Memantine and Constraint-Induced Aphasia Therapy in Chronic Poststroke Aphasia

Marcelo L. Berthier, MD, PhD,[1] Cristina Green, PhD,[1] J. Pablo Lara, MD, PhD,[2] Carolina Higueras, PhD,[1] Miguel A. Barbancho, MD,[2] Guadalupe Dávila, PhD,[3] and Friedemann Pulvermüller, PhD[4]

Objective: We conducted a randomized, double-blind, placebo-controlled, parallel-group study of both memantine and constraint-induced aphasia therapy (CIAT) on chronic poststroke aphasia followed by an open-label extension phase.

Methods: Patients were randomized to memantine (20mg/day) or placebo alone during 16 weeks, followed by combined drug treatment with CIAT (weeks 16–18), drug treatment alone (weeks 18–20), and washout (weeks 20–24), and finally, an open-label extension phase of memantine (weeks 24–48). After baseline evaluations, clinical assessments were done at two end points (weeks 16 and 18), and at weeks 20, 24, and 48. Outcome measures were changes in the Western Aphasia Battery-Aphasia Quotient and the Communicative Activity Log.

Results: Twenty-eight patients were included, and 27 completed both treatment phases. The memantine group showed significantly better improvement on Western Aphasia Battery-Aphasia Quotient compared with the placebo group while the drug was taken (week 16, $p = 0.002$; week 18, $p = 0.0001$; week 20, $p = 0.005$) and at the washout assessment ($p = 0.041$). A significant increase in Communicative Activity Log was found in favor of memantine-CIAT relative to placebo-CIAT (week 18, $p = 0.040$). CIAT treatment led to significant improvement in both groups ($p = 0.001$), which was even greater under additional memantine treatment ($p = 0.038$). Beneficial effects of memantine were maintained in the long-term follow-up evaluation, and patients who switched to memantine from placebo experienced a benefit ($p = 0.02$).

Interpretation: Both memantine and CIAT alone improved aphasia severity, but best outcomes were achieved combining memantine with CIAT. Beneficial effects of memantine and CIAT persisted on long-term follow-up.

Ann Neurol 2009;65:577–585

Aphasia, a disorder of language functions after acquired brain damage, occurs in nearly one third of stroke victims and is regarded as one of the more devastating cognitive sequelae.[1–3] Poststroke aphasia (PSA) is usually followed by a period of spontaneous recovery that ends after 1 year.[1–6] Speech and language therapy (SLT) is the treatment of choice for chronic PSA,[2–6] and significant improvements of language and communication deficits can be achieved when SLT is administered intensively or for prolonged periods, or both.[4–6] Only recently, new intensive SLTs yielded significant improvement of language performance at the chronic stage, even several years after stroke onset.[4–15] At the same time, pharmacotherapy in conjunction with SLT suggest that additional benefit may arise from drug treatment.[1,16–19] In this article, we ask whether chronic PSA can be improved more substantially by conjoined application of intensive SLT together with drug treatment. We chose constraint-induced aphasia therapy (CIAT), an intensive form of language-action therapy emphasizing massing of practice, focusing on communicative needs, and embedding of language use into action contexts.[7–15]

Long-lasting cognitive and language deficits after stroke result from a direct lesion of neural tissue that leads to disrupted functional connectivity because of changes in network excitability and abnormal activity of multiple neurotransmitter systems,[1,14,16–23] including an excess of glutamate release.[23–27] In animal models of ischemic stroke, an upregulation of *N*-methyl-D-aspartate receptor–dependent function has been found in ischemic cores and neighboring cortical regions.[24] This glutamatergic overactivation results in intracellular calcium overload, eventually causing excitotoxic neuronal dysfunction and death.[23] In human stroke survivors, this cascade of intracellular events may contribute to the abnormal activity in "eloquent" perilesional regions, as well as in other connected regions.[14,22–27] It

From the [1]Unidades de Neurología Cognitiva y Afasia y Neurofisiología Humana; [2]Centro de Investigaciones Médico-Sanitarias; [3]España Área de Psicobiología, Facultad de Psicología, Universidad de Málaga, Málaga, Spain; and [4]Cognition and Brain Sciences Unit, Medical Research Council, Cambridge, United Kingdom.

Address correspondence to Dr Berthier, Unidad de Neurología Cognitiva y Afasia, Centro de Investigaciones Médico-Sanitarias (CIMES), Universidad de Málaga, Campus Teatinos, 29071 Málaga, España. E-mail: mbt@uma.es

Potential conflict of interest: M.L.B. has received honoraria from Pfizer, Eisai, Janssen-Cilag, Novartis, and Lundbeck, and consultancy fees from Merz, Eli Lilly, and GlaxoSmithKline. C.G. has received honoraria from Janssen-Cilag and GlaxoSmithKline.

