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Safety and improvement of movement function after stroke with atomoxetine: A pilot randomized trial

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Abstract.

Background: Intensive, task-oriented motor training has been associated with neuroplastic reorganization and improved upper extremity movement function after stroke. However, to optimize such training for people with moderate-to-severe movement impairment, pharmacological modulation of neuroplasticity may be needed as an adjuvant intervention.

Objective: Evaluate safety, as well as improvement in movement function, associated with motor training paired with a drug to upregulate neuroplasticity after stroke.

Methods: In this double-blind, randomized, placebo-controlled study, 12 subjects with chronic stroke received either atomoxetine or placebo paired with motor training. Safety was assessed using vital signs. Upper extremity movement function was assessed using Fugl-Meyer Assessment, Wolf Motor Function Test, and Action Research Arm Test at baseline, post-intervention, and 1-month follow-up.

Results: No significant between-groups differences were found in mean heart rate (95% CI, -12.4–22.6; $p=0.23$), mean systolic blood pressure (95% CI, -1.7–29.6; $p=0.21$), or mean diastolic blood pressure (95% CI, -10.4–13.3; $p=0.08$). A statistically significant between-groups difference on Fugl-Meyer at post-intervention favored the atomoxetine group (95% CI, 1.6–12.7; $p=0.016$).

Conclusion: Atomoxetine combined with motor training appears safe and may optimize motor training outcomes after stroke.

Keywords: Upper extremity, neurorehabilitation, safety, vital signs, occupational therapy, motor training

1. Introduction

Stroke is a major public health concern, as there are over 795,000 new strokes annually in the

United States at a cost of \$34 billion (Mozaffarian et al., 2015). Interventions to minimize tissue damage in acute stroke have had some success (Eissa, Krass, & Bajorek, 2012). However, there is still a crucial need for interventions to maximize recovery of movement function after neurologic damage has occurred (Nudo, Plautz, & Frost, 2001). These interventions can capitalize on neuroplastic change (the capacity of the

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brain to reorganize). Neuroplastic change correlates with recovery of movement function after brain lesions (Nudo et al., 2001; Sawaki et al., 2014). Intensive, task-oriented motor training is an example of a therapeutic intervention that adheres to principles of neuroplastic change (Kleim & Jones, 2008). This intervention has been shown to improve mildly impaired movement function after stroke (Wolf et al., 2006). However, it has not been established as effective to mitigate chronic, severe impairment of upper extremity (UE) movement function after stroke (Bonifer & Anderson, 2003). In general, further research is needed to advance the effectiveness of interventions targeting chronic, severe impairment of UE movement function after stroke. In particular, optimizing intensive, task-oriented training for people with severe impairment may require adjuvant interventions to upregulate neuroplasticity (Hayward, Barker, & Brauer, 2010).

For more than a decade, the research community has viewed pharmacological intervention as a potentially valuable tool for optimizing therapy after stroke. Specifically, a variety of drugs have been examined as potential interventions to promote recovery of movement and speech functions (Floel et al., 2005; Foster, Good, Fowlkes, & Sawaki, 2006; Walker-Batson et al., 2001). Research in animals and humans indicates that some medications, such as amphetamine, may enhance outcomes of motor training (Feeney & Sutton, 1987). One of the proposed mechanisms by which amphetamine may enhance outcomes of motor training is by increasing central levels of norepinephrine (Feeney & Sutton, 1987), a neurotransmitter that appears to serve a major role in the plasticity process (Feeney & Sutton, 1987). Drugs that stimulate central levels of norepinephrine have been shown to promote recovery of movement and cognitive function, while drugs that inhibit norenergic pathways yield a deleterious effect in this regard (Feeney & Sutton, 1987; Wang et al., 2011). At the same time, the number of patients in the several clinical trials who have received motor training paired with amphetamine after stroke is very small, due to amphetamine's potential interaction with many other medications as well as its potential for addiction. Furthermore, the existing research about amphetamine has shown it to have inconsistent results as well as significant unwanted effects (Wang et al., 2011).

