Effect of methylphenidate and/or levodopa coupled with physiotherapy on functional and motor recovery after stroke – a randomized, double-blind, placebo-controlled trial

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Objective – Amphetamine-like drugs are reported to enhance motor recovery and activities of daily living (ADL) in stroke rehabilitation, but results from trials with humans are inconclusive. This study is aimed at investigating whether levodopa (LD) and/or methylphenidate (MPH) in combination with physiotherapy could improve functional motor recovery and ADL in patients with stroke. *Material and methods* – A randomized, double-blind, placebo-controlled trial with ischemic stroke patients randomly allocated to one of four treatment groups of either MPH, LD or MPH + LD or placebo combined with physiotherapy was performed. Motor function, ADL, and stroke severity were assessed by Fugl-Meyer (FM), Barthel index (BI), and National Institute of Health Stroke Scale (NIHSS) at baseline, 15, 90, and 180 days respectively. *Results* – All participants showed recovery of motor function and ADL during treatment and at 6-month follow-up. There were slightly but significant differences in BI and NIHSS compared to placebo at the 6-month follow-up. *Conclusion* – Ischemic chronic stroke patients having MPH and/or LD in combination with physiotherapy showed a slight ADL and stroke severity improvement over time. Future studies should address the issue of the optimal therapeutic window and dosage of medications to identify those patients who would benefit most.

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Introduction

The burden of stroke-related disability is enormous and expected to increase with our aging population (1). Following stroke, 40–67% of patients may have a persisting motor deficit which may not improve despite ongoing physiotherapy (2).

Many novel therapeutic treatments in stroke rehabilitation have recently been identified and are currently being investigated in clinical trials (3). An area of promise in stroke rehabilitation is that of 'rehabilitation pharmacology'. The potential may exist for these new pharmacological interventions to expedite and improve the recovery process. It has been hypothesized that pharmacological interventions administered to stroke patients may have the potential to modulate neuronal and synaptic plasticity (4). In human clinical trials, there were inconsistent results regarding the effect of D-amphetamine (5), selective serotonin reuptake inhibitors (6), donepezil (7), or levodopa (LD) (8) on post-stroke recovery. Previous investigations into the effectiveness of methylphenidate (MPH) during early post stroke rehabilitation have shown it be a safe medication with the potential of advancing recovery (9). However, the result of a study by Restemeyera et al. (10) suggested that a single dose of LD is not sufficient for improvement in motor function after

chronic stroke. There is a dose-response effect associated with the drug (11), and its effectiveness is improved after administration of multiple doses on an intermittent schedule (12). Although significant advances have been made in development of potential pharmacotherapies for stroke rehabilitation, definitive scientific evidence of the clinical effectiveness of such therapies is still lacking (13).

Much effort has been made to identify medications that could increase the capacity of CNS regeneration and maximize the gains of rehabilitating motor and/or cognitive functions in incapacitated patients. The results of published studies to date, however, are not convincing.

Aim

We hypothesized that psychostimulant drugs combined with physiotherapy would improve recovery from stroke. To investigate this hypothesis, a placebo-controlled comparative drug study with LD and/or MPH in combination with physiotherapy was set up.

Material and methods

Study design

An interventional, randomized, double-blind, placebo-controlled trial on patients with chronic ischemic stroke in a 2×2 factorial design with patients being given four different treatments. With an 80% power to detect a 20% difference from baseline to 3 and/or 6 months a significance level of 0.05, one hundred patients were needed.

A computerized randomization was performed by a person not involved in the research process. Full written informed consent was obtained from the patients before randomization or an assent was taken from a relative/caregiver if the participant was incapable of giving his/her consent. Each patient's treatment status was kept unavailable from the patients themselves, the caregivers, the study physicians, and the physiotherapists. The patients' demographic data including age, gender, established stroke risk factors, paretic side, stroke duration, and any history of stroke were collected. The Ministry of Health in Iran and University of Social Welfare and Rehabilitation Ethics Committee approved the study, and it was performed according to the Declaration of Helsinki (14).

Case-finding procedures

Participants were consecutively enrolled from eight acute care hospitals in the cities of Tehran and Qom, Iran, when being referred to outpatient rehabilitation treatment at the Neurorehabilitation Clinic of Rofeydeh Hospital affiliated to the University of Social Welfare & Rehabilitation, Tehran, Iran from March 2006 to September 2008.