Received Jul 29, 2008, and in revised form Oct 22. Accepted for publication Oct 31, 2008.

Published in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.21597

is also possible that the excess of glutamate release prevents the dynamic reorganization of lesioned networks to a new state in which language functions are performed through compensatory mechanisms.[22–25]

In this study, we chose the *N*-methyl-D-aspartate receptor antagonist memantine because this compound may reinstantiate cortical activity and cognitive functions including language, memory, and learning.[25–27] The rationale for using memantine to treat PSA comes from the hypothesis of glutamate-induced neurotoxicity in cerebral ischemia and from the results of two large randomized controlled trials (RCTs) of memantine performed in patients with mild-to-moderate vascular dementia.[26,27] In these studies, memantine significantly improved performance relative to placebo on the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog), an instrument heavily reliant on language, memory, and praxis.[28] We here report the first RCT to investigate the efficacy of both memantine and CIAT on chronic PSA followed by an open-label extension phase of memantine.

Subjects and Methods

Randomized, Placebo-Controlled Phase

PARTICIPANTS. Patients were recruited through local language rehabilitation centers, aphasia support groups, and newspaper advertisements. Inclusion criteria were: (1) age between 18 and 70 years, (2) unilateral cortical-subcortical or subcortical lesions caused by a single infarction or hemorrhage, (3) aphasia diagnosis according to the Western Aphasia Battery (WAB),[29] and (4) presence of aphasia for 1 year or longer. Exclusion criteria were: (1) presence of a severe language deficit (mutism, recurrent utterances, neologistic jargon, or WAB comprehension score < 4), (2) history of any other neurological or psychiatric disease impairing language and communicative ability (eg, dementia), (3) severe visual agnosia (eg, inability to identify visually presented objects), (4) severe limb apraxia (eg, inability to manipulate objects) and severe speech apraxia (difficulty executing or sequencing oral-motor movements, or both), (5) severe depression,[30] (6) pregnancy, (7) recent myocardial infarction, (8) uncompensated congestive heart failure, (9) uncontrolled hypertension, (10) hypersensitivity toward memantine, and (11) ongoing medication with agents interfering with memantine (including amantadine, dextromethotphan, or ketamine).[23] Any concomitant medication was kept unchanged during the study.

The study was conducted in accordance with the Declaration of Helsinki, and the protocol and its amendments were approved by the Local Community Ethics Committee for Clinical Trials and by the Spanish Medical Agency. Written informed consent was obtained from every patient or caregiver. The study was undertaken between March 2005 and November 2007. The study is registered with EudraCT (2004-002337-39), and the protocol for the study was filed with the open clinical trial registry (www.clinicaltrials.gov; Identification No. NCT00196703).

STUDY DESIGN. The study design consisted of a single-center, randomized, placebo-controlled, double-blind, parallel-group study of memantine and CIAT with an open-label extension phase of memantine. Patients were allocated randomization numbers consecutively, and using a computer-generated randomization code, we assigned patients in a 1:1 fashion to the two groups. Blinding was established with identical film-coated tablets for oral intake containing either memantine (5 or 10mg) or placebo. Tablets were dispensed into patient-coded containers by a non-blinded pharmacist. Researchers, as well as patients and their caregivers, were unaware of and could not determine the study drug assignment by appearance or otherwise. The study design is shown in Figure 1.

DRUG TREATMENT. All patients underwent a 3-week up-titration phase of either memantine or placebo. Memantine was titrated in 5mg weekly increments as recommended[23,25,26,31] from a starting dose of 5 to 20mg/day. After the dose-escalation phase, all patients received a fixed dose of either memantine (10mg) or placebo twice daily without CIAT during the next 3 months (week 16). Then, during weeks 16 to 18, the drug treatment was combined with CIAT. This phase of combined treatment was followed by a 2-week period (weeks 18–20) where patients received memantine or placebo treatment alone and, finally, by a 4-week period of drug washout (weeks 20–24). Evaluations of aphasia and communication were performed at baseline and at the end of weeks 16 and 18 (end points), and of weeks 20 and 24 (washout). Compliance was determined at every visit by tablet counts.

