

Donepezil as an adjuvant to constraint-induced therapy for upper-limb dysfunction after stroke: An exploratory randomized clinical trial

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Abstract—Donepezil, a primarily central acetylcholinesterase inhibitor, could potentiate learning in subjects with stroke by amplifying cholinergic input to the cerebral cortex from the nucleus basalis of Meynert. We tested this possible adjuvant effect of donepezil in a prospective randomized, double-blind, placebo-controlled, parallel-group study of 20 subjects 1 or more years following stroke undergoing constraint-induced therapy (CIT) for upper-limb dysfunction. CIT had substantial and significant effects on both primary outcome measures, the Wolf Motor Function Test (WMFT) and the Motor Activity Log (amount), and all secondary measures, including the Box and Block Test, the Actual Amount of Use Test, the Fugl-Meyer Motor Scale-Upper Extremity, and the Caregiver Strain Index. Subjects receiving donepezil achieved differential gains on the WMFT approaching statistical significance ($p = 0.067$, corrected for multiple comparisons), but not on other measures. This study is inconclusive, but a larger randomized controlled trial with adequate statistical power should be pursued because of the potential benefits of the treatment to stroke survivors.

Key words: constraint-induced therapy, donepezil, hemiparesis, rehabilitation, stroke.

INTRODUCTION

We report a prospective randomized, placebo-controlled, parallel-group trial of donepezil, 10 mg/d, as

an adjunct to constraint-induced therapy (CIT) for persistent upper-limb dysfunction caused by stroke 1 or more years prior. The pairing of a pharmacological intervention with a behavioral intervention was motivated by the concept that although a drug may be capable of enhancing the process of altering neural connectivity that underlies functional improvement, a drug cannot supply the information to the brain that will actually be represented as new connectivity. For this, a behavioral intervention is needed.

Abbreviations: AD = Alzheimer's disease, CIT = constraint-induced therapy, CSI = Caregiver Strain Index, GDS = Geriatric Depression Scale, MAL = Motor Activity Log, MRD-VAMC = Malcom Randall Department of Veterans Affairs Medical Center, SIS = Stroke Impact Scale, WMFT = Wolf Motor Function Test.

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Donepezil

Donepezil, a reversible inhibitor of central and peripheral acetylcholinesterase, acts to increase acetylcholine concentrations in cholinergic synapses. Anticholinergic medications have long been recognized to inhibit the formation of declarative memories (memories for facts) in humans [1], presumably by blocking cholinergic input from the medial septal nuclei to the hippocampus. More recently, lesions of the nucleus basalis of Meynert (which supplies cholinergic projections to the entire cerebral cortex) have been shown to abrogate the dramatic reorganization of sensory cortex that normally occurs after sciatic nerve section in rats [2]. This reorganization constitutes a form of procedural (skill) memory.

Many studies have now implicated the nucleus basalis and its cholinergic projections as a critical factor in procedural memory formation and in neural plasticity underlying recovery from brain injury. The administration of anticholinergic drugs or lesions of nucleus basalis impairs operant conditioning in animals [3]. Lesions of nucleus basalis substantially preclude modifications in somatosensory cortex normally elicited by major alterations in the pattern of sensory input [4]. The administration of anticholinergic drugs impairs the functional recovery of experimental animals from brain trauma, whereas the administration of cholinergic agents potentiates recovery [5]. Kilgard and Merzenich have shown that when adult rats are given microstimulation of the nucleus basalis at the same time that they are repeatedly passively exposed to brief auditory tones of a particular frequency, a dramatic reorganization of the primary auditory cortex occurs, such that the majority of neurons become tuned to the auditory stimulus frequency [6]. This is another modality of procedural memory.

Thus, whereas the septohippocampal and nucleus basalis-association cortex systems are implicated in forming declarative memories, the nucleus basalis-primary sensory and motor systems appear to be implicated in the formation of procedural memories. Both types of memory formation may be viewed as a form of neural plasticity. For both types, cholinergic cortical input appears to be the mechanism by which the behavioral importance of specific stimuli is signaled to the cerebral cortex. The abundant limbic inputs to the medial septal nuclei and the nucleus basalis provide the means by which these nuclei are informed of behavioral importance [7].

