

Physiotherapy Coupled With Dextroamphetamine for Rehabilitation After Hemiparetic Stroke

A Randomized, Double-Blind, Placebo-Controlled Trial

David J. Gladstone, BSc, MD, FRCPC; Cynthia J. Danells, BScPT, MSc; Armi Armesto, RN, BScN, MHSM; William E. McIlroy, BSc, PhD; W. Richard Staines, PhD; Simon J. Graham, PhD, PEng; Nathan Herrmann, MD, FRCPC; John P. Szalai, PhD; Sandra E. Black, MD, FRCPC; for the Subacute Therapy with Amphetamine and Rehabilitation for Stroke (STARS) Study Investigators*

Background and Purpose—Hemiparesis is the commonest disabling deficit caused by stroke. In animals, dextroamphetamine (AMPH) paired with training enhances motor recovery, but its clinical efficacy is uncertain.

Methods—In a randomized, double-blind, placebo-controlled trial, 71 stroke patients were stratified by hemiparesis severity and randomly assigned to 10 sessions of physiotherapy coupled with either 10 mg AMPH or placebo. Study treatments were administered by 1 physiotherapist, beginning 5 to 10 days after stroke and continuing twice per week for 5 weeks. Outcomes were assessed by 1 physiotherapist at baseline, after each treatment session, at 6 weeks, and at 3 months. The primary outcome was motor recovery (impairment level) on the Fugl-Meyer (FM) scale. Secondary outcomes assessed mobility, ambulation, arm/hand function, and independence in activities of daily living.

Results—Baseline hemiparesis was severe overall (mean FM score 27.7 ± 20.0). Motor scores improved during treatment in both groups (mean change, baseline to 3 months 29.5 ± 16.6). Repeated-measures ANOVA revealed no significant differences in recovery between the treatment groups for the entire cohort ($n=67$) or for subgroups with a severe hemiparesis ($n=43$), moderate hemiparesis ($n=24$), or cortically based stroke ($n=26$). In the moderate subgroup, there was a significant drug \times time interaction for upper extremity motor recovery ($F=5.14$; $P<0.001$), although there was a significant baseline imbalance in motor scores in this subgroup.

Conclusion—In stroke patients with a severe motor deficit, 10 mg AMPH coupled with physiotherapy twice per week for 5 weeks in the early poststroke period provided no additional benefit in motor or functional recovery compared with physiotherapy alone. Patients with moderate severity hemiparesis deserve further investigation. Increased intensity and longer duration drug/therapy dosing regimens should be explored, targeting the upper and lower limbs separately. (*Stroke*. 2006;37:179-185.)

Key Words: amphetamines ■ physiotherapy ■ randomized controlled trials ■ rehabilitation

“R ehabilitation pharmacology” experiments in animals suggest that poststroke recovery may be enhanced by combining rehabilitative training with dextroamphetamine (AMPH), possibly because of increased noradrenergic neurotransmission and facilitation of activity-dependent neuroplasticity.¹⁻⁴ Maximum improvement occurs when drug administration is coupled with task-specific practice.^{2,5} A dose-response effect has been identified,⁶ and multiple doses

on an intermittent basis appear most effective.³ Specificity has been shown for the noradrenergic agonists, implicating norepinephrine as a neurochemical mediator of recovery; drugs decreasing noradrenergic activity impair recovery and can reinstate deficits after recovery.^{1,2,4} Biologic plausibility has been established by studies showing that AMPH induces physiological or structural changes in the brain that may be relevant to recovery. In rats, AMPH upregulates neural

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*See last page for list of investigators and participating hospitals.

From the Regional Stroke Centre (North and East GTA-Ontario Region Stroke Network) and Division of Neurology (D.J.G., A.A., W.E.M., W.R.S., S.E.B.), Department of Medicine, and Neurosciences Research, Sunnybrook and Women's College Health Sciences Centre, Department of Medicine, University of Toronto, Ontario, Canada; Heart and Stroke Foundation Centre for Stroke Recovery (D.J.G., C.J.D., W.E.M., W.R.S., S.J.G., S.E.B.), Canada; Graduate Department of Rehabilitation Sciences (C.J.D., W.E.M.), University of Toronto, Ontario, Canada; Department of Imaging Research, Sunnybrook and Women's College Health Sciences Centre and Department of Medical Biophysics (S.J.G.), University of Toronto, Ontario; Department of Psychiatry (N.H.), Sunnybrook and Women's College Health Sciences Centre, Department of Psychiatry, University of Toronto, Ontario, Canada; and Department of Biostatistics (J.P.S.), Sunnybrook and Women's College Health Sciences Centre, University of Toronto, Ontario, Canada.