In the beginning, a trained physician assessed all referred patients for inclusion and exclusion criteria. Non-eligible patients were offered the standard rehabilitation care. All therapists were trained to provide a standardized rehabilitation program to all patients. Two trained physicians evaluated the patients completely, initially, for medical history and general, neurologic and outcome-specific physical examination. These two physicians were following up patients at all sessions, ensuring that all patients received standard rehabilitation and the evaluation was performed adequately. The rehabilitation program was usually scheduled to be administered in the morning. Blood pressure and heart rate were monitored immediately before medication and 2 h after intake.

Inclusion and exclusion criteria

Ischemic patients with a paretic arm and/or leg following a stroke that had occurred 15–180 days previously and being able to follow the instructions were recruited in this study.

As MPH is a potentially hypertensive agent, comorbidities which could be negatively affected by the drug implicated exclusion. The exclusion criteria were hemorrhagic stroke, myocardial infarction or angina pectoris within the last 4 weeks, decompensated cardiac insufficiency, unstable metabolic disease, sequelae of earlier cerebral lesion, non-controlled hypertension (systolic blood pressure ≥ 170 mm Hg, diastolic blood pressure ≥ 110 mm Hg), tachycardia (≥ 100 bpm), major cognitive deficit (aphasia, apraxia, neglect, concentration, and memory deficits) or psychiatric disease that hindered adequate participation in the study, glaucoma, uncontrolled epilepsy, hypersensitivity to MPH or LD, prominent agitation, or current antidepressant treatment. Patients receiving alfa-adrenergic antagonists or agonists, neuroleptics, benzodiazepines, or a MAO inhibitor were excluded as well.

Medication protocol

The MPH/LD/placebo drugs were randomly distributed in boxes labeled 1–100. A computerized random-number generator was used by a person not involved in the study, to generate the random allocation sequence list with four groups.

The drug protocol developed for this study was based on what was prescribed and suggested in previous studies (15). The reasons for choosing MPH and LD were the following: they were suggested from animal and human experiments (16–18), they had rare side effects (19), and they were readily available in Iran when compared to amphetamines. In contrast to amphetamine, MPH does not cause addiction, and doses of ≤40 mg do not lead to insomnia or loss of appetite in adults (13). In this four-group intervention model, drug treatment was given in the form of identical white tablets of 2×10 mg of either MPH or placebo of identical appearance and a tablet with either 125 mg LD or placebo. It was administrated at least 60 min before the training session to coincide with the timing of peak pharmacological action of drugs (20). Treatments continued 5 days a week for a total of 15 drug therapy sessions, a frequency often used in the above-mentioned studies.

Patients received the boxes in consecutive order. Placebo and drugs were prepared by a hospital pharmacist independent of the investigators to be indiscernible.

The potential side effects of LD, including cardiovascular symptoms, nausea, vomiting, and psychosis, were assessed and recorded. Also for MPH, the possible side effects were closely monitored including insomnia, nausea, or nervousness, over the first 24 h after administration.

Physiotherapy intervention

Patients received daily 45-min physical therapy sessions. A goal-oriented approach was used in each session to accomplish a range of activities encompassed in a standard treatment: mobilization, selective movements exercise, sensory-motor, visual, perceptual and cognition training programs related to sitting, standing, balance, transfer, ambulatory activities, and other activities of daily living (21). The theoretical framework of treatment was neurodevelopmental wherein the approach was aimed at normal movement facilitation versus abnormal movement inhibition (22). Increasingly, complex functional activities were introduced over time to cause progressive improvements in trunk and limb muscle control (22). The content, not the volume of the training, varied from each patient depending of the severity of his or her paresis. Individuals received additional rehabilitation treatment depending on their neurological impairments such as speech therapy.

Outcome measures

Motor function – Motor function skills were assessed quantitatively using the FM scale which is developed for use in clinical rehabilitation settings. It is a stroke-specific impairment index that is widely used for assessment of motor recovery. Its reliability and validity are well documented (23–25). On this scale, a score of 0 means no motor function (flaccid hemiplegia) and a score of 100 indicates normal motor function (divided into 66 points for normal arm motor function and 34 points for normal leg motor function). Each item is scored on a 3-point ordinal scale (0 cannot perform, 1 performs partially, and two performs fully). Motor function was assessed by a physiotherapist at baseline, at the end of the 15th session, and at follow-up (3 and 6 months after baseline).