Although we now have compelling evidence of the deleterious effects of anticholinergic agents/nucleus

basalis lesions on neural plasticity in both animals and humans and of the dramatic effect of nucleus basalis activation in modifying neural network connectivity, only one human disorder exists in which the potential therapeutic benefits of cholinergic agents have been thoroughly assessed: Alzheimer's disease (AD). Tacrine, donepezil, rivastigmine, and galantamine, all inhibitors of acetylcholinesterase, have minimal immediate effects on cognitive function but have been shown to slow cognitive decline in patients with AD [8]. It is unlikely that this is related to amelioration of the underlying disease process. It has generally been assumed that the benefits of these acetylcholinesterase inhibitors were mediated through normalization of cortical and hippocampal acetylcholine in these patients (who have severe neuronal loss in the nucleus basalis and the medial septal nuclei), possibly with attendant beneficial effects on signal-to-noise ratio. The data reviewed in the foregoing discussion, however, suggest that the beneficial effects of cholinergic agents might be mediated through enhancement of neural plasticity. Thus, patients with AD treated with acetylcholinesterase inhibitors may experience slower cognitive decline because they are able to take better advantage of the cognitive rehabilitation implicit in their interactions with those around them in daily life.

CIT, to the extent that it is effective, enhances motor skills, and it achieves this improvement incrementally through extended practice. Thus, the functional improvements acquired during CIT meet the definition of procedural memory [9]. Subjects with purely cortical strokes may not have deficits in cortical acetylcholine, absent damage to subcortical projections from nucleus basalis. In such subjects, we posit that donepezil might enhance the process of procedural learning through rehabilitation by inducing supranormal levels of cortical acetylcholine. Scali et al. have shown that chronic administration of donepezil (1.5 mg/kg bid) to aged rats results in a 39 percent inhibition of cortical acetylcholinesterase and a 75 percent increase in cortical acetylcholine levels [10]; the same degree of inhibition of cortical acetylcholinesterase has been demonstrated in human subjects with AD receiving donepezil 3 to 5 mg/d [11]. In subjects with subcortical strokes (e.g., lacunar infarctions or middle cerebral artery distribution infarcts damaging deep white matter), cholinergic projections may be damaged from nucleus basalis. In this situation, donepezil might potentiate procedural learning during rehabilitation by relative normalization of cortical acetylcholine levels.

Constraint-Induced Therapy

The impact of donepezil as an adjuvant to rehabilitation could easily be obscured if the rehabilitation approach used had only a modest therapeutic effect, if it were applied to patients with highly variable deficits, and if the therapeutic approach itself could vary substantially from practitioner to practitioner. We used CIT because, of available physical therapies, it appears to be optimal in addressing these concerns [12] and therefore meets the essential requirements of a “behavioral engine” to drive studies of adjuvant therapy.

METHODS

Subjects

Subjects were recruited from inpatient and outpatient populations at the Malcom Randall Department of Veterans Affairs (VA) Medical Center (MRDVAMC), Shands Hospital at the University of Florida, and Shands Rehabilitation Hospital in Gainesville; Shands at Jacksonville and the Brooks Rehabilitation Hospital in Jacksonville; and through newspaper articles and advertisements and contact with stroke support groups. The study was conducted at the VA Rehabilitation Research and Development Brain Rehabilitation Research Center at the MRDVAMC. We recruited 24 subjects with moderate upper-limb paresis caused by stroke to the study, and 20 completed the study. Subjects had to be between the ages of 18 and 80. No restrictions were related to sex, ethnicity, or handedness. Subjects who had experienced one or more strokes on the same side of the brain were included unless they had a history of a clinical ischemic or hemorrhagic event affecting the other hemisphere, or had evidence of more than a lacune or minor ischemic demyelination affecting the other hemisphere. Subjects with a history of a learning disorder, mental retardation, drug or alcohol abuse, more than very minor head trauma, subarachnoid hemorrhage, severe chronic obstructive pulmonary disease, cardiac dysrhythmias requiring medical treatment, serious medical illness, dementia, medically resistant depression prior to stroke, or schizophrenia were excluded. Aphasia and other cognitive deficits did not preclude inclusion as long as subjects were sufficiently sentient to be able to understand the potential risks and benefits of the study, to personally provide informed consent, and to understand and cooperate with the treatment. The use of anticholinergic medications absolutely precluded study participation. Other drugs that might

potentially inhibit neuroplasticity (neuroleptics, α -1 noradrenergic antagonists, α -2 noradrenergic agonists, anticonvulsants, benzodiazepines, tricyclic antidepressants) constituted relative contraindications to study entry [13]; in general, subjects were not entered who were on more than one of these drugs. Patients taking these medications, within these limitations, were included because our concern about the difficulties of patient recruitment outweighed our estimate of the risk to neuroplasticity posed by limited exposure to these medications, a risk that remains uncertain in human subjects and may be quite modest. Indeed, absolute exclusion of any individual taking any of these medications would have eliminated nine subjects.