Correspondence to David Gladstone, MD, FRCPC, Division of Neurology and Regional Stroke Centre, Room A442, Sunnybrook and Women's College Health Sciences Centre, 2075 Bayview Ave, Toronto, Ontario, Canada M4N 3M5. E-mail david.gladstone@sw.ca

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sprouting and synaptogenesis in peri-infarct cortex and contralateral cortex.⁷ At the synaptic level, AMPH and other noradrenergic agonists facilitate long-term potentiation, the cellular model of learning and memory.⁸ In humans, 10 mg AMPH facilitates the effects of motor training on use-dependent plasticity as measured by transcranial magnetic stimulation,⁹ suggesting that this dose is sufficient for producing a measurable neurophysiological effect in humans.

Small pilot trials have demonstrated safety, feasibility, and proof-of-concept for the use of AMPH in poststroke motor rehabilitation for carefully selected patients, but clinical efficacy remains uncertain.^{10–20} A statistically significant small magnitude enhancement of aphasia recovery has been demonstrated when AMPH is paired with speech-language therapy.²¹ Despite the limited data, some rehabilitation centers already prescribe AMPH or similar agents as part of clinical routine. It is unclear which patients, if any, may benefit from such intervention. This study aimed to investigate more definitively the efficacy of AMPH-coupled physiotherapy on recovery from hemiparesis, as measured by validated scales of motor impairment and disability at standardized times after stroke.

Methods

Study Participants

We studied patients with acute unilateral cerebral hemispheric stroke causing hemiplegia or hemiparesis. Hemiparesis severity was rated on days 5 to 10 after stroke on the Fugl-Meyer (FM) motor scale²² as severe (0–35) or moderate (36–79); patients with mild hemiparesis (80–100) were not included. Patients were included if they were medically fit to participate in a rehabilitation program, had no significant premorbid disability, and provided informed consent. Exclusions included brain stem/cerebellar stroke; pre-existing deficit that could interfere with assessments; dementia; unstable angina, congestive heart failure, unstable arrhythmia, or uncontrolled hypertension; psychosis; and use of α -adrenergic antagonists/agonists or monoamine oxidase inhibitors.

Design and Setting

We used a randomized, double-blind, placebo-controlled, repeated-measures design. Participants were recruited from 5 acute care hospitals (Toronto, Canada; January 2000 to April 2003). Randomization was stratified by hospital and severity of motor deficit. A blocked randomization sequence was used. Study treatments began in hospital and continued on transfer to 1 of 6 participating local inpatient rehabilitation centers. Research ethics board approval was obtained at each site. All participants, investigators, study physiotherapist, and treating clinicians were blinded to each patient's treatment status.

Drug Intervention

A total of 10 mg of AMPH sulfate (Dexedrine) or identical placebo capsules was administered as a single oral dose followed 90 minutes later by a 1-hour physiotherapy session to coincide with the timing of peak pharmacological action of AMPH. The first treatment began 5 to 10 days after stroke. This time frame was chosen: (1) to initiate rehabilitation early (during the period of maximum recovery and neuroplasticity); (2) to allow time for patients to stabilize medically before enrollment; and (3) to permit exclusion of patients who were rapidly improving during the first week, and thus achieve a more homogenous sample of patients with persisting moderate-severe hemiparesis. Treatments continued every third or fourth day for a total of 10 drug therapy sessions (ie, every Monday/Thursday or every Tuesday/Friday for 5 weeks). Drug administration was verified

at the time of each scheduled dose, and any protocol deviations were documented.