Atomoxetine, a potent and selective inhibitor of the presynaptic norepinephrine transporter (Simpson & Perry, 2003), has been approved by the Food and Drug Administration for treatment of attention deficit

hyperactivity disorder (Simpson & Perry, 2003). Unlike amphetamine, atomoxetine lacks affinity for dopaminergic and serotonergic receptors and therefore has no potential for abuse (Simpson & Perry, 2003). A small study using atomoxetine has been shown to enhance motor memory formation in 10 healthy participants (Foster et al., 2006) using an established laboratory paradigm (Classen, Liepert, Wise, Hallett, & Cohen, 1998). However, atomoxetine has not been systematically evaluated for improvement of movement function after stroke. The present, double-blind, sham-controlled study was the first to address this evidence gap by evaluating the effects of atomoxetine on cardiovascular safety and movement function in subjects with chronic, moderate-to-severe impairment in movement function after stroke. The central hypothesis was that subjects who received atomoxetine paired with intensive, task-oriented UE motor training would have similar changes in blood pressure and heart rate, as well as similar rate of adverse events, as a placebo group (ie, subjects who received a placebo paired with intensive, task-oriented UE motor training). Additionally, it was hypothesized that the atomoxetine group would show initial indications of more improved movement function than the placebo group.

2. Methods

In accordance with the Declaration of the World Medical Association (www.wma.net), this study was approved by the authorized institutional human research review boards at the institutions governing the research (ie, Wake Forest University, Winston-Salem, NC; the University of Kentucky, Lexington, KY; Cardinal Hill Hospital, Lexington, KY). All study procedures were in accordance with these institutions' guidelines. The research setting was a neurorehabilitation research lab. Subjects were recruited from Cardinal Hill Rehabilitation Hospital, University of Kentucky, Wake Forest University, and local communities.

2.1. Eligibility criteria

To remove the potential confound of spontaneous motor recovery, only individuals at least 6 months from the onset of stroke were recruited. To ensure safety and minimize potential confounding variables, the following exclusion criteria were selected: a) history of traumatic head injury; b) history of severe

alcohol or drug abuse; c) history of psychiatric illness; d) unstable cardiac dysrhythmia; e) untreated hypertension (systolic pressure >160 mm Hg and/or diastolic pressure >100 mm Hg); f) history of myocardial infarction or unstable angina; g) positive pregnancy test or being of childbearing age and not using contraception; h) glaucoma; i) history of hypersensitivity or idiosyncrasy to sympathomimetic drugs; j) within 3 months of recruitment, addition or change in the dosage of drugs known to exert detrimental effects on recovery of movement function (Boroojerdi, Ziemann, Chen, Butefisch, & Cohen, 2001; Butefisch et al., 2002; Goldstein & Davis, 1990; Sawaki et al., 2002; Sawaki, Werhahn, Barco, Kopylev, & Cohen, 2003); or k) aphasia or cognitive deficit severe enough to preclude informed consent.

As required by the authorized institutional human research review boards at the institutions where the research was conducted, all subjects provided written informed consent after receiving a verbal and written explanation of the purposes, procedures, and potential hazards of this study, which used a parallel-group block design within the conceptual framework of a superiority trial. After screening and informed consent, a convenience sample of 12 subjects who were 21 years of age or older was enrolled. All subjects had moderate-to-severe UE deficit in movement function (the inability to extend the affected metacarpophalangeal joints at least 10°; and the wrist, 20° (Wolf et al., 2006)). After enrollment, subjects participated in a baseline evaluation of movement function, 10 consecutive weekdays of intervention, 1 evaluation immediately after the intervention period, and a 1-month follow-up evaluation. After baseline evaluation, the principal investigator (PI) used a computerized experimental design generator and randomizer program to govern group assignment. This program generated a simple random allocation sequence (1 : 1) for assigning subjects into 2 equal-sized groups (ie, either the atomoxetine group or the placebo control group). The PI generated the random allocation sequence, enrolled subjects, and assigned subjects to interventions. Subjects were ordered by the randomizer in strict accordance with the order of enrollment.

2.2. *Intervention component 1: Atomoxetine (real or placebo)*

The initial recommended and safe dose of atomoxetine (Strattera, by Eli Lilly) in subjects over

70 kg is 40 mg/day; therefore this dose was administered in this study (Simpson & Perry, 2003), for the intervention group. Placebo capsules were identical to atomoxetine capsules. Drug condition (ie, real versus placebo) was the only independent variable. In each intervention session (10 total sessions), dosing occurred just prior to intensive, task-oriented UE motor training.