Patients had to meet the following motor and functional criteria to enter the study:

1. Active motions of the wrist and hand: 10° of wrist extension from a relaxed flexed position, 10° of extension of any two digits at any joint, and 10° of thumb extension at either joint. All active motions had to be repeated three times within 1 minute.
2. Passive range of motion: 90° of flexion and abduction and 45° external and internal rotation at the shoulder, 45° elbow supination and pronation, elbow extension limited by no more than 30°, wrist extension to at least neutral position, and digit extension limited by no more than 30°. Participants were not required to exhibit any active shoulder or elbow motion.
3. Ability to sit independently for at least 2 minutes. Ability to ambulate was not required.
4. Motor Activity Log (MAL) [14] score was 3 or less.

Procedure

This study was approved and monitored by the Investigational Review Board of the University of Florida Health Science Center and the Subcommittee for Clinical Investigation of the MRDVAMC. All participants provided informed consent.

Randomization and Drug Treatment

Subjects were randomized to donepezil 5 mg or placebo. They took a single tablet daily for 2 weeks, then two tablets daily for 4 weeks. Compliance was determined by pill counts. During the last 2 weeks on medication, subjects underwent CIT. Our research pharmacist (KMH), who provided the medication in coded containers, completed the randomized allocation of subjects to the treatment or placebo groups. All other participants in the study were officially blinded until after

the 6-month follow-up exams were completed. However, because four subjects receiving donepezil experienced prominent gastrointestinal side effects, blinding was not completely effective.

Constraint-Induced Therapy

An occupational therapist, physical therapist, or physical therapy assistant conducted CIT 6 hours a day Monday through Friday with one to three participants at a time [12,15]. Participants contracted to wear the mitt on their unaffected hand 90 percent of their total waking hours except when use of that hand was required for considerations of safety, hygiene, and specifically agreed-upon activities, such as driving to and from the laboratory. A home diary was used to document daily compliance in wearing the mitt. During the midtherapy weekend, subjects were required to complete a checklist of activities of daily living drawn from the MAL. Subjects were required to telephone the laboratory during this weekend and leave a message regarding use of the involved limb. Following completion of CIT, research therapists contacted subjects only to schedule follow-up testing.

CIT included massed repetition, task practice with shaping (approach of a desired motor or behavioral objective by small steps and successive approximations), and intensive timed activities. The participants used CIT in meal preparation, eating, and cleaning up with the staff. The daily interventions were designed around a menu of functional activities that incorporated variations of strength, endurance, coordination, dexterity, and range of motion. We used interest inventories and role checklists to incorporate each participant's unique personality traits and interests into the menu. The participants gave daily input regarding the activities they performed in the laboratory and when they returned home or to the motel. In this way, a variety of purposeful and meaningful activities were incorporated with attention to unique limitations. Encouragement was provided continuously. Therapists sought to prevent participants from failing by providing assistance as necessary or changing the task. If an activity was strongly disliked or appeared to be too difficult, it was eliminated from the menu for the next day.

Assessment

The following tests were performed 1 to 3 days before the drug or placebo was initiated, immediately after CIT was concluded, and 6 months later: Actual Amount of Use Test (AAUT) [16,17], Box and Block Test (BBT) [18,19],

Wolf Motor Function Test (WMFT) [14,20], Fugl-Meyer Motor Scale-Upper Extremity [21], the MAL [14], a finger-tapping test (ratio of keyboard taps with a finger of involved hand to a finger of uninvolved hand, over 10 s, averaged over three trials), the Stroke Impact Scale (SIS) Version 2.0 [22], Caregiver Strain Index (CSI) [23], and the Geriatric Depression Scale (GDS) [24]. Two probes measurements were performed each of the 10 days of CIT: card flipping (number of cards flipped from a deck with the impaired hand in 20 s) and grip strength, as measured by a dynamometer (average of three measures). The two primary outcome measures were the WMFT (time) for the affected limb and the MAL (amount). All other measures were secondary.