Physiotherapy Intervention

One physiotherapist provided the study treatments for all participants. Treatment was based on neurodevelopmental principles of remediation with the goal of facilitating return of normal movements and inhibiting abnormal movement patterns. Sessions were individualized based on patient abilities, "hands-on," goal-oriented, and required active participation. Movements were practiced within progressively more complex functional activities to facilitate return of selective muscle control of trunk and limbs (eg, progression from independent midline sitting with trunk control to transitional movements [reach, sit-to-stand], to standing with symmetrical weight-bearing, to stepping with controlled weight shift and walking). Treatment of the limbs progressed from recruiting muscle activity for stabilization in support or weight-bearing to controlled, coordinated, selective movements for function and manipulation. Patients were challenged to work at a level just above their ability, and assistance with the missing components of normal movement was provided. All participants continued to receive standard care (organized inpatient stroke team care and multidisciplinary rehabilitation) that is provided free of charge to all residents of Ontario, and the amount of physiotherapy provided as part of standard care was documented for each patient.

Outcome Measures

The primary outcome measure was the FM motor scale, a stroke-specific impairment index that is widely used for assessment of motor recovery.^{22,23} Excellent intrarater and inter-rater reliability and validity have been demonstrated.^{23,24} The motor domain ranges from 0 (flaccid hemiplegia) to 100 (normal movement), with 66 points for the upper extremity and 34 points for the lower extremity. Each item is scored on a 3-point ordinal scale (0 cannot perform, 1 performs partially, and 2 performs fully). All motor assessments were performed by 1 physiotherapist at 13 standardized times: baseline (within 24 hours of the first study treatment), at each of the 10 treatment sessions, 3 to 4 days after the final treatment (\approx 6 weeks after stroke), and 3 months. All secondary outcomes were measured by 1 physiotherapist: Functional Independence Measure,²⁵ Chedoke-McMaster Disability Inventory to assess general mobility,²⁶ Clinical Outcome Variable Scale (COVS) to quantify ambulation,²⁷ and Chedoke-McMaster Arm and Hand Activity Inventory to assess upper limb function.²⁸ The study coordinator monitored for drug toxicity by patient/caregiver interview and hospital chart review. A

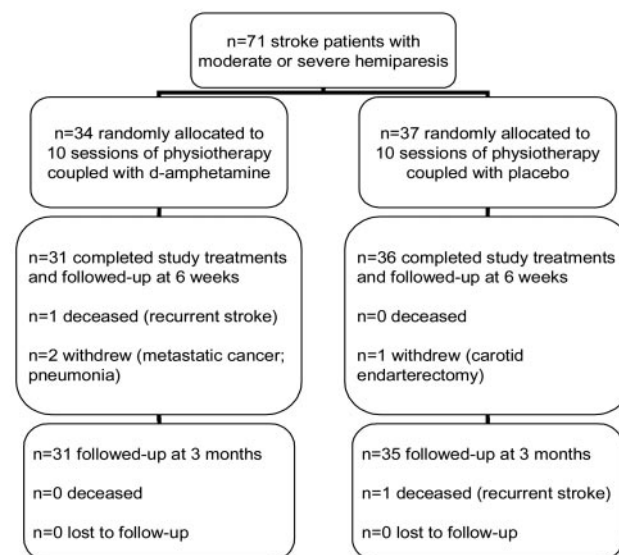


Figure 1. Patient flow diagram.