2.3. *Intervention component 2: Intensive, task-oriented UE motor training*

In each intervention session, 2 hours of intensive, task-oriented UE motor training commenced 60 minutes after atomoxetine or placebo intake to maximize peak plasma drug concentration during motor training (Simpson & Perry, 2003). All subjects participated in motor training, which was delivered in a 1 : 1 ratio between an occupational therapist and a subject. Training focused on skill acquisition through the use of unilateral (ie, impaired hand) and bilateral activities to improve movement function of the impaired hand. Tasks targeted functional goals (eg, activities of daily living) or goal subcomponents (eg, pinching, grasp/release, or functional reach patterns). Tasks were repeated at rate of approximately 10 to 50 repetitions each session according to the demands of the task. Tasks had progressive difficulty, meaning that task demands elicited progressively more skilled performance over time (shaping) (Wolf et al., 2006).

2.4. *Evaluation and outcome measures*

To evaluate drug effects and monitor for adverse events, heart rate and blood pressure were measured and recorded by the PI prior to administration of atomoxetine or placebo. Drug administration proceeded if no abnormalities were present. Blood pressure and heart rate were then continuously monitored every 30 minutes until 30 minutes after the session had ended. A daily log of each subject's reported sense of well-being or complaints associated with each session was recorded by the PI before and after each session.

To evaluate movement function, the Fugl Meyer Assessment (FMA), the Action Research Arm Test (ARAT), and the WMFT were administered at baseline, after the intervention period, and at 1-month follow-up. The FMA is a quantitative measure of motor recovery, balance, sensation, coordination and speed. It is based on the principle that recovery of

movement function occurs in a predictable progression (Duncan, Propst, & Nelson, 1983). The FMA is feasible for use after stroke and has been extensively applied in this condition (Duncan et al., 1983). The inter-rater reliability (0.886–0.984 according to the subset for lower or UE) and test-retest reliability ($=0.99$) of FMA are high (Duncan et al., 1983). The total possible score for UE movement function is 66. The highest possible FMA motor score for a tested UE is 66. The minimal clinically important difference (MCID) for FMA is 9 to 10 points; and the minimal detectable change (MDC) is 5.2 (Pandian & Arya, 2014). Based on its responsiveness and validity, FMA was used as the primary outcome measure.

The ARAT was developed specifically to measure UE grasp, grip, pinch, and gross movement using 4 specific tests (van der Lee, Beckerman, Lankhorst, & Bouter, 2001). Each item is graded on a 4-point ordinal scale with a total possible score of 57. The inter-rater reliability ($=0.99$) and test-retest reliability ($=0.98$) of ARAT are extremely high. The highest possible ARAT score for a tested UE is 57. The MCID for ARAT is 5.7 points; and the MDC is 3.5 (Pandian & Arya, 2014).

The WMFT is a time- and function-based evaluation and encompasses a battery of 17 tasks (Wolf et al., 2006). It is performed using a 16" \times 43" laminated template on a standardized table. All tasks simulate functional tasks and are applied sequentially according to the task complexity. The WMFT has established reliability and validity and has been extensively applied in several studies to evaluate UE motor capacity after stroke (Wolf et al., 2006). The inter-rater reliability (0.93–0.99) and test-retest reliability ($=0.97$) of WMFT are considered excellent (Whitall, Savin, Harris-Love, & Waller, 2006). The MCID for WMFT is 1.5 to 4 seconds; and the MDC is 12 seconds (Pandian & Arya, 2014). Time-based measures were collected for the paretic (ie, more affected) and non-paretic (is, less affected) UEs.

2.5. Blinding

Subjects, care providers, and assessors of movement function were blinded to group assignment in that they were not made aware of which condition any subject was assigned to. Additionally, personnel administering atomoxetine (real or placebo) did not administer intensive, task-oriented UE motor training. Furthermore, atomoxetine and placebo

capsules were visually identical, as prepared by a pharmacy.