CONSTRAINT-INDUCED APHASIA THERAPY. CIAT is an intensive form of language-action therapy for aphasia performed in a small group setting (two to three patients and the speech therapist).[7–15] Participants were grouped according to their similarities in aphasia characteristics (eg, verbal output and comprehension) and severity, and all of them received 30 hours of CIAT within 2 weeks (3 hours/day).[9,14] In a therapeutic game context, participants had to request picture cards from each other, by using descriptions of the depicted objects, and understand requests made by others and the therapist. The full treatment set comprises 616 picture cards (5 categories including name of objects [words of

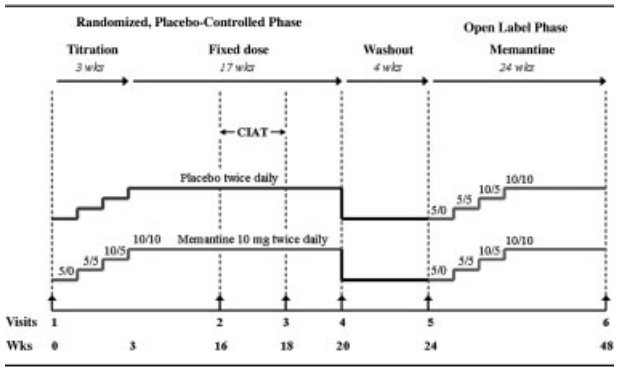

Fig 1. Study design. CIAT = constraint-induced aphasia therapy.

high, medium, and low frequencies], colors, numbers, actions, and phonological minimal pairs ["ajo-ojo" "garlic-eye"]). In each therapy application, 2 identical sets of 16 to 20 color cards were distributed equally to the patients (8–10 cards/person).[7,14] Difficulty levels were adjusted to the patients' communicative abilities by choosing cards suited to each patient's level of performance. Each patient had to obtain from other participants as many twin cards as possible that matched his or her own cards. This had to be done by communicating verbally with the other three participants, by asking questions, making requests, and providing descriptions at different levels.[7,14] Feedback of communicative success was regularly given, together with guidance, help, and reinforcement. Other forms of communication (gesturing, drawing, or writing) replacing verbal language were constrained. Barriers in front of and on either side of each patient prevented them from seeing each other's hands or cards. Reinforcement was administered as necessary for each patient. Communication rules were introduced by shaping and modeling (for details and materials, see P 1990 http://www.ub.uni-konstanz.de/kops/volltexte/2002/879/).

OUTCOME MEASURES. The outcome measures were the mean score change from baseline to end points in the Aphasia Quotient (AQ) of the WAB[29] and the Communicative Activity Log (CAL)[9] at weeks 16 (drug alone) and 18 (drug-CIAT). The Western Aphasia Battery-Aphasia Quotient (WAB-AQ) results from the sum of subtests of spontaneous speech (fluency and information content), auditory comprehension, repetition and naming, and it is a global measure of severity of aphasia.[29] The CAL rates the patient's amount and quality of everyday communication through 18 questions (eg, question 6: "How frequently would the patient use the telephone?").[9] All questions were answered on a 6-point scale (0 = never; 6 = very frequently) by a caregiver who rated the patient's communicative behavior during the week before aphasia testing. The Spanish versions of the WAB-AQ and CAL were sensitive to rate treatment effects in different samples of chronic aphasic patients treated with CIAT or drugs.[7–19] The number (%) of patients who improved at end points compared with their own baselines scores ("responders") was examined using a prespecified degree of improvement on WAB-AQ (≥5 points) and CAL (≥5.4 points).[32,33] Improvement was arbitrarily defined by an increase of test score (WAB and CAL) by more than 5% of its range.[32,33] This pragmatic approach was taken because normative data for therapy improvement were unavailable for either WAB or CAL.

STATISTICAL ANALYSES. The sample size calculation, obtained from our previous drug trials in chronic PSA (difference in mean of 5.000 points on the WAB-AQ with a standard deviation of 4.000),[1,19] showed that 12 participants in each group would be needed ($\alpha < 0.05$, two-sided, power = 80%). On the assumption of a dropout rate of 15%,[19] the recruitment of 28 patients was planned. Between-group comparisons at specific time points were performed on change in absolute values or means from baseline for the WAB-AQ, WAB subtests, and CAL using analysis of covariance adjusted for baseline scores. For within-group comparisons, *t* tests were used to compare baseline values versus those at other time points. χ^2 tests were performed to analyze categorical variables, and the Mann–Whitney *U* test was used for between-group comparisons of responders (WAB-AQ and CAL scores) to treatment. Effect sizes (Cohen's *d* statistic) were calculated for significant results.[31] Analyses were conducted for observed cases, and the last observation carried forward was used for a single patient who missed one drug evaluation (week 20). All statistical tests were two sided with significance level set at $\alpha < 0.05$. No adjustment for multiple testing was made.