TABLE 1. Patient Characteristics

	AMPH (n=31)	Placebo (n=36)	<i>P</i> Value
Demographics			
Age (y)	67.8±16.2	67.8±13.9	0.99
Male sex, %	50.0%	55.6%	0.65
Married, %	46.7%	66.7%	0.10
Living at home, %	96.7%	94.4%	0.65
Living alone, %	40.0%	16.7%	0.034*
Employed full time or part time, %	25.0%	30.6%	0.62
Premorbid modified Rankin scale score 0 or 1, %	96.8%	94.4%	0.65
Premorbid Functional Independence Measure score (0–126)	124.8±3.9	125.4±1.0	0.36
Stroke lesion characteristics			
Left hemisphere/right hemisphere/brain stem, %	51.6%/45.2%/3.2%	44.4%/52.8%/2.8%	0.82
Cortical involvement/pure subcortical, %	37.0%/63.0%	40.6%/59.4%	0.78
Infarct/hemorrhage, %	90.3%/9.7%	94.4%/5.6%	0.66
Baseline stroke severity			
Hemiparesis			
Fugl-Meyer motor score (0–100)	26.9±17.6	30.0±22.6	0.54
Fugl-Meyer upper limb motor score (0–66)	10.8±9.5	17.4±17.3	0.06
Fugl-Meyer lower limb motor score (0–34)	16.1±10.2	12.6±8.0	0.13
Overall sensorimotor status			
Fugl-Meyer total (0–226)	134.1±26.3	139.7±29.3	0.42
Fugl-Meyer balance score (0–12)	6.0±2.9	5.9±2.8	0.94
Fugl-Meyer sensation score (0–24)	14.7±10.2	16.4±9.8	0.49
Fugl-Meyer joint motion score (0–44)	43.0±2.1	43.4±0.9	0.23
Fugl-Meyer joint pain score (0–44)	43.6±1.0	43.8±0.5	0.14
Neurological deficits			
NIHSS score	9.7±5.2	10.0±5.4	0.82
Pure motor stroke, %	29.0%	40.0%	0.35
Sensory loss, %	58.1%	47.1%	0.38
Visual field defect, %	26.7%	20.6%	0.57
Aphasia, %	29.0%	22.9%	0.57
Neglect, %	29.0%	20.0%	0.39
Disability and dependence			
Functional Independence Measure score (13–126)	69.6±20.5	67.3±21.7	0.66
Chedoke-McMaster Disability Inventory score (0–100)	42.2±19.9	36.8±12.1	0.18
Clinical Outcome Variable Scale (ambulation) score (0–84)	37.7±15.0	34.9±11.8	0.39
Nonfunctional ambulation (Clinical Outcome Variable Scale <4), %	90.3%	86.1%	0.60

Results expressed as mean±SD, unless specified otherwise.

checklist was used to identify symptoms of psychomotor stimulation. All adverse events and prescription medications were documented.

Statistical Analysis

Baseline characteristics were analyzed using descriptive statistics and compared using Student's *t* test or χ^2 test. The efficacy of AMPH versus placebo was assessed over 13 time points (baseline to 3 months) in a 2×13 repeated-measures ANOVA for scores on the FM scale. Prespecified analyses assessed recovery in separate models for the moderate and severe subgroups and for patients with cortical stroke. For the secondary outcomes, the 2 groups were compared at baseline, 6 weeks, and 3 months in a 2×3 repeated-measures ANOVA.

Results

Patient Characteristics

Of 71 patients enrolled, 67 completed the study treatments and were included in the analysis. Follow-up was complete at 6 weeks; at 3 months, 66 patients were alive and all had complete follow-up (Figure 1). Mean age was 68 years, and the majority were living at home and independent before admission (Table 1). Two patients were enrolled with a presumed internal capsule lacunar stroke, but repeat imaging revealed a brain stem infarct. At baseline, hemiparesis was severe overall (mean FM motor

TABLE 2. Adverse Events

	AMPH	Placebo
Abdominal pain	0	1
Headache	1	1
?Focal motor seizure	1	0
Visual hallucinations	1*	0
Delirium	1†	1
Acute renal failure	1‡	1
Gout	0	1
Pneumonia	1	1
Urinary tract infection	1	4
Leg DVT	1	2
Presyncope/syncope	0	4§
Bradycardia	0	1
Angina	0	1

*Following first dose only; †following treatment with scopolamine; not temporally related to administration of AMPH; ‡acute on chronic renal failure; §due to orthostatic hypotension in all 4 cases.

score 27.7 ± 20.0), all had a modified Rankin scale score ≥ 3 , and 88.0% had no functional ambulation.

The 2 groups were well balanced in terms of baseline demographic characteristics and stroke severity in the entire cohort ($n=67$) and in the severe hemiparesis subgroup ($n=43$). In the moderate hemiparesis subgroup ($n=24$), there was a significant imbalance in baseline FM scores in the AMPH group versus placebo: total motor scores 46.6 ± 10.6 versus 57.9 ± 7.5 , $P=0.006$; upper extremity motor scores 21.2 ± 8.6 versus 39.1 ± 8.0 , $P<0.001$; lower extremity motor scores 25.4 ± 6.6 versus 18.8 ± 7.0 , $P=0.027$.