2.6. Statistics

Analyses of vital signs utilized linear mixed effects models with random intercept and slope to account for the 8 repeated measurements over time from each subject. Similarly, for FMA, ARAT, and WMFT, a longitudinal repeated measures model was used that accounts for time, trial arm, and their interaction. These models incorporate an unstructured working covariance matrix, and the Kenward and Roger degrees of freedom method was used for inference (Kenward & Roger, 1997). These analyses correspond to the use of repeated measures MANOVA, but with the allowance of missing data. Primary interest was in the comparison of mean changes in outcomes from baseline to immediately post-intervention and to 1-month follow-up for the 2 trial arms. For more detail, the separate impacts of each trial arm on the mean change of each outcome are presented. Longitudinal repeated measures ANCOVA models were also fit for each outcome due to slight imbalances at baseline. However, results were very similar and thus are not presented. All available data were utilized for analyses. All tests were 2-sided, with statistical significance pre-specified as $P < 0.05$. Furthermore, all tests were pre-specified. Multiple testing corrections were not directly utilized due to their known limitations (Altman, 2000; Perneger, 1998). Information provided in Table 4 can be utilized to obtain formal multiple testing corrections. Analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

Figure 1 shows participant flow. Table 1 shows clinical characteristics and demographic data for the sample. A total of 12 subjects (6 women) with chronic stroke, mean age of 55 years (range, 35–66 years), and mean interval of 25 months after stroke (range 6–52 months) were enrolled. Recruitment and all evaluations took place between April 2006 and June 2010. The study ended when projected enrollment was reached. Twelve subjects completed all intervention sessions, baseline evaluation, and evaluation at immediately post-intervention. Nine subjects completed the 1-month follow-up evaluation ($n=3$ in the atomoxetine group and $n=6$ in the placebo