Statistical Analysis

All data were analyzed with a SAS version 8.2 (SAS Institute, Cary, North Carolina). Descriptive statistics were obtained on the 12 assessment measures. For each of these measures, the changes at 2 weeks and at 6 months from the baseline were assessed in a single analysis with the use of PROC GLM, with a group and a time effect included in the model. The group effect tested differences in improvement between the donepezil and placebo groups, the time effect studied whether changes at 6 months remained the same compared to those at 2 weeks, and importantly, the intercept parameter indicated whether the scores changed from baseline. We also ran paired *t*-tests on change in score from baseline to 2 weeks and baseline to 6 months on each of the 12 assessment scores to determine whether the scores improved over the two time periods. The same models were fitted again, controlling for baseline Fugl-Meyer Motor Scale-Upper Extremity. To determine if there was a significant drug effect on the rate of improvement in card flipping and hand dynamometer force assessment scores over a 12-day period, we completed longitudinal analyses, including a time effect, a quadratic time effect, a treatment group effect, and a time by group interaction effect. All statistical tests were two-tailed.

RESULTS

Twenty subjects completed the study, eleven in the donepezil group and nine in the placebo group. Three participants withdrew because of side effects of the drug, frustration with wearing the mitt, or transportation difficulties. One subject was dismissed from the study

because of failure to take the study medication. All other subjects were highly compliant. Ten of the eleven subjects in the donepezil group took the medication at prescribed dosage throughout the study, and one subject variably took 5 or 10 mg during CIT because of nausea. We obtained 6-month follow-up data on all but one participant, who moved out of state.

The baseline characteristics of the two groups are detailed in **Tables 1** and **2**. The donepezil group comprised three women and eight men and the placebo group five women and four men. In the donepezil group, seven of the strokes were in the left brain, and in the placebo group, six were in the left brain. In both groups, the lesion was opposite the preferred hand in seven subjects. In the donepezil group, six subjects had hemispheric large vessel distribution infarctions, four hemispheric hemorrhages, and one a hemispheric lacune. In the placebo group, five subjects had hemispheric large vessel distribution infarcts,

three hemispheric hemorrhages, and one a brainstem hemorrhage. In the donepezil group, two subjects were taking α -1 noradrenergic antagonists (doxazosin, labetalol), one an α -2 noradrenergic agonist (clonidine), and one baclofen. In the placebo group, one was taking two α -2 agonists (clonidine, Tizanidine), one an anticonvulsant (carbamazepine), one an α -1 antagonist (terazosin), one a tricyclic antidepressant (amitriptyline), and one had an intrathecal baclofen pump. That is, only one subject was taking more than one potentially antineuroplastic drug, and the number of subjects in each group taking drugs that might have inhibited neuroplasticity was roughly equal. Subjects in the donepezil group were more severely impaired, but no measure of the difference was statistically significant.

The results of the analysis of treatment effects are detailed in **Table 3**. The two primary outcome measures were the WMFT (time) for the affected limb only and the

Table 1.

Baseline characteristics of groups.

Variable	Donepezil (Mean \pm SD)	Placebo (Mean \pm SD)
Age at Time of Stroke	53.73 \pm 15.88	55.11 \pm 15.37
Age at Time of Study Entry	63.09 \pm 15.30	58.22 \pm 15.23
Education (yr)	13.45 \pm 2.34	14.22 \pm 3.42
Years Since Stroke	9.36 \pm 13.09	3.22 \pm 1.99
WMFT (affected arm, normal arm) (s)	22.46 \pm 21.63	12.93 \pm 13.14
WMFT (affected arm only) (s)	24.44 \pm 21.90	14.80 \pm 13.38
Box and Block Test (No. of blocks)	14.00 \pm 12.01	16.33 \pm 12.25
Dynamometer (kg)	14.45 \pm 7.81	8.63 \pm 5.60
Finger Tapping (No. of taps)	18.91 \pm 15.29	15.84 \pm 10.15
Card Flipping (No. of cards)	4.82 \pm 4.42	4.22 \pm 2.73
Stroke Impact Scale: Item 9*	61.11 \pm 8.21	70.50 \pm 13.22

*Analog rating of percentage recovered from stroke. SD = standard deviation WMFT = Wolf Motor Function Test

Table 2.