Treatment

Study treatments began on poststroke day 8.1 ± 1.9 for the AMPH group and 8.6 ± 1.5 for the placebo group ($P=0.33$). There were no differences between the groups in the proportion of patients treated at each of the acute care hospitals ($P=0.88$) or rehabilitation hospitals ($P=0.47$). Patients who did not receive inpatient rehabilitation (3 AMPH; 3 placebo) received the remainder of their study treatments at home. The 2 groups did not differ in the total amount of physiotherapy (minutes) received during the intervention period, either as part of the study (582.7 ± 48.6 versus 566.4 ± 63.6 ; $P=0.25$) or as part of standard care (684.0 ± 265.9 versus 636.4 ± 347.8 ; $P=0.58$). Four patients (0 AMPH; 4 placebo) received tissue plasminogen activator. Twenty-three patients were exposed to ≥ 1 doses of the following medications during the intervention period: benzodiazepine (7 AMPH; 6 placebo), neuroleptic (0 AMPH; 1 placebo), selective serotonin reuptake inhibitor (6 AMPH; 9 placebo), and methylphenidate (0 AMPH; 1 placebo). Excluding these patients from the primary analysis did not affect the results. No patients received phenytoin or phenobarbital, and AMPH was not prescribed outside of the trial for any patient.

Safety and Tolerability

The study drug was well tolerated and no patient had to discontinue treatment (Table 2). There were virtually no observable psychostimulant effects of AMPH, which prevented the

study physiotherapist from having any indication of group assignment. The success of blinding was assessed by comparing the physiotherapist's predicted versus actual drug assignments for each patient, which were no greater than chance (49% agreement). Only 1 patient had a symptom that was probably related to AMPH (visual hallucinations after the first dose).

Recovery in the Entire Cohort

Motor scores and independence in activities of daily living improved during treatment in both groups (Table 3). Mean improvement on the FM motor scale was 24.7 ± 15.5 during the intervention (baseline to 6 weeks) and 4.5 ± 6.0 after the intervention (6 weeks to 3 months). At 3 months, nearly one third had recovered to a mild hemiparesis (FM motor score 80 to 100); mean Functional Independence Measure score 105.8 ± 20.6 ; and three quarters regained independent ambulation (Clinical Outcome Variable Scale score ≥ 4).

Efficacy

Repeated-measures ANOVA over the 13 time points revealed no significant differences (main or interaction effects) between the AMPH and placebo groups on the primary outcome of recovery on the FM motor scale for the entire cohort ($F=0.88$; $P=0.35$) or in separate models for the severe ($F=0.02$; $P=0.90$) or moderate ($F=2.99$, $P=0.10$) subgroups (Figure 2). Separate models for upper extremity and lower extremity motor scores revealed no significant main effects in the entire cohort or in the severe subgroup.

In the moderate hemiparesis subgroup, there was a significant main effect of AMPH on upper extremity motor recovery (between-group difference 11.6 points; 95% CI, 4.6 to 18.5; $F=11.88$; $P=0.002$) with a significant drug \times time interaction ($F=5.14$; $P<0.001$; Figure 2).

A separate analysis for the subgroup of patients with only cortical or mixed cortical/subcortical stroke (ie, pure subcortical and brain stem strokes excluded) revealed no significant between-group difference in motor recovery ($F=0.01$; $P=0.92$).

There were no significant between-group differences on any of the secondary outcome measures. At 3 months, there was no difference between the groups in the proportion of patients discharged home, remaining in inpatient rehabilitation, or admitted to a nursing home/retirement home for the entire cohort ($P=0.56$) or the severe ($P=0.60$) or moderate ($P=0.73$) subgroups. After inpatient rehabilitation, 82.8% of AMPH-treated patients and 85.3% of placebo-treated patients returned home ($P=0.96$).

Discussion

To our knowledge, this is the largest published trial investigating amphetamine-coupled stroke rehabilitation. The addition of AMPH 10 mg to physiotherapy was safe and well tolerated but provided no benefit on total motor scores or disability measures compared with physiotherapy alone when given for 10 doses over 5 weeks. Both groups improved during the treatment period, then plateaued after the intervention, suggesting a possible benefit of the additional physiotherapy provided in this study. Our trial design, modeled after Walker-Batson et al,¹² used an intermittent dosing protocol and tight coupling of AMPH with rehabilitative training to