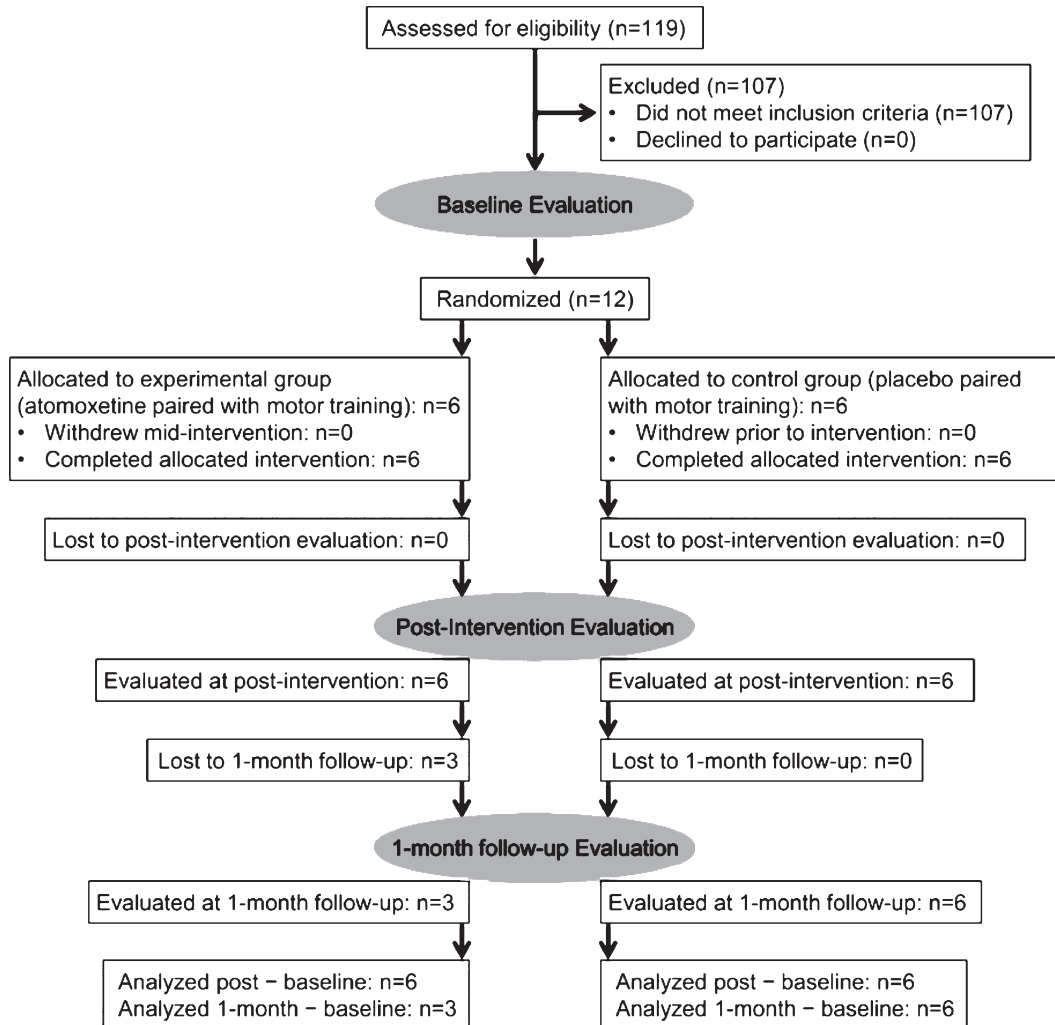


Fig. 1. Participant flow. Each stage of the study is represented, from eligibility assessment through analysis of final evaluation data. The number of randomly assigned subjects who received intended treatment in each group is shown, along with losses to follow-up.

group). Losses to 1-month follow-up occurred due to either transportation constraints or subjects' enrollment in other research studies immediately after post-intervention evaluation.

Effects of atomoxetine on vital signs were not significantly different when compared with placebo (Fig. 2). The interaction was not significant ($p=0.23$) for the mean heart rate over time between the 2 trial arms. After taking out the interaction, there was not a significant trial arm difference ($p=0.53$). Specifically, adjusting for time, the estimated mean heart rate was 5.1 [95% CI: (-12.4, 22.6)] beats per minute higher for atomoxetine relative to placebo. The interaction was not significant ($p=0.21$) for changes in mean of systolic blood pressure over time between the 2 trial arms. After taking out the interaction,

there was no statistical difference between the 2 trial arms ($p=0.08$). Specifically, adjusting for time, the estimated mean systolic blood pressure was 14.0 [95% CI: (-1.7, 29.6)] mm Hg lower for atomoxetine relative to placebo. The interaction was not significant ($p=0.995$) for changes in mean diastolic blood pressure over time between the 2 trial arms. After taking out the interaction, there was not a significant trial arm difference ($p=0.79$). Specifically, adjusting for time, the estimated mean diastolic blood pressure was 1.4 [95% CI: (-10.4, 13.3)] mm Hg higher for atomoxetine relative to placebo.

Table 2 shows the each subject's reported sense of well-being or complaints. While there were reports of mental fatigue, increased sleepiness, and

Table 1
Clinical characteristics and demographic data

Subject	Age (years)	Group	Sex	Affected Hemisphere	Stroke Type	Months Post-Stroke
1	39	ATM	M	Right	Ischemic	52
2	35	ATM	F	Left	Ischemic	28
3	50	ATM	F	Left	Ischemic	25
4	65	ATM	F	Left	Ischemic	19
5	49	ATM	M	Left	Ischemic	19
6	65	ATM	M	Left	Ischemic	24
ATM	50.5 ± 12.6		3F/3M	5Left/1Right	6 ischemic	27.7 ± 12.4
7	58	Placebo	M	Left	Ischemic	16
8	53	Placebo	M	Right	Ischemic	37
9	66	Placebo	F	Left	Ischemic	6
10	66	Placebo	F	Right	Ischemic	48
11	58	Placebo	M	Left	Hemorrhagic	8
12	58	Placebo	F	Right	Hemorrhagic	13
Placebo	59.8 ± 5.2		3F/3M	3Left/3Right	4 ischemic/2 Hemorrhagic	21.3 ± 17.1

Abbreviations: ATM, Atomoxetine; F, Female; M, Male.

exhaustion associated with both conditions, there was no clear indication of unwanted effects related to atomoxetine.

Table 3 summarizes baseline scores on outcome measures for the 2 trial arms. Table 4 shows changes in UE movement function associated with intervention. From baseline to immediately post-intervention, within-group changes for the atomoxetine group indicated significant improvement on FMA (95% CI, 5.4–13.2; $p=0.0003$) and ARAT (95% CI, 4.6–10.7; $p=0.0002$). Within-group changes for the placebo group indicated significant improvement on ARAT (95% CI, 2.3–8.4; $p=0.003$) and WMFT paretic UE (95% CI, $-0.35 - -0.03$; $p=0.02$). From baseline to 1-month follow-up, within-group changes in the atomoxetine group indicated significant improvement on FMA (95% CI, 5.9–17.9; $p=0.002$) and ARAT (95% CI, 5.1–15.1; $p=0.001$). Within-group changes for the placebo group indicated significant improvement on FMA (95% CI, 1.5–10.2; $p=0.015$), ARAT (95% CI, 2.6–10.4; $p=0.005$) and WMFT paretic UE (95% CI, $-0.37 - -0.04$; $p=0.02$). Between-groups comparison of changes from baseline to immediately post-intervention revealed significantly more improvement on FMA (95% CI, 1.6–12.7; $p=0.016$) for the atomoxetine group compared with the placebo group. No between-groups differences were found at 1-month follow-up.