Baseline characteristics of groups.

Test (Score Range: Best Score Underlined)	Donepezil			Placebo		
	25%	Median	75%	25%	Median	75%
Actual Amount of Use Test: Amount (0– <u>2</u>)	0.28	0.66	1.00	0.36	0.69	1.27
Actual Amount of Use Test: Quality (0– <u>5</u>)	0.65	1.00	1.52	0.81	1.00	2.29
Fugl-Meyer Motor Score-Upper Extremity (0– <u>66</u>)	31	35	42	39	46	49
Motor Activity Log: Amount (1– <u>5</u>)	0.73	1.03	1.18	1.3	1.35	1.45
Motor Activity Log: Quality (1– <u>5</u>)	0.77	0.90	1.55	1.03	1.47	1.55
Stroke Impact Scale: Item 8* (0– <u>100</u>)	63.89	72.22	83.33	50.00	66.67	72.22
Geriatric Depression Scale (0– <u>30</u>)	1	4	12	5	5	8

*Ability to participate in activities that are meaningful and help you find purpose in life.

MAL (amount). These and all other motoric outcome measures as well as the CSI improved significantly with CIT. No significant change was found in GDS score or scores on scales 8 and 9 of the SIS. A group effect was noted for the WMFT that approached significance ($p = 0.067$, corrected for multiple comparisons) but not for other outcome measures; subjects in the donepezil group demonstrated greater improvement (i.e., larger reduction) in WMFT scores (**Figure**). Because the subjects in the donepezil group were, on average, somewhat more severely impaired at baseline (though not significantly), we also analyzed the effects of CIT and donepezil treatment on outcome scores controlling for baseline upper-limb Fugl-Meyer score; the results obtained were similar to those for the uncontrolled analysis.

We also asked whether there was any evidence that donepezil speeded response to treatment. The results of our analysis of the daily probes (card flipping and hand dynamometer force) provided no support for this hypothesis. In addition, we found that the change in the card-flipping score over the course of CIT was slightly larger in the placebo group than the donepezil group ($p = 0.04$).

DISCUSSION

Our study suggests that donepezil might have an adjuvant effect on intensive upper-limb physical therapy following stroke, as reflected in the WMFT time by group effect. However, this effect did not achieve statistical significance. Furthermore, a group effect was not observed in our other primary outcome measure, the MAL (amount), or in any of our secondary outcome measures. We also cannot rule out the possibility that the WMFT group effect was due to inhomogeneity of variance between the two treatment groups (see especially middle graph, left column, **Figure**). This inhomogeneity could be due to chance differences in change in variance over time in the two groups, or it could be the result of a differential response of some subjects to donepezil that increased their gains from CIT and thereby increased the variance in the donepezil group. Therefore, our results do not support the routine administration of donepezil as an adjunct to restitutive physical therapy. We believe they do justify the conduct of a larger study. In such a study, the potential impact of donepezil (or rivastigmine—discussed later) on maintenance of therapeutic gains might also be assessed by having subjects continue drug

Table 3.
Outcome analysis of treatment effects.