Activities of daily living – Autonomy in ADL was evaluated using the Barthel index (BI) (26). BI was developed as a scoring technique measuring the patient's performance in 10 ADL. The BI is considered a reliable disability scale for patients with stroke (27). The items can be divided into one group that is related to self-care (feeding, grooming, bathing, dressing, bowel and bladder care, and toilet use) and one group related to mobility (ambulation, transfers, and stair climbing) (15). The maximal score is 100 in five-point increments. The lowest score is 0, representing a totally dependent, bedridden state (28).

Stroke severity – The National Institute of Health Stroke Scale (NIHSS) is used to assess stroke severity (29). It consists of 11 items and the maximum possible score is 31. A score of 0 indicates no clinically relevant neurological abnormality. The NIHSS is not time-consuming to administer, taking < 8 min to perform (30). Good overall interrater reliability has been shown in multicenter stroke trials (31), and the NIHSS has shown a very good sensitivity, specificity, and accuracy in predicting clinical results at 3 months (32).

Statistics – Descriptive statistics calculated for these data were means, standard deviations, frequencies, and percentages used to describe age, gender, days since stroke onset, history of previous stroke, paretic side, and risk factors. Data of the four treatment groups and the mean change from baseline to 15, 90, and 180 days of BI, FM, and NIHSS were compared by ANOVA or Kruskal–Wallis test, as appropriate. Significant results were further investigated with post hoc test (Tukey).

One-Sample Kolmogorov–Smirnov was used to check normality of distribution of variables. The significance level was established at 0.05.

Results

Patient characteristics

Hundred patients, diagnosed with ischemic stroke, were recruited from March 2006 to September 2008. During 6-month follow-up, 15 patients died and seven patients dropped out, data which were not included in the analysis. They were not different to the other patients with regard to demographic, motor function, stroke severity, or ADL. Seventy-eight patients completed the treatment and follow-up process with data included in the analysis (Fig. 1). Baseline characteristics of the patients of the respective group are presented in Table 1. Patients were compared regarding age, gender, risk factors, stroke duration, history of stroke, and paretic side. The mean age of patients was 64 ± 9.8(65.4 ± 9.2 for men and 61.8 ± 10.6 for women), and 2.6% were younger than 45, 46.1% were 45–64 years of age and 51.3% $\geq$65 years. Through logistic regression analysis,

Groups: MPH: Methylphenidate, LD: Levodopa, MPH& LD: Methylphenidate & Levodopa, P: Placebo
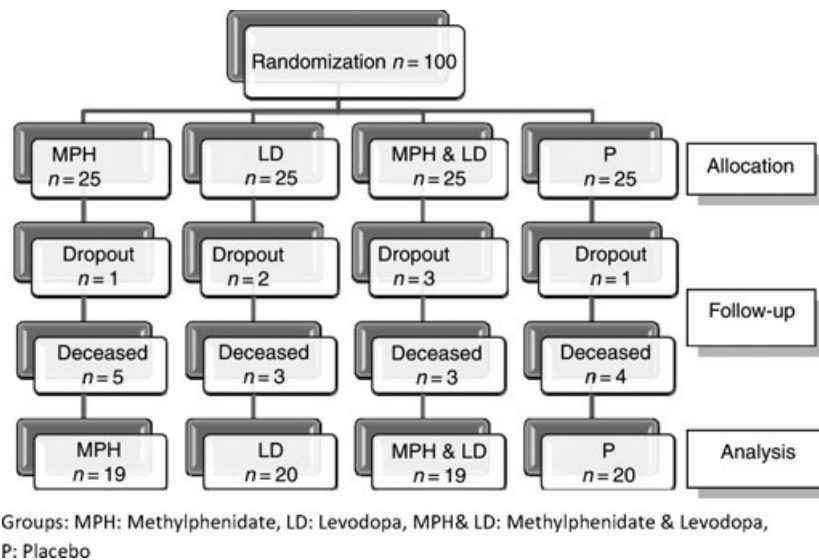
Figure 1. Patients flow chart, describing subjects excluded and included in treatment process; MPH, methylphenidate; LD, levodopa; MPH & LD, methylphenidate & levodopa; P, placebo.