4. Discussion

The present study was the first-ever investigation of the safety and efficacy of atomoxetine paired with motor training for people with moderate-to-severe

deficit in movement function after stroke. Findings constituted novel evidence that atomoxetine has a safe cardiovascular profile and preliminary efficacy to support clinically meaningful outcomes of intensive task-oriented UE motor training after stroke, even in cases of chronic, moderate-to-severe impairment.

A previous case series study of 3 subjects with chronic, mild movement deficit after stroke showed that atomoxetine paired with not only motor training but also non-invasive neuromodulation (repetitive transcranial magnetic stimulation (rTMS)) may improve FMA and WMFT, as evident at post-intervention and at 1-month follow-up (Kinoshita et al., 2016). However, atomoxetine was delivered concomitantly with other interventions; and there was no control group. Additionally, there was no systematic evaluation of cardiovascular or safety data. In contrast, the present study demonstrated that the effects of atomoxetine on blood pressure and heart rate were not significantly different from placebo; and no serious adverse events occurred in either group. Additionally, although both groups showed significantly improved movement function immediately after intervention, the atomoxetine group showed significantly more improvement on the primary outcome measure (ie, FMA) than the placebo group. Notably, the estimated mean FMA and ARAT change exceeded MCID only for the atomoxetine group, both at post-intervention and at 1-month follow-up.

The present study's limitations included small sample size. A larger sample size is recommended for future studies. Additionally, examining the effects of atomoxetine beyond 1 month could substantiate the drug's long-term efficacy. Also, as the present study administered a daily dose of 40 mg during the