Measure	Baseline Mean (95% CI)	2 Wk Mean (95% CI)	6 Mo Mean (95% CI)	Change (Baseline—2 wk): Mean (95% CI)	Change (Baseline—6 mo): Mean (95% CI)	Group Effect	
						Coefficient*	p-value
WMFT							
Overall	20.13 (11.3, 28.9)	13.59 (6.9, 20.3)	16.40 (8.6, 24.2)	-6.51 (-10.6, -2.4) [†]	-2.77 (-5.9, 0.4) [‡]	-5.262	0.0335 [†]
Donepezil	24.44 (9.7, 39.2)	15.50 (4.3, 26.7)	17.92 (4.9, 30.9)	-8.94 (-16.5, -1.4) [†]	-5.19 (-10.1, -0.3) [†]	—	—
Placebo	14.86 (4.5, 25.1)	11.26 (2.7, 19.9)	14.72 (3.5, 25.9)	-3.54 (-5.8, -1.3) [†]	-0.07 (-4.1, 3.9)	—	—
MAL Amount	1.18 (0.9, 1.4)	4.27 (3.9, 4.6)	2.60 (2.1, 3.1)	3.09 (2.8, 3.4) [†]	1.42 (1.0, 1.8) [†]	-0.186	0.5228
MAL Quality	1.09 (0.9, 1.3)	3.54 (3.2, 3.9)	2.54 (2.1, 2.9)	2.45 (2.1, 2.8) [†]	1.44 (1.1, 1.7) [†]	-0.110	0.6593
AAUT Amount	0.71 (0.5, 0.9)	1.32 (1.1, 1.5)	0.97 (0.8, 1.2)	0.61 (0.5, 0.8) [†]	0.25 (0.1, 0.4) [†]	0.155	0.1685
AAUT Quality	1.25 (0.9, 1.6)	1.92 (1.7, 2.2)	1.47 (1.1, 1.8)	0.67 (0.4, 0.9) [†]	0.20 (0.0, 0.4) [‡]	0.167	0.2982
Fugl-Meyer Motor	39.40 (35.7, 43.1)	44.40 (40.2, 48.6)	43.42 (38.3, 48.5)	5.00 (2.6, 7.4) [†]	3.63 (1.0, 6.3) [†]	-1.065	0.5428
Box and Block Test	15.05 (9.5, 20.6)	20.10 (14.7, 25.5)	18.11 (12.5, 23.8)	5.05 (2.7, 7.4) [†]	2.58 (1.0, 4.2) [†]	-1.274	0.3684
Finger-Tapping	17.53 (11.4, 23.6)	22.05 (16.4, 27.7)	21.89 (15.0, 28.8)	4.52 (0.3, 8.7) [†]	4.28 (0.7, 7.9) [†]	-2.85	0.2916
GDS	6.25 (4.1, 8.4)	6.00 (4.3, 7.7)	5.31 (2.3, 8.3)	-0.47 (-2.5, 1.5)	-0.56 (-4.5, 3.4)	1.173	0.5683
SIS 8	70.47 (63.4, 77.6)	70.49 (58.1, 82.9)	72.01 (58.3, 85.7)	2.78 (-8.5, 14.1)	-0.85 (-13.3, 11.5)	-4.411	0.5835
SIS 9	65.53 (59.6, 71.5)	72.00 (63.7, 80.3)	64.17 (54.0, 74.3)	7.93 (-0.5, 16.4) [‡]	-0.75 (-11.9, 10.4)	5.803	0.3721
CSI [§]	5.20 (3.6, 6.8)	3.84 (2.2, 5.5)	2.67 (1.2, 4.1)	-1.63 (-2.6, -0.6) [†]	-2.47 (-3.5, -1.4) [†]	-0.954	0.1787

*Group coefficient for donepezil

[†] $p < 0.05$

[‡] $p < 0.10$; p -values have not been adjusted for multiple comparisons.

[§]Range 0–13, lower is better.

AAUT = Actual Amount of Use Test

CI = confidence interval

CSI = Caregiver Strain Index

GDS = Geriatric Depression Scale

MAL = Motor Activity Log

SIS = Stroke Impact Scale

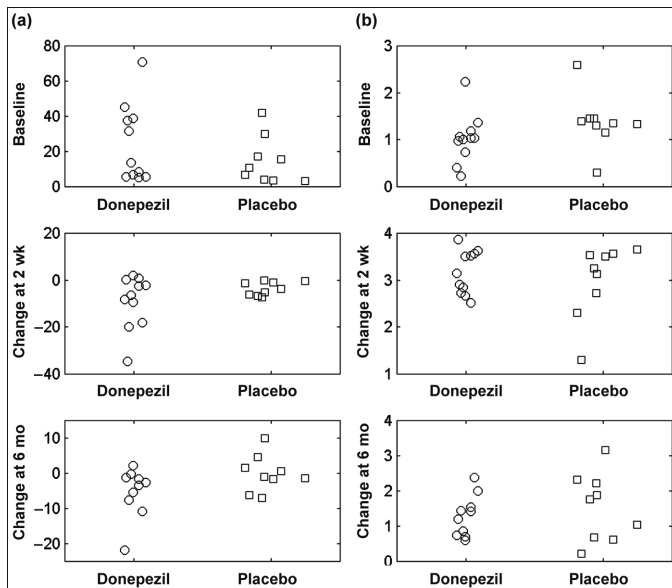


Figure.