Open-Label Extension Phase

Patients who completed the double-blind phase were invited to participate in the open-label extension. Baseline evaluation for the open-label phase coincided with the double-blind study termination visit (week 24). Thus, 4 weeks after stopping memantine or placebo, all patients, including those who had received memantine during the double-blind phase, switched directly to memantine for 24 weeks. All procedures, including dosage adjustments and blinding, were similar to that in the double-blind phase. No patient received SLT during this period.

Results

Randomized, Placebo-Controlled Phase

Of 37 patients screened, a total of 28 patients were included, and only one patient in the placebo group did not complete the study (last evaluation in week 18) (Fig 2). Table 1 shows baseline characteristics and treatment randomization. The aphasia profiles of the groups were similar and representative of typical samples of patients with chronic aphasia (Table 2).[2–5] The treatment groups were well matched with respect to baseline demographic and clinical characteristics, ex-

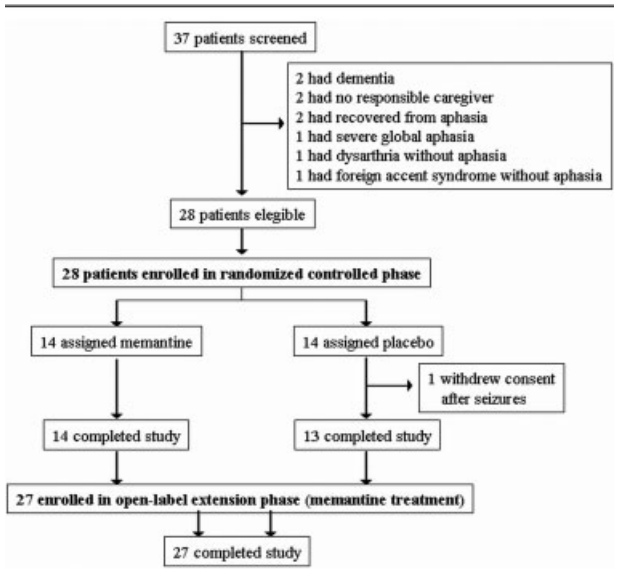

Fig 2. The revised CONSORT diagram showing the flow of participants in the randomized, placebo-controlled and open-label extension phases of memantine.

Table 1. **Baseline Characteristics**

Variable	Memantine Group (n = 14)	Placebo Group (n = 14)
Mean age (SE) (range), yr	53.7 (2.1) (36-65)	48.5 (2.1) (40-66)
Male sex, n (%)	7 (50)	11 (78)
Right handedness, n (%)	14 (100)	14 (100)
Antiepileptic agents, n (%)	4 (29)	7 (50)
Psychoactive agents, n (%)	6 (43)	5 (37)
Mean education (SE), yr	10.0 (0.8)	9.64 (0.7)
Mean time since onset of aphasia (SE), yr	1.8 (0.2)	6.4 (2.1)
Mean WAB-AQ (SE) (range) (maximum = 100)	67.1 (5.5) (23.2-91)	65.8 (3.0) (41.8-84.4)
Mean WAB-Apraxia (SE) (maximum = 60)	49.5 (3.1)	51.4 (1.6)
Mean Communicative Aphasia Log (SE) (maximum = 108)	71.5 (1.9)	77.9 (2.7)
Mean stroke aphasia depression questionnaire (SE) (maximum = 84)	37.6 (2.2)	37.7 (0.8)

The longer time after stroke in the placebo group resulted from the inclusion of four patients with ≥10 years of evolution (range, 10-32 years). The baseline scores on the Western Aphasia Battery-Aphasia Quotient (WAB-AQ) in these four outliers were similar to those obtained from the remaining placebo-group patients (n = 10), and three of the four outliers were responders in the WAB-AQ (score gain ≥ 5) in one or both end-point evaluations (weeks 18 and 20).

SE = standard error.

cept for time since stroke ($p = 0.053$), which tended to be longer in the placebo group.

A significant improvement in WAB-AQ scores was observed in the memantine group compared with placebo group, with large effect sizes at both end points (week 16, Cohen's *d*: 1.27; week 18, Cohen's *d*: 1.44) and at week 20 (Cohen's *d*: 1.28), and a medium effect size at week 24 (Cohen's *d*: 0.65) (see Table 2; Fig 3). Positive changes were also observed in WAB-language subtests except for repetition (Table 3).