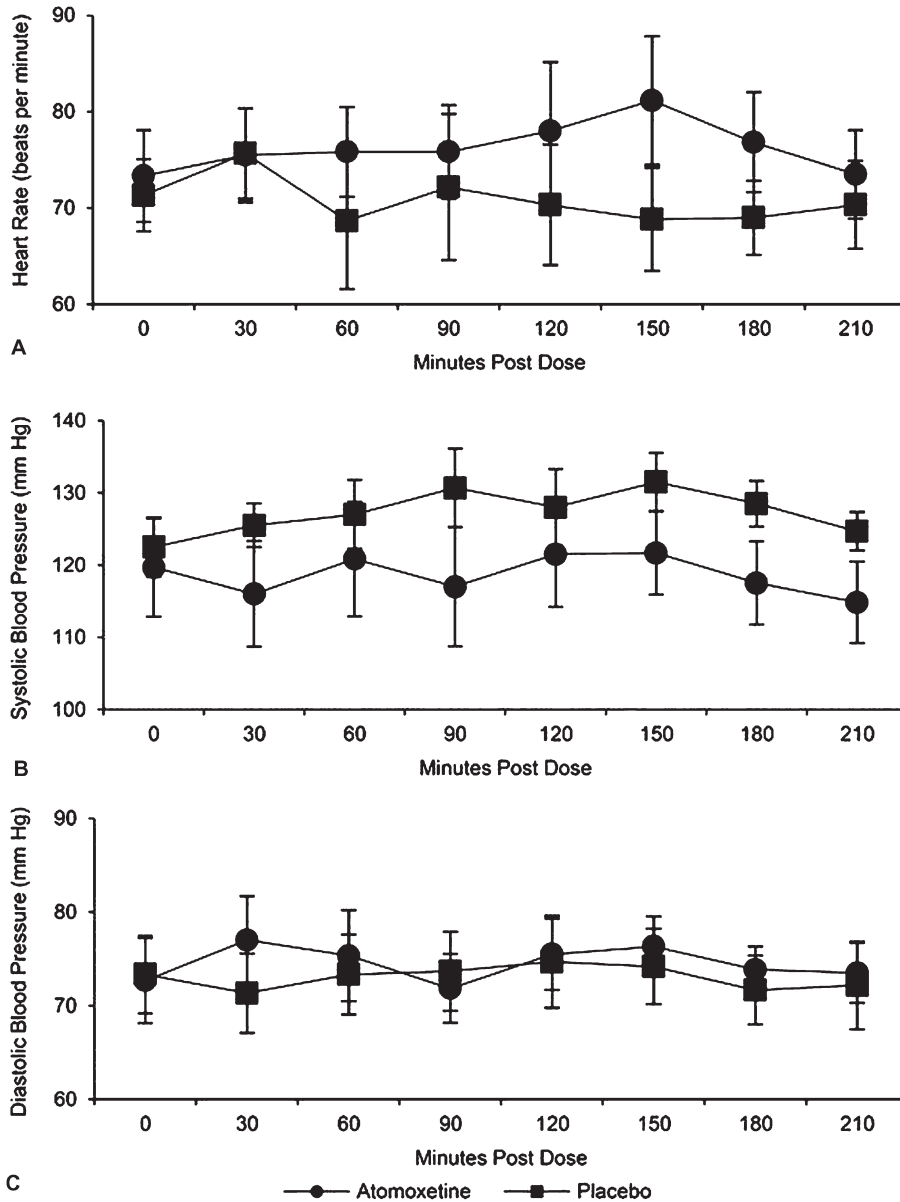


Fig. 2. Vital signs by group as a function of time post dose. No significant between-groups differences were evident for (A) heart rate, (B) systolic blood pressure, or (C) diastolic blood pressure.

10-day intervention, future studies should conduct a dose-escalation study of atomoxetine in order to achieve the optimal dose according to each participant's weight. The optimal dose for treatment of ADHD is 1.2 mg/kg/day, which in a 70 kg individual corresponds to 80 mg (Simpson & Perry, 2003).

Future studies are recommended to expand the scope of the present study. For example, variables affecting functional recovery may be particularly amenable to change during the sub-acute stage of

stroke recovery. Given the positive influence of early therapy on UE movement function after stroke (Wolf et al., 2006), as well as the efficacy of atomoxetine to improve UE movement function in healthy subjects (Foster et al., 2006), it would be worthwhile to explore the impact of atomoxetine paired with motor training during sub-acute stroke recovery. Other recommended research should examine effects of drugs other than atomoxetine that increase central levels of norepinephrine. For example, reboxetine

is a norepinephrine reuptake inhibitor that has exhibited positive short-term effects on movement function in cases of chronic stroke (Wang et al., 2011; Zittel, Weiller, & Liepert, 2007), but further research is needed to establish that these benefits are long-lasting. The alpha 2 antagonist atipamezole has been

Table 2
Daily log of subjects' complaints

Subject	Group	Reported Complaints
1	Atomoxetine (ATM)	Mental fatigue on days 6 and 8
2	ATM	None
3	ATM	Sleepiness and fatigue during first 4 days
4	ATM	Slightly fatigued on days 2 and 5
5	ATM	None
6	ATM	Slightly fatigued at the end of all sessions
7	Placebo	Headache on day 9
8	Placebo	Fatigued day 4
9	Placebo	Dizziness on day 1
10	Placebo	None
11	Placebo	None
12	Placebo	None

Table 3

Group scores at baseline (sample mean \pm standard deviation).
Sample size was 6 in each group

Outcome measures for upper extremity (UE) movement function	Baseline scores atomoxetine group	Baseline scores for placebo group
Fugl-Meyer Assessment (points)	29.3 \pm 11.3	39.8 \pm 21.3
Action Research Arm Test (points)	19.2 \pm 12.8	29.3 \pm 23.0
Wolf Motor Function Test (log[sec]):		
more affected UE	1.53 \pm 0.48	1.20 \pm 0.75
less affected UE	0.53 \pm 0.39	0.56 \pm 0.35

associated with improvement of movement function in acute post-stroke stages, but research on its effects in chronic stroke is lacking (Beltran, Papadopoulos, Tsai, Kartje, & Wolf, 2010). Future research that systematically compares the effects of these drugs (which have a similar selective mechanism of action as atomoxetine) with the effects of atomoxetine would help to establish which of these drugs may have the most beneficial and safe impact on outcomes of intensive task-oriented UE motor training for people with chronic, moderate-to-severe impairment after stroke.