Baseline and change scores for two primary outcome measures. Ordinate for (a) Wolf Motor Function Test (affected arm only) is in seconds, and ordinate for (b) Motor Activity Log (amount) is average scale score. Note differing scales of ordinate axes.

treatment after completion of physical therapy. For the study to achieve better blinding of subjects and therapists, use of an active placebo would be desirable, such as pyridostigmine, which would have a similar side-effect profile but no central nervous system effects. Given the results of the present study, for such a trial to have an 80 percent likelihood of achieving a statistically significant drug effect on our first primary outcome measure (the WMFT), 50 subjects would be required; on our second primary outcome measure (the MAL), a total of 234 (calculation from 6-month change scores) to 312 (calculation from 2-month change scores) subjects would have to be recruited.

Our study also demonstrated that CIT produced a substantial and significant improvement in all measures of upper-limb motor function. Two caveats are in order here as well. First, even though a significant improvement in function was still evident at 6 months, the 6-month results reflected considerable regression of function compared to the 2-week results and no improvement was found in SIS scales probing quality of life. Second, the impact of CIT was highly variable; some subjects improved a great deal and others not at all. These findings suggest a need for the further development of measures to preserve gains over the long run and for further investigation of predictors of

response to CIT. The improvements observed with CIT in this study do suggest that it met one of the essential requirements of a behavioral engine, as we have defined it (see Introduction: Constraint-Induced Therapy).

The reasons for our failure to demonstrate a more clear-cut effect of donepezil are not certain. One reason could be that the magnitude of the donepezil effect is intrinsically small, as observed in subjects with AD. Also possible is that our effort to increase cortical acetylcholine was not very successful, since we used a dose of donepezil far lower than that shown in animal studies (1.5 mg/kg) to increase cortical acetylcholine; in these same studies, rivastigmine (0.75 mg/kg bid) induced a 590 percent increase in these levels, possibly making it a better choice for future studies of acetylcholinesterase inhibitors as adjuvants to behavioral rehabilitation [10].

Donepezil-induced increases in cortical acetylcholine may also have led to receptor down-regulation, which would undermine the potential therapeutic effect. Acetylcholinesterase inhibitors may work best in cortical acetylcholine deficiency states. There is, for example, some evidence of efficacy of these agents in head trauma [25–27], which is likely to be associated with cortical cholinergic depletion (as in AD) caused by shearing of nucleus basalis axons [5,28]. Furthermore, donepezil and galantamine, another central acetylcholinesterase inhibitor, have recently been shown to provide some benefit in patients with vascular dementia [29,30]; up to 70 percent of the patients in these studies had diffuse ischemic deep white matter involvement, which may plausibly have damaged cholinergic projections to the cortex and hippocampus [31].

Donepezil may have been only modestly effective because, in the intense environment in which our subjects worked, acetylcholine levels in the cortex may have already been optimal. Abundant work in animal models of traumatic brain injury has shown that enrichment of the environment is the single most effective therapeutic modality, and to the extent that pharmacological treatments are effective, they at best emulate the effects of an enriched environment to one degree or another [28]. Donepezil may have an adjuvant effect primarily when cortical and hippocampal neural activity is not reliably deemed valuable—perhaps not the case in the intense environment of rehabilitation or when enriched environments are provided for animals.

Finally, it is possible that neural reorganization achieved with CIT occurs predominantly in the brainstem and spinal cord. A number of areas here receive

cholinergic projections, e.g., the medial medullary reticular formation—the source of the medullary reticulospinal tract [32], but no evidence has been found so far that acetylcholine potentiates learning in these systems as it does in the cerebral cortex.

CONCLUSION

We conclude that donepezil might have an adjuvant effect on the outcome of intensive restitutive physical therapies such as CIT and that a larger trial is warranted. Such a trial might also employ a central acetylcholinesterase inhibitor that achieves greater elevations of cortical acetylcholine, such as rivastigmine. Blinding would be aided by use of an active placebo such as pyridostigmine. Greater potentiation of CIT-induced gains might be achieved by continuing the drug throughout follow-up. All trials of drugs that might serve as adjuvants to CIT would benefit from a greater understanding of which subjects are more likely to benefit from CIT. Until this is known, the potential impact of these drugs on trial results will be undermined by the substantial numbers of subjects who show no response or a very modest response to the behavioral therapy.

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