The effect of memantine alone and/or combined with CIAT (week 18) on improving WAB-AQ scores still remained highly significant compared with placebo after excluding patients (n = 4) from the placebo group with longer duration of PSA (>10 years) [week 18: t (22) = 3.57, $p = 0.002$] and patients from both groups receiving antiepileptic treatment (memantine group: n = 4; placebo group: n = 7) [week 18: t (15), 2.53, $p = 0.023$] and psychoactive compounds (memantine group: n = 6; placebo group: n = 5) [week 16: t (15) = 2.97, $p = 0.009$; week 18: t (15) = 3.11, $p = 0.007$]. Moreover, within-group analyses of WAB-AQ scores at end points (weeks 16 and 18) demonstrated that treatment with antiepileptic or psychoactive drugs, or both, did not affect outcomes.

Within-group comparisons between baseline and pre-CIAT assessment (week 16) demonstrated a significant increase in WAB-AQ in the memantine group, reflecting the effect of active drug alone, but no change was present in the placebo group (see Table 3). Both groups showed a significant improvement on WAB-AQ over the 2 weeks of CIAT (weeks 16 vs 18), and a significant between-group difference also emerged when comparing improvements between weeks 16 and 18 (before vs just after SLT), indicating that the effect of CIAT was stronger in the memantine group compared with the placebo group [t (26) = 2.18, $p = 0.038$]. Improvements in WAB-AQ scores remained stable across the 2 weeks after CIAT (weeks 18 vs 20) in both treatment groups. In the final month (weeks 20 vs 24), language improvement remained at its high level in the placebo group but declined [t (13) = 3.93, $p = 0.002$] in the memantine group, reflecting vanishing of the drug effect during washout. However, comparing WAB-AQ values between the beginning and end of the study, a general improvement emerged for both memantine treatment groups with a better outcome for patients who had received memantine in addition to CIAT ($p = 0.041$; see Table 3). The last observation carried forward analysis showed similar results as those using observed cases.

The scores for the memantine group on CAL were numerically better than those for the placebo group at all postbaseline evaluations, and a significant increase in CAL score was found in favor of memantine-CIAT relative to placebo-CIAT after correcting for baseline scores (baseline vs week 18) ($p = 0.040$, analysis of covariance) (see Table 3). The effect of combined

Table 2. **Characteristics of Aphasia Type and Lesion Location**

Patient No./Age/Sex	Duration of Aphasia (yr)	Aphasia Type	Severity	Cause	Lesion Location
Memantine Group					
1/54/M	4.1	Anomic	Mild	Infarction	TP
2/36/M	3.0	Conduction	Mild	Infarction	TP
3/67/F	1.4	Anomic	Moderate	Infarction	FTP-BG
4/47/F	1.0	Broca	Severe	Infarction	FTP-BG
5/60/F	3.2	Anomic	Mild	Infarction	BG-PVWM
6/60/M	1.1	Anomic	Mild	Infarction	TP
7/53/F	1.5	Broca	Moderate	Infarction	FTP-BG
8/55/M	2.5	Anomic	Mild	Infarction	INS-BG
9/65/M	1.6	Anomic	Moderate	Infarction	BG-IC
10/50/M	1.0	Anomic	Moderate	Infarction	FTP-BG
11/50/F	1.1	Anomic	Moderate	Infarction	FTP-BG
12/56/F	1.5	Broca	Severe	Infarction	FTP-BG
13/47/F	1.0	Broca	Moderate	Hemorrhage	FTP-BG
14/52/M	1.7	Anomic	Mild	Infarction	FTP-I
Placebo Group					
15/47/M	1.2	Anomic	Moderate	Infarction	FTP-BG
16/43/F	10.0	Anomic	Mild	Hemorrhage	FTP-BG
17/66/F	10.2	Anomic	Moderate	Infarction	FTP-BG
18/43/M	3.2	Wernicke	Moderate	Hemorrhage	FTP-I
19/46/F	4.0	Anomic	Mild	Infarction	FTP-BG
20/47/M	5.0	Conduction	Moderate	Hemorrhage	FTP-BG
21/56/M	2.4	Broca	Moderate	Infarction	FT-BG
22/45/M	1.9	Broca	Moderate	Infarction	FTP
23/48/M	11.1	Broca	Moderate	Infarction	FTP-BG
24/44/M	2.11	Transcortical motor	Moderate	Infarction	BG-INS-TP
25/43/M	2.1	Conduction	Mild	Infarction	TP
26/46/F	32.0	Broca	Severe	Hemorrhage	FT-BG
27/65/M	4.4	Broca	Moderate	Infarction	TP
28/40/M	1.0	Transcortical motor	Moderate	Infarction	FTP-BG