Table 1 Demographic characteristics

	All	MPH	LD	MPH & LD	P	P value
Mean age, SD	64 (9.8)	64.05 (10.8)	66.3 (9.5)	60.2 (9.1)	65.3 (9.6)	0.230
Gender						
Men	48	9	14	11	14	0.403
Women	30	10	6	8	6	
Days since stroke, mean days (SD)	65.6 (34.2)	66.26 (40.7)	67.8 (32.1)	73.6 (41.5)	54.9 (18.1)	0.386
Prior stroke, n (%)						
Yes	6 (7.7)	3 (15.8)	2 (10)	0 (0)	1 (5)	0.297
No	72 (92.3)	16 (84.2)	18 (90)	19 (100)	19 (95)	
Risk factors, n (%)						
HTN	57 (73.1)	18 (31.6)	15 (26.3)	11 (19.3)	13 (22.8)	0.059
DM	44 (65.4)	9 (20.4)	14 (31.8)	6 (13.6)	15 (34.1)	0.021
HLP	39 (50.0)	12 (30.8)	8 (20.5)	10 (25.6)	9 (23.1)	0.500
HD	22 (28.2)	3 (13.6)	7 (31.8)	6 (27.3)	6 (27.3)	0.564
Smoking	18 (23.1)	5 (27.8)	5 (27.8)	4 (22.2)	4 (22.2)	0.959
Paretic side						
Right/left	45/33	10/9	13/7	11/8	11/9	0.874
n (%)	(57.7/42.3)	(52.6/47.4)	(65/35)	(57.9/42.1)	(55/45)	

MPH, methylphenidate; LD, levodopa; MPH & LD, methylphenidate & levodopa; P: placebo; HTN, hypertension; DM, diabetes mellitus; HLP, hyperlipidemia; HD, heart disease; SD, standard deviation.

Table 2 Mean and standard deviation of Baseline Barthel Index, Fugl-Meyer, and NIHSS scores of three actively treated and placebo-treated groups

| | MPH | LD | MPH & LD | P | |
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	P value
Barthel index					
Total	51.8 (16.1)	54.5 (20.6)	52.6 (17)	56.7 (17.2)	0.821
Self care	36.84 (36.8)	37.50 (37.5)	36.58 (36.6)	38.25 (38.2)	0.974
Mobility	15.00 (15)	17.00 (17)	16.05 (16)	18.50 (18.5)	0.423
Fugl-Meyer					
Total	38.3 (32.3)	46.4 (32.2)	33.8 (28.5)	41.1 (31.1)	0.639
Arm motor	23.2 (23.3)	29.7 (22.7)	19.1 (20.3)	24.9 (22.3)	0.519
Leg motor	15.1 (10.1)	16.7 (10.4)	14.7 (10.9)	16.2 (9.8)	0.919
NIHSS					
	5.9 (2.8)	4.3 (2.6)	7.1 (2.7)	5.5 (3.6)	0.065

MPH, methylphenidate; LD, levodopa; MPH & LD, methylphenidate & levodopa; P: placebo; SD, standard deviation.

Table 3 Mean and standard deviation of Baseline Barthel Index, Fugl-Meyer, and NIHSS scores in 3 and 6 months and mean changed scores of three actively - treated and placebo-treated groups

| | MPH | LD | MPH & LD | P | |
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	P value
Barthel index					
3 months					
Total	71.58 (16)	76.75 (12.4)	72.37(14.4)	70.50 (14.4)	0.548
Self care	41.8	46.2	42.4	40.5	0.777
Mobility	29.7	30.5	30.0	30.0	0.205
6 months					
Total	77.4 (14.5)	84.5 (8.5)	83.2 (15.4)	73.25 (14.1)	0.343
Self care	53.7	57.0	56.84	49.75	0.224
Mobility	23.7	27.5	26.32	23.50	0.123
Mean changes scores: 6 months to baseline					
Total	25.5 (14.2)	30 (18.9)	30.5 (13.3)	16.5 (9.6)	0.011
Self care	16.8	19.5	20.3	11.5	0.038
Mobility	8.7	10.5	10.3	5.0	0.021
Fugl-Meyer					
3 months					
Total	57.0 (35.3)	66.3 (31.7)	57.7 (37.1)	53.4 (34.4)	0.685
Arm motor	34.0 (26.1)	40.7 (24.6)	34.9 (26.1)	32.4 (24.5)	0.752
Leg motor	23.0 (9.7)	25.6 (7.7)	22.7 (11.4)	21.0 (10.7)	0.534
6 months					
Total	58.0 (35.5)	68.2 (31.4)	56.9 (35.5)	54.4 (34.2)	0.597
Arm motor	34.7 (26.3)	41.7 (25.1)	33.8 (25)	32.8 (24.3)	0.675
Leg motor	23.3 (9.6)	26.5 (7.1)	23.1 (11.1)	21.6 (10.7)	0.757
Mean changes scores: 6 months to baseline					
Total	19.7 (13.7)	21.8 (12.2)	23.1 (19)	13.3 (12.7)	0.169
Arm motor	11.5 (9.3)	12 (10.2)	14.7 (17.6)	7.9 (8.9)	0.374
Leg motor	8.2 (6.1)	9.8 (5.3)	8.4 (5.1)	5.4 (4.4)	0.081
NIHSS					
3 months	2.9 (2.6)	1.8 (2)	3.7 (3)	4.0 (3.6)	0.089
6 months	2.6 (2.5)	1.7 (1.9)	3.5 (3)	3.6 (2.8)	0.104
Mean changes scores: 6 months to baseline					
	−3.3 (1.4)	−2.6 (1.2)	−3.6 (1.6)	−1.9 (1.4)	0.001

