenidate treatment scored lower on the HAM-D ($F(1,18) = 5.714$, $p = .028$), lower on the ZDS ($F(1,18) = 4.206$, $p = .055$), and higher on the M-FIM ($F(1,18) = 5.374$, $p = .032$) (table 3). Analysis of FMS scores showed no between-groups difference ($F(1,18) = 2.400$, $p > .05$). However, a ceiling effect occurred on the FMS wherein 9 of the 21 patients had initial scores greater than or equal to 80. To account for the ceiling effect, an analysis was conducted for patients whose initial FMS scores were less than 80. ANCOVA analysis of these scores revealed that methylphenidate patients scored higher on the FMS than placebo patients ($F(1,9) = 4.060$, $p = .075$) (table 3). Thus, patients receiving methylphenidate treatment showed less depression, more success in activities of daily life, and better motor recovery. There was no difference between the methylphenidate and placebo groups on the MMSE ($F(1,18) = .385$, $p = .543$) and number of side effects manifested ($F(1,18) = .005$, $p = .942$) (table 3).

Double-Blind Evaluation

Study personnel were not able to correctly guess patient group classification at a level greater than chance. The percentage of correct classifications were as follows: psychiatrist, 42%; psychologist, 33%; physical therapist, 44%; physiatrist, 40%; nurse, 25%. Moreover, only 53% of the patients themselves correctly identified the treatment group to which they were assigned.

Table 2: Neurologic Characteristics of Patient Sample

Variable	Methylphenidate Patients ($n = 10$)	Placebo Patients ($n = 11$)
Days since stroke*	17.9 (3.74)	18.73 (3.57)
Laterality of stroke		
Left	6	4
Right	3	7
Bilateral	1	0
Stroke location†		
Cortical	4	8
Subcortical	3	3
Both	1	0
Handedness†		
Left	0	0
Right	8	11
Previous stroke		
Yes	4	2
No	6	9

* Reported values are means (standard errors).
† Data for two methylphenidate patients were missing.

DISCUSSION

The results of this study indicate that methylphenidate is a safe and effective adjunct treatment for the rehabilitation of acute stroke patients. Patients receiving methylphenidate showed improvements in mood, ability to conduct activities of daily living, and motor functioning. Furthermore, these improvements were not accompanied by an increased number of side effects.

Patients and researchers participating in double-blind studies frequently are not completely blinded, especially in studies using psychotropic agents with obvious side effects.[20] Patients and study personnel were effectively blinded in this investigation, as demonstrated by the low level of accuracy with which they identified patient group assignments. Hence, the minimal side effects encountered with methylphenidate may have helped to ensure the integrity of the double-blind design.

The results of this investigation coincide with those reported by Lazarus and coworkers[10] and demonstrate that methylphenidate can be used to treat elderly, medically ill, acute stroke patients without eliciting major side effects. Especially in comparison with standard antidepressants, methylphenidate has important clinical advantages. In the study by Lipsey and colleagues[3] using tricyclic antidepressant (TCA) nortriptyline, 35% (6 of 17) of the active treatment group dropped out with common TCA side effects: 3 became delirious, 1 was oversedated, 1 was excessively dizzy, and 1 had syncope. The study did show that patients improved significantly in measures of depression, but activities of daily living were unaffected. Another study[4] using the heterocyclic antidepressant trazodone showed a trend towards improvement in ability to conduct activities of daily living; unfortunately, 43% of the patients (6 of 14) dropped out because of side effects. Only 2 of 14 patients receiving trazodone were able to reach the target dose of 200mg. In our study only 1 patient dropped out, and that was because of a preexisting condition not clearly related to methylphenidate. Fifty percent (5 of 10) of patients given methylphenidate were able to reach the target dose of 30mg.

In addition to being relatively free from side effects that impair recovery, psychostimulant drugs have been shown to improve cognitive functions (ie, memory and attention) in patients with traumatic brain injury.[21,22] Our study did not find any difference between treatment groups in cognitive improvement, although measurement was limited by a relatively insensitive instrument (MMSE).

Methylphenidate acts by directly stimulating release of dopamine and norepinephrine, as well as blocking catecholamine reuptake.[23] Animal studies[24] suggest that even small focal cortical lesions produce widespread depletion of biogenic amines, and it has been postulated that stimulant medications exert an antidepressant effect by correcting stroke-induced reductions in these substances.[3] There is also evidence from animal data suggesting that catecholamine neurons may modulate motor recovery after brain injury[25] and drugs that antagonize catecholamine receptors (eg, haloperidol[6] and phenoxybenzamine[26]) may have negative effects on rehabilitation. Given the apparently overlapping mechanisms of recovery for depression and motor deficits, methylphenidate may be an ideal treatment agent in an acute, poststroke population. Free from side effects that hamper rehabilitation and bolstered by rapid onset of action, methylphenidate may improve mood, motiva-

Table 3: Means and Standard Errors for Pretreatment and Improvement Scores on Outcome Measures

Variable	Methylphenidate Patients		Placebo Patients	
	Pretreatment	Improvement	Pretreatment	Improvement
HAM-D	20.000 (2.967)	14.316 (1.522)	25.636 (2.829)	19.455 (1.488)
ZDS	43.300 (3.177)	32.949 (2.123)	42.273 (3.030)	38.970 (2.024)
M-FIM	97.000 (5.829)	116.460 (3.569)	90.818 ((5.558)	104.945 (3.401)
FMS*	34.500 (12.803)	55.259 (7.073)	29.750 (9.053)	37.777 (4.994)
MMSE	23.600 (1.764)	23.551 (.692)	21.364 (1.682)	24.151 (.660)
Side effects†	4.200 (.956)	3.232 (.659)	4.900 (.956)	3.300 (.659)

* Only 12 subjects were selected for this analysis.
† Data were unavailable for one patient.

tion, motor function, and mental status at a critical point in the recovery process to enable increased patient participation in therapy.

The advantages of methylphenidate treatment have been clearly described, but limitations of this study should also be discussed. The sample size was relatively small, which may have affected the ability to detect differences between groups with some measures. Findings for the ZDS and FMS are marginally significant, although the effects are in the expected directions. Marginal statistical significance could lead to a type II error, but both analyses probably suffered from inadequate power due to the small sample size. Inspection of FMS scores revealed a ceiling effect that also interfered with analysis of motor improvement. In addition, there was unequal distribution between groups regarding lesion location, which may have influenced the results. Although both groups were equivalent with regard to all neurologic and demographic variables, data on size of infarct and mechanism of injury were not collected. Useful information might also have been provided using a longer follow-up period, but owing to the risk of drug dependency,[13] the study was limited to the immediate poststroke recovery period. Prolonged use (beyond 4 weeks) of methylphenidate is not recommended.[13] Patients who develop depression later in the recovery cycle are almost certainly more appropriately treated with traditional antidepressants.

This study represents the first known double-blind, placebo-controlled evaluation of methylphenidate as a treatment for poststroke depression, cognitive impairment, and motor deficit. We hope that these findings will redirect attention to the clinical benefits of methylphenidate treatment in early poststroke rehabilitation.

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Supplier

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