All lesions were in the left hemisphere.
TP = temporoparietal; FTP = frontotemporoparietal; BG = basal ganglia; PVWM = periventricular white matter; INS = insula; IC = internal capsule.

treatment with CIAT (week 18) on improving CAL scores remained significant compared with placebo after excluding patients (n = 4) from the placebo group with longer duration of PSA (>10 years) [week 18: t (22) = 2.62, p = 0.016] and patients from both groups receiving psychoactive compounds (memantine group: n = 6; placebo group: n = 5) [week 18: t (15) = 2.47, p = 0.026]. Moreover, within-group analyses of CAL scores at end points (weeks 16 and 18) demonstrated that treatment with antiepileptic or psychoactive drugs, or both, did not affect outcomes. Table 4 shows the number of individual patients who responded to treatment. Scores on WAB-AQ and CAL were numerically greater in the memantine group than in the placebo group in all postbaseline evaluations, with differences reaching significance on WAB-AQ at both end points (weeks 16 and 18).

No adverse effects were documented. One patient withdrew from the placebo group because of a seizure episode 1 week after termination of CIAT.

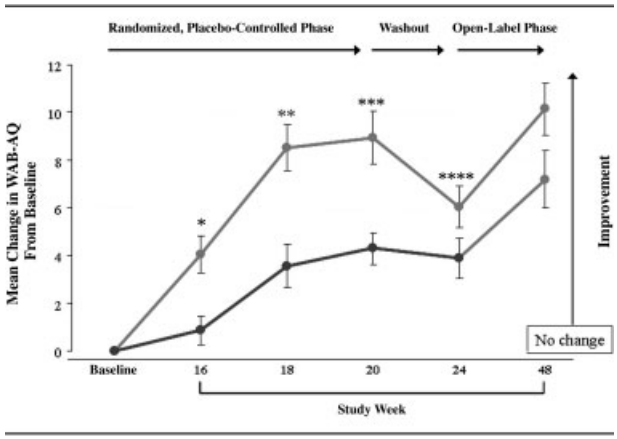

*Fig 3. Mean (± standard error) changes from baseline to end points (weeks 16 and 18) in Western Aphasia Battery-Aphasia Quotient (WAB-AQ) scores over time in the randomized, placebo-controlled, and open-label extension phases of memantine. *p = 0.002 indicates a significant improvement in WAB-AQ in the group treated with memantine alone compared with the group treated with placebo alone (week 16). **p = 0.0001 indicates a significant improvement in the group treated with combined memantine and constraint-induced aphasia therapy (CIAT) relative to the group treated with combined placebo-CIAT (week 18). ***p = 0.005 indicates the maintenance of significant gains in the memantine-treated group compared with the placebo-treated group 2 weeks after CIAT (week 20). ****p = 0.041 indicates between-group differences at washout. See text for details on open-label extension phase.*

Open-Label Extension Phase

All patients (n = 27) who completed the double-blind study were enrolled and completed the open-label extension phase. Patients treated with memantine during the double-blind phase are hereafter referred to as the MEM-MEM group, whereas patients who were treated with placebo in the double-blind phase are hereafter referred to as the PLA-MEM group. Aphasia evaluation at the end of the washout period (week 24), before initiation of the open-label extension, demonstrated that both groups did not show a total loss of treatment benefits with WAB-AQ scores remaining greater than the original baseline values (mean change from baseline to week 24: MEM-MEM group = 6.0 ± 0.8; PLA-MEM group = 3.9 ± 0.8).

Analysis of the WAB-AQ at the end of the open-label extension phase (week 48) showed significant improvements relative to the new baseline (week 24) on the MEM-MEM group [t (13) = 3.80, p = 0.002], and these clinically relevant benefits also tended to be greater than scores obtained at end points (weeks 16 and 18) during the double-blind study. Significant improvements in WAB-AQ were again observed when patients treated with placebo were switched to memantine [PLA-MEM group, t (12) = 2.68, p = 0.02; see Table 3). Between-group comparisons showed a tendency for greater improvement in the MEM-MEM group compared with the PLA-MEM group (p = 0.08). The PLA-MEM group, which had received no active drug before, showed a significant performance increase compared with end points (weeks 16 and 18) (p = 0.001) and with week 20 (p = 0.003). Safety and tolerability results in the extension phase were consistent with the shorter-term results.