TABLE 3. Outcomes at Six Weeks and Three Months

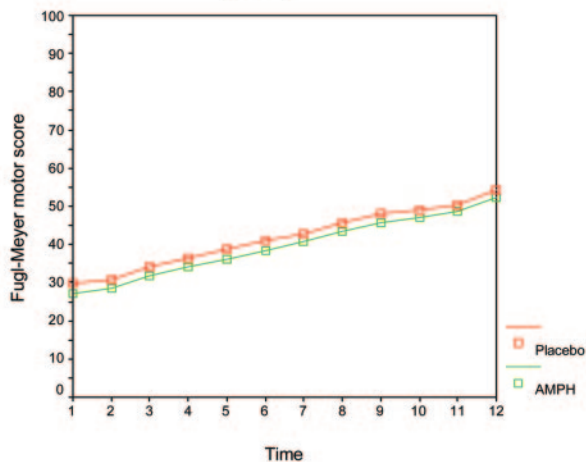
	Entire Cohort			Severe Group			Moderate Group		
	AMPH (n=31)	Placebo (n=36)	<i>P</i> Value	AMPH (n=20)	Placebo (n=23)	<i>P</i> Value	AMPH (n=11)	Placebo (n=13)	<i>P</i> Value
6-wk outcomes									
Chedoke Arm and Hand Activity Inventory score	29.2±24.5	35.4±28.3	0.34	17.8±13.3	19.1±16.6	0.78	49.8±27.2	66.8±17.1	0.09
Ambulatory (Clinical Outcome Variable Scale ambulation performance 4–7), %	48.4%	47.2%	0.92	30.0%	21.7%	0.54	81.8%	92.3%	0.44
Independent ambulation with environmental barriers (Clinical Outcome Variable Scale 6–7), %	22.6%	11.1%	0.21	15.0%	4.3%	0.23	36.4%	23.1%	0.48
Mean change scores: baseline to 6 wk									
Fugl-Meyer motor total	25.4±15.1	24.4±15.9	0.81	21.1±14.7	23.7±18.6	0.61	33.2±13.3	25.7±10.1	0.13
Fugl-Meyer upper extremity motor	17.9±15.2	15.6±13.4	0.52	12.0±13.7	14.8±15.6	0.54	28.5±12.0	17.1±8.8	0.013*
Fugl-Meyer lower extremity motor	7.5±5.0	8.8±5.7	0.32	9.1±4.4	9.0±5.6	0.93	4.6±4.8	8.6±6.1	0.09
Functional Independence Measure	26.1±18.1	29.8±15.2	0.37	22.0±14.2	28.6±12.1	0.11	33.5±22.6	31.8±20.0	0.85
Chedoke-McMaster Disability Inventory	22.3±16.9	26.7±14.7	0.26	20.2±15.3	22.6±11.7	0.56	26.2±19.6	33.9±17.1	0.31
Clinical Outcome Variable Scale	19.6±14.2	21.4±11.6	0.58	17.2±13.4	19.5±10.3	0.52	24.1±15.2	24.7±13.3	0.92
3-mo outcomes									
Fugl-Meyer balance score	9.8±2.7	9.6±2.5	0.68	8.9±2.9	8.9±1.9	0.96	11.4±1.5	10.8±3.1	0.55
Fugl-Meyer sensation score	21.1±5.9	20.5±6.4	0.70	20.6±6.4	19.0±7.5	0.47	22.0±5.0	23.3±1.3	0.38
Fugl-Meyer joint motion score	40.9±3.2	41.4±3.2	0.51	40.0±3.6	40.4±3.5	0.68	42.6±1.5	43.4±1.0	0.15
Fugl-Meyer joint pain score	41.3±3.0	42.0±3.0	0.34	40.6±3.3	41.1±3.4	0.58	42.6±1.6	43.7±0.9	0.07
Chedoke Arm and Hand Activity Inventory score	30.9±30.0	35.9±32.4	0.52	21.7±18.9	23.7±20.5	0.74	47.6±39.5	61.6±38.5	0.41
Ambulatory (Clinical Outcome Variable Scale 4–7), %	74.2%	77.1%	0.78	60.0%	69.6%	0.51	100.0%	91.7%	1.00
Independent ambulation with environmental barriers (Clinical Outcome Variable Scale 6–7), %	32.3%	25.7%	0.56	25.0%	4.3%	0.08	45.5%	66.7%	0.41
mRS 0, 1, 2, %	48.4%	42.9%	0.65	35.0%	17.4%	0.19	72.7%	91.7%	0.32
Mean change scores: baseline to 3 mo									
Fugl-Meyer motor	29.3±15.7	29.7±17.5	0.92	26.0±16.8	28.6±20.6	0.67	35.1±12.0	31.8±9.6	0.47
Fugl-Meyer upper limb motor	21.1±15.5	19.5±14.8	0.68	16.1±15.8	18.0±17.1	0.72	30.1±10.5	22.5±8.6	0.07
Fugl-Meyer lower limb motor	8.2±5.4	10.1±6.2	0.18	10.0±4.8	10.6±6.2	0.70	5.0±5.2	9.3±6.4	0.10
Functional Independence Measure	36.9±14.5	38.2±17.1	0.74	37.0±11.3	39.8±15.2	0.50	36.7±19.7	35.2±20.6	0.86
Chedoke-McMaster Disability Inventory	29.3±17.5	34.5±16.3	0.21	29.6±16.6	32.0±15.1	0.61	28.7±19.7	39.2±18.2	0.20
Clinical Outcome Variable Scale	25.3±14.1	27.9±12.6	0.43	25.1±13.9	27.0±11.4	0.63	25.5±15.3	29.6±15.2	0.52