MPH, methylphenidate; LD, levodopa; MPH & LD, methylphenidate & levodopa; P: placebo; SD, standard deviation.

hypertension (HTN) was the most common risk factor, 73.1%, followed by diabetes mellitus, 65.4%, hyperlipidemia, 50%, heart disease, 28.2%, and smoking 23.1%. Right-side paresis was found in 57.7% of patients.

Outcome and mean improvement

Baseline data of motor function (FM), ADL (BI), and stroke severity (NIHSS) were homogeneous and well balanced in all four groups. Separate model for arm and leg motor scores in FM, self-care, and mobility in BI revealed no significant differences in baseline data (Table 2).

All participants showed recovery of motor function (FM), ADL (BI), and stroke severity (NIHSS) during the observation period. According to post hoc test, there were no significant differences between the active drug and placebo groups between follow-ups (3 and 6 months) in BI, FM, and NIHSS scores, but there were significant between-group differences in scores of mean changes of total BI and NIHSS on 6 months to baseline (F (3, 74) = 4.000, P = 0.011) and (F (3, 74) = 5.728, P = 0.001), respectively, with a greater gain in the combined MPH & LD groups. Table 3 shows the scores and outcome at follow-ups for FM (total score, arm, and leg), BI scores (total score, self-care, and mobility), and NIHSS. Mean improvement to first follow-up (baseline to 3 months) of the FM was not significant, 23.9, 19.9, 18.7, 12.3 in the LD + MPH; LD, MPH and placebo group, respectively. There were no significant differences between the active drug groups and placebo groups between follow-ups (3 and 6 months) in BI, FM and NIHSS scores. No adverse side effects were observed. Differences in gain of motor function between groups were not significant, and according to a secondary power analysis, for a 80% power with 50% higher differences between groups, there would be a need for at least 30 patients in each group.

Discussion

We found a significant recovery of the BI and NIHSS for patients who received MPH + LD from baseline to 6 months compared to placebo. This addition of LD and/or MPH in combination with physiotherapy was safe and well tolerated and indicated a slight but significant ADL improvement over time. However, all patients improved their motor recovery and independence as measured by the ADL as expected as most post-ischemic patients have a natural recovery potential over time (15, 33). The interpretation of this result is complicated by the fact that the corresponding mean change in the FM motor

score was not significant. It could be that the drug effect has more of a fortifying effect on the patient with ischemic stroke resulting in improved functioning rather than a specific motor effect. As patients in this study were recruited on average 2 months after stroke, and there are large variables in motor abilities in patients, one could assume that the motor function prior to active drug intake was too 'good' to show further improvement in some patients. The potential of achieving further improvement and catching it through the scales could be reduced by a ceiling effect. However, FM seems to be more sensitive than the BI to changes in disability. It is well-documented that the BI suffers from a pronounced ceiling effect; and therefore, should be carefully utilized for distinguishing between severely affected patients and not for patients at a high functional level (34).

There was no significant benefit on total motor scores compared with physiotherapy alone when given for 15 treatments over 15 days. The results of this investigation are in line with those reported by Sonde et al. (15), Platz (35), Restemeyer (10), and Sprigg (36), where patients were unable to demonstrate a superiority of LD and/or MPH compared to placebo. Sonde et al. (15) used an identical trial design as in our study and also found no benefit in 36 patients on the FM motor scale or the BI. In a study by Treig et al. (37), no significant differences were found between the placebo-control and amphetamine-treated group on either the Rivermead Motor Assessment or the BI.