Discussion

We investigated the effects of memantine, CIAT, and their combination in patients with chronic PSA. The main results of this RCT were: (1) significant improvement of aphasia severity with memantine alone, (2) replication of aphasia improvement with CIAT, (3) greater improvement of combined treatment with me-

Table 3. **Mean Change in Outcome Measures from Baseline**

	Randomized, Placebo-Controlled Phase							
	Week 16				Week 18			
	Memantine	Placebo	95% CI	p[a]	Memantine and CIAT	Placebo and CIAT	95% CI	p[a]
Mean WAB (SE)								
Aphasia Quotient	4.0 (0.7)[b]	0.8 (0.5)	1.2-5.1	**0.002**	8.5 (0.9)[b]	3.5 (0.8)[c]	2.2-7.6	**0.0001**
Spontaneous Speech	0.5 (0.2)	−0.7 (0.2)	−0.7-1.3	0.077	2.2 (0.3)[b]	0.9 (0.4)[e]	0.1-2.4	**0.024**
Auditory Comprehension	0.3 (0.1)[b]	−0.1 (0.1)[d]	−0.0-1.0	0.086	0.4 (0.1)[b]	−0.0 (0.1)[c]	0.1-0.9	**0.037**
Repetition	0.3 (0.2)	0.5 (0.1)[c]	−0.6-0.3	0.988	0.3 (0.1)	0.6 (0.2)[d]	−0.8-0.2	0.764
Naming	0.7 (0.1)[b]	0.1 (0.1)	0.1-1.0	**0.015**	1.2 (0.1)[b]	0.3 (0.2)	0.2-1.4	**0.009**
Mean CAL (SE)	3.2 (1.5)	0.2 (1.4)	−1.3-7.3	0.182	6.0 (1.3)[c]	1.0 (2.2)	−0.4-10.4	**0.040**

CI = coefficient interval; CIAT = constraint-induced aphasia therapy; WAB = Western Aphasia Battery; SE = standard error; CAL = communicative activity log.

[a]p value indicates between-group comparisons, analysis of covariance with adjustment for baseline values unless otherwise noted.
[b]$p \leq 0.0001$; [c]$p \leq 0.005$; [d]$p \leq 0.01$; [e]$p \leq 0.05$ indicates within-group comparisons.

mantine and CIAT compared with their effects when applied separately, (4) significant reduction of language proficiency after memantine withdrawal, and (5) stability of the CIAT-related improvement 6 weeks after the end of therapy. The main result of the open-label extension phase was the maintenance of memantine benefits at long-term follow-up.

Analyses of outcome measures showed positive results in global severity of aphasia (WAB-AQ and its subtests of spontaneous speech, comprehension, and naming) at both end points (memantine alone and memantine-CIAT) and in everyday communication (CAL) at one end point (memantine-CIAT). After washout of memantine, the drug-related benefit in aphasia severity vanished to some degree, but still leaving both treatment groups at scores significantly greater than baseline.

Clinically relevant treatment effects were also justified by the analysis of the number of "responders" shown by WAB-AQ and CAL. Individual responder analysis showed improvements on the WAB-AQ in all 14 patients with memantine-CIAT treatment, whereas placebo-CIAT treatment improved performance in 9 patients. The open extension phase showed benefits for both the patients originally randomized to the memantine arm during the double-blind phase (MEM-MEM group) and those originally treated with placebo who later switched to memantine (PLA-MEM group). Responder analysis demonstrated that during the open-label extension phase, all 27 patients showed improvements on the WAB-AQ and 13 of them on CAL scores. However, the improvement of CAL scores during the open-label extension phase should be interpreted with caution because the caregivers, who rated the patients' ability to communicate in everyday situations, knew that the patients were receiving the active drug. Memantine was safe and well tolerated with no adverse events in the double-blind study or in the open-label extension phase.

Positive effects of drug therapy on PSA have been reported in a range of previous studies (for overview, see Berthier's,[1] Pulvermüller and Berthier's,[14] and Small's[16] studies). Additive effects of the established benefits of SLT and drug treatment have been suggested by previous RCT with piracetam[17] and amphetamine[18] in subacute PSA and with donepezil in chronic PSA.[19] Consistent with this earlier work, this study confirmed benefits in a group undergoing both SLT and drug therapy, compared with SLT plus placebo. Our results further suggest a synergistic effect of drug and intensive training applied together that was manifest in the difference in performance gain (WAB-AQ) at both end points (weeks 16 and 18) and in the tendency toward better outcomes in the MEM-MEM groups at the end of the extension phase. Because our study was based on the wisdom that memantine effects plateau at 4 weeks after intake of full dosage,[23,31] and a memantine-only group was therefore not included, we were unable to rule out the theoretical possibility that memantine without CIAT during weeks 16 to 18 might have yielded benefits at week 18 similar to those of combined therapy.