parallel the design of animal studies demonstrating AMPH-facilitated recovery.³ Our study extends previous trials by inclusion of patients with moderate in addition to severe motor deficits, separation of cortical from pure subcortical strokes, and analysis of repeated-measures data collected over multiple time points during the intervention period. Follow-up was complete, and our sample size was sufficient to detect a ≥15-point difference in improvement between the groups if such a difference existed. We minimized variability in the rehabilitation intervention because all study treatments were administered by 1 physiotherapist, and we minimized regional differences in rehabilitation practices because this was a single-

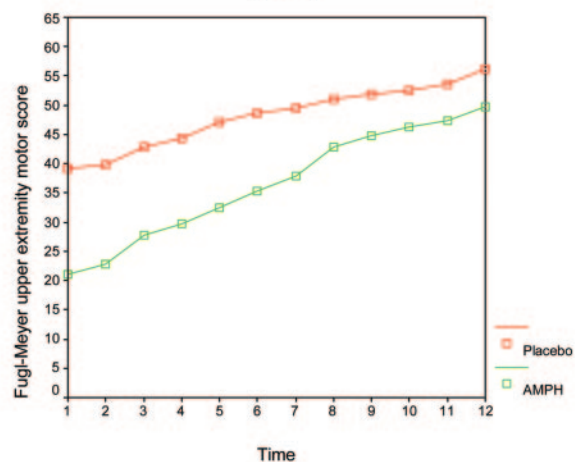
city study. Inter-rater variability was eliminated because all primary and secondary outcomes were rated by 1 examiner.

Previous studies of AMPH in poststroke motor rehabilitation have been limited by small sample sizes (8 to 45 patients) and differing methodologies. Most have focused exclusively on patients with severe hemiparesis or have not reported outcomes in moderate patients. Three published trials investigated AMPH coupled with physiotherapy using a similar 5-week intermittent dosing schedule, with the timing of outcome assessments identical to our study. The study by Walker-Batson et al has been cited widely for suggesting efficacy of AMPH;¹² however, with only 10 subjects, the

A Overall motor recovery in the entire cohort (n=67)



B Upper extremity motor recovery in the moderate subgroup (n=24)



Time 1 = baseline; Time 2-11 = treatment sessions (every 3rd/4th day for 5 weeks); Time 12 = end of treatment (6 week) follow-up

Figure 2. Motor scores in the AMPH and placebo groups before, during, and after the 5-week intervention period. A, Overall motor recovery in the entire cohort (n=67). B, Upper extremity motor recovery in the moderate subgroup (n=24).

observed benefit of AMPH could have resulted from random chance and the poor recovery in their placebo group (mean change only 11 points from baseline to end of treatment). Sonde et al used an identical trial design to our study and also found no benefit in 36 patients on the FM motor scale or Barthel Index, although 10 mg of d,l-amphetamine instead of d-amphetamine was used.¹⁸ Treig et al studied 24 patients in a nearly identical design and found no significant difference between AMPH and placebo on the Rivermead Motor Assessment or Barthel Index.¹⁹ Together, these 2 studies and our present data, although confirming the safety and feasibility of AMPH in stroke rehabilitation, do not demonstrate enhancement in motor recovery with this dosing regimen and treatment schedule.