The effectiveness of amphetamine-like drugs on motor recovery might depend on the stage of disease. Studies that reported a beneficial effect of d-amphetamine on motor recovery included patients early after stroke, i.e. 3–30-day post-stroke (5, 22) while in this study patients in the LD and/or MPH groups entered the trial on average 9.3 weeks after stroke. Comparable investigations did not speak to the optimal recruitment period or the most effective treatment timeline (36). In trials that did not report an improvement in motor recovery after amphetamine treatment, patient recruitment occurred commonly 3–10 days post stroke (38–39). In a review by Goldstein, it was confirmed that pharmacotherapy success depends heavily on proper timing of drug administration and frequency of physical therapy sessions (40).

Furthermore, timing between medication and exercise therapy has been similar in positive and negative trials, i.e. exercise therapy has been provided within 3 h of drug administration (41),

or 120 min (35) or 60 min (37), as in this study, after drug administration.

Different drug regimes have been tested earlier; the regime utilized here, and pioneered by others (8, 15, 19), was driven by concern for potential adverse effects. As we did not find any side effects, it is possible that higher and more frequent doses are possible, as tested in experimental models by Scheidmann and Grade (8, 9) MPH is originally prescribed for attention deficit hyperactivity disorder patients and often administrated at 0.5–0.75 mg/kg bodyweight with a maximum of 60 mg daily. Then, it would most probably be safe and possibly have a more powerful effect with 40 mg daily.

Pharmacological intervention may be beneficial in patients who have previously failed to respond to motor training in isolation (42). The question of whether using pharmacologic interventions combined with physiotherapy is of any clinical value remains unclear. In this study, we have investigated the effect of norepinephrine-facilitating drugs on ischemic stroke patients in motor function and ADL during chronic phases. LD and/or MPH were administered in the current study as amphetamine has documented deleterious cardiovascular side effects (40). Catecholamine neurons have been shown in animal models of brain injury to possibly alter motor recovery (43), and drugs that antagonize catecholamine receptors (e.g., haloperidol (44) and phenoxybenzamine (45) may have negative effects on rehabilitation. Norepinephrine was shown to be the active chemical in clinical trials involving amphetamine (46); therefore, a combination of LD and decarboxylase inhibitor was administered to increase norepinephrine levels in the synapse (8).

MPH acts by directly stimulating release of dopamine and norepinephrine, as well as blocking catecholamine reuptake (47) thereby having effects on both dopaminergic and noradrenergic modulations.

A shortcoming of our study was the small number of patients; we experienced similar difficulty with patient recruitment that other studies have faced because of a wide range of exclusion criteria (15). Although we chose wide inclusion criteria of patients with stroke, the majority of screened stroke patients did not meet the initial eligibility criteria, and they were excluded from entering the study. However, 78 of the 100 eligible patients terminated the study. There is significant potential of benefits from an increase in regimented physical therapy (22). Fifteen 45-min sessions of physiotherapy may not have been sufficient to induce or support plastic brain changes. In a study by Scheidtmann et al. (8) stroke patients receiving

100 mg LD per day for 3 weeks improved significantly more than the placebo-treated control group. Furthermore, to date, no clinical study testing amphetamine in stroke has taken into account ischemic lesion size or localization (15, 36).

Although patients followed a standardized physical therapy schedule, it was still necessary to individualize therapy sessions based on patient abilities (22).

It remains to be clarified why the results of animal experiments and the positive results of some clinical trials could not be replicated in other clinical trials including this study. Clinical efficacy of LD and/or MPH in combination with physiotherapy may require higher drug doses, more frequent and longer duration of treatments, improved patient selection regarding stroke localization and duration i.e. arteries affected and appropriate time window for intervention, respectively.

Conclusion

Ischemic chronic stroke patients having MPH and/or LD in combination with physiotherapy showed a slight ADL and stroke severity improvement over time. There were no side effects reported, and our findings will redirect attention to the clinical benefits of this type of drug treatment in rehabilitation. Future studies should address the issue of the optimal therapeutic window and dosage of medications, as well as to identify those patients with stroke must probable to benefit of treatment.

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