Finally, neuroimaging evidence may be crucial to advance understanding of how the noradrenergic effects of atomoxetine may influence neuroplastic change after stroke. However, there is a scant evidence base in this regard. Yamada and colleagues evaluated the effects of atomoxetine combined with intensive speech therapy in 4 participants with post-stroke aphasia. All participants demonstrated improved language function measured by the Western Aphasia Battery and the Token Test. Improvements were associated with increased perilesional blood flow using single photon emission computed tomography (Yamada, Kakuda, Yamamoto, Momosaki, & Abo, 2016). Separate studies have evaluated off-label use of atomoxetine in subjects with Parkinson's disease. For instance, Rae and colleagues conducted a double-blind, placebo-controlled, randomized crossover study in 10 participants with moderate idiopathic Parkinson's disease. While there was inter-individual variability, increased functional brain network activity indicated

Table 4

Estimated means, 95% confidence intervals, and *p*-values corresponding to mean change from fitting a single repeated measures model for each variable

Outcome measures of upper extremity (UE) movement function	Post-intervention – Baseline			1-month follow-up – Baseline		
	Atomoxetine (ATM)	Placebo	ATM–Placebo	ATM	Placebo	ATM–Placebo
Fugl-Meyer Assessment (points)	9.3 (5.4, 13.2) <i>p</i> = 0.0003	2.2 (-1.7, 6.1) <i>p</i> = 0.24	7.2 (1.6, 12.7) <i>p</i> = 0.016	11.9 (5.9, 17.9) <i>p</i> = 0.002	5.8 (1.5, 10.2) <i>p</i> = 0.015	6.1 (-1.3, 13.5) <i>p</i> = 0.10
Action Research Arm Test (points)	7.7 (4.6, 10.7) <i>p</i> = 0.0002	5.3 (2.3, 8.4) <i>p</i> = 0.003	2.3 (-1.9, 6.6) <i>p</i> = 0.25	10.1 (5.1, 15.1) <i>p</i> = 0.001	6.5 (2.6, 10.4) <i>p</i> = 0.005	3.6 (-2.8, 10.0) <i>p</i> = 0.24
Wolf Motor Function Test (WMFT) more affected UE (log[sec])	-0.10 (-0.26, 0.06) <i>p</i> = 0.18	-0.19 (-0.35, -0.03) <i>p</i> = 0.02	0.09 (-0.13, 0.31) <i>p</i> = 0.39	-0.11 (-0.28, 0.06) <i>p</i> = 0.19	-0.20 (-0.37, -0.04) <i>p</i> = 0.02	0.10 (-0.14, 0.34) <i>p</i> = 0.40
WMFT less affected (log[sec])	0.01 (-0.13, 0.15) <i>p</i> = 0.91	-0.13 (-0.26, 0.01) <i>p</i> = 0.07	0.13 (-0.06, 0.33) <i>p</i> = 0.16	0.01 (-0.22, 0.25) <i>p</i> = 0.90	-0.07 (-0.28, 0.14) <i>p</i> = 0.46	0.09 (-0.23, 0.40) <i>p</i> = 0.56

For Fugl-Meyer Assessment and Action Research Arm test, an increase represents improvement. For WMFT, a decrease represents improvement.

improved modulation of frontal-subcortical areas for response inhibition. Additionally, investigators found increased sensitivity of the inferior frontal gyrus to afferent inputs originating from the pre-supplementary motor cortex. The investigators suggested that the selective effects of atomoxetine may have partially restored noradrenergic denervation that may play a role in impaired inhibitory responses in Parkinson's disease (Rae et al., 2016). Borchert and colleagues performed an fMRI study to evaluate the effects of atomoxetine in 33 participants with idiopathic Parkinson's disease. They found that atomoxetine increased connectivity from the right inferior frontal gyrus to the dorsal anterior cingulate. Change was associated with change in a simple measure of executive function (Borchert et al., 2016).

In conclusion, findings of the present study indicated that atomoxetine appears safe to pair with motor training in the context of stroke rehabilitation. Furthermore, atomoxetine appears to have potential to optimize clinical outcomes of intensive task-oriented training for people with chronic, moderate-to-severely impaired movement function after stroke. Overall, given the promising results of the present feasibility study, a full-scale investigation with expanded outcome measures, including measures of neuroplastic change, is warranted.

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