We observed a greater rate of upper limb motor recovery for patients with a moderate severity hemiparesis. However, interpretation of this result is complicated by the fact that randomization failed to produce treatment groups that were balanced in terms of baseline motor scores in the moderate subgroup: baseline upper extremity motor scores were significantly worse in the AMPH group versus placebo (mean difference 17.9 points; $P < 0.001$), yet by 6 weeks, the 2 groups had improved to almost the same level. The lower initial motor scores could have favored the AMPH group because of regression to the mean; indeed, natural history studies show that the recovery rate during the first 6 weeks is greater for patients with initially more severe hemiparesis compared with those with moderate or mild hemiparesis.²⁴ Furthermore, the ceiling effect of the scale limits its ability to measure change in milder stroke patients,²³ and this may explain why the placebo group did not appear to improve as much relative to the AMPH group. Therefore, any apparent benefit of AMPH in accelerating motor recovery in this subgroup should be considered hypothesis-generating only. Similarities in the design of our study with other studies could facilitate meta-analysis to address this hypothesis.

Limitations of this study reflect challenges inherent in the design of any stroke rehabilitation trial.²⁹ We experienced similar difficulty with patient recruitment that other studies have faced (≈ 40 patients screened for every 1 enrolled) because of strict entry criteria. Although we chose a highly select group of stroke patients, there remained substantial within-subject variability in recovery because of the wide heterogeneity in stroke type, lesion size, lesion location, accompanying deficits, comorbidities, and other unmeasured factors. Such variability in individual recovery has plagued many rehabilitation studies because small treatment effects are difficult to detect. The physiotherapy intervention was standardized as much as possible, but inevitably, therapy sessions depended on individual patient abilities, treatment time was divided between the upper and lower extremities, and it was not possible to control the content or intensity of other rehabilitation services provided outside of the trial as part of standard care.

This study has implications for research and clinical practice. First, our data do not support the routine use of AMPH as a treatment outside of a clinical trial. Second, this study reinforces the complexities of extrapolating results from animal (mostly rodent) models to human trials and forces us to rethink the design of future studies.²⁹ Clinical efficacy of AMPH-coupled rehabilitation may require higher drug doses, more frequent and longer duration treatments, a more focused and standardized rehabilitation intervention, and improved patient selection. Based on our subgroup analysis, further studies should target patients with moderate paresis; this is consistent with other trials showing that patients with moderate paresis are more responsive to additional training than those with severe motor deficits.³⁰ Theoretically, patients with small cortical strokes should be the best candidates for AMPH, and future trials should stratify patients by lesion characteristics. The 10-mg dose is likely too low, given that in rats and cats, the optimal dose is > 1

mg/kg.⁶ Dose-limiting toxicity has been a reason that other investigational stroke treatments have failed in clinical trials after appearing successful in animals. Recently, 20 mg per day of AMPH has been shown to be safe in stroke patients, although it is associated with small increases in blood pressure and heart rate.¹⁴ Moreover, the “dosage” of physiotherapy is likely a critical factor: many more additional hours of therapy are probably necessary to produce measurable benefit.³¹ Ideally, the chosen therapy should be one that has demonstrated efficacy, is reproducible and can be standardized among trial participants, and is specifically focused on either the upper limb or lower limb/gait. Further insights from experiments in nonhuman primates and ongoing clinical studies are eagerly awaited and may allow more rational clinical trial design.

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Participating hospitals and site investigators: G. Moddel, Scarborough Hospital; L. Lee, J. Perry, B. Murray, J. Sahlas, Sunnybrook and Women's; N. Bayer, St. Michael's Hospital; F. Silver, C. Jaigobin, University Health Network; R.M. Gladstone, A. Esmail, S. Cohen, North York General Hospital; H. Dombrower, Baycrest Centre; V. Hajek, C. Whitehead, M. Bayley, Toronto Rehabilitation Institute; M. Waldman, St. John's Rehabilitation Institute; M. Rotbard, Providence Centre; and R. Soric, D. Richardson, West Park Rehabilitation Centre.

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