Previous studies confirmed that patients with chronic PSA improve their language proficiency significantly, over a 2-week period of CIAT, a specific high-intensity SLT emphasizing language-action links.[7–15] This study now provides the first evidence for a synergistic effect of drugs (memantine) and intensive SLT (CIAT). This calls for an explanation why memantine, in addition to its own beneficial effect (week 16), would lead to an amplification of learning effects brought about by CIAT (week 18). One possibility is

Table 3. **Continued**

Randomized Placebo-Controlled Phase								Open-Label Extension Phase			
Week 20				Week 24				Week 48			
Memantine Washout	Placebo Washout	95% CI	p^a	Memantine Washout	Placebo Washout	95% CI	p^a	Memantine Washout	Placebo Washout	95% CI	p^a
8.9 (1.1)[b]	4.3 (0.6)[b]	1.8-7.4	**0.005**	6.0 (0.8)[b]	3.9 (0.8)[d]	−0.3-4.6	**0.041**	10.1 (1.0)[b]	7.2 (1.1)[b]	−0.4-6.2	0.083
2.3 (0.4)[b]	1.2 (0.3)[e]	0.7-2.2	**0.035**	1.7 (0.4)[d]	1.1 (0.3)[d]	−0.5-1.7	0.119	2.7 (0.3)[b]	1.6 (0.2)[b]	0.0-2.1	**0.045**
0.4 (0.1)[b]	−0.2 (0.9)[e]	0.1-1.3	0.122	0.2 (0.1)[b]	0.1 (0.2)[c]	−0.3-0.6	0.354	0.5 (0.1)[e]	0.1 (0.1)	−0.1-0.8	0.233
0.5 (0.2)[e]	0.8 (0.9)[d]	−0.9-0.4	0.969	0.3 (0.1)	0.4 (0.2)	−0.7-0.4	0.774	0.4 (0.1)[d]	1.1 (0.2)[d]	−1.2-0.0	0.376
1.0 (0.2)[b]	0.4 (0.1)[e]	0.0-1.1	**0.064**	0.7 (0.1)[b]	0.2 (0.2)	−0.3-09	0.319	1.3 (0.2)[b]	0.9 (0.2)[e]	−0.1-1.0	0.368
3.4 (2.0)	−0.7 (2.3)	−2.3-10.6	0.142	3.1 (1.8)	−0.7 (1.8)	−1.3-9.2	0.269	4.0 (2.0)	1.0 (2.7)	−4.0-10.0	0.289

Table 4. **Number of Responders by Study Week on Outcome Measures (Observed Cases)**

Week	Memantine			Placebo			Difference from Placebo Mann–Whitney *U* Test *p*	
	Responders (%)			Responders (%)				
	n	WAB-AQ	CAL	n	WAB-AQ	CAL	WAB-AQ	CAL
16	14	8 (57)	7 (50)	14	3 (21)	4 (28)	0.057	0.254
18	14	14 (100)	9 (75)	14	7 (50)	6 (49)	0.047	0.264
20	14	12 (86)	7 (50)	13	8 (61)	5 (38)	0.012	0.554
24	14	12 (86)	6 (42)	13	8 (61)	4 (28)	0.181	0.524

Responders were defined as patients showing an improvement on Western Aphasia Battery-Aphasia Quotient (WAB-AQ) scores ≥ 5 and Communicative Activity Log (CAL) scores ≥ 5.4.

that memantine enhanced experience-dependent neural plasticity elicited by intensive CIAT.[14] This significant effect could be related to the role of glutamatergic synaptic transmission in learning and memory processes.[23] Although it is widely accepted that phasic, synaptic *N*-methyl-D-aspartate receptor activation is necessary for learning-related synaptic plasticity, abnormal tonic activity before or after synapse under pathological conditions (eg, stroke, poststroke epilepsy) reduces such correlation and, therefore, acts against learning at the cellular level.[23,25,26,35] Treatment with memantine may readjust neuron activity to a physiological level, thus possibly acting against a range of cognitive deficits (arousal, attention, language, and memory encoding).[23] Although this mechanism may underlie the augmentation of CIAT effects by memantine, it is also possible that memantine exerted its function by improving the modulation of surviving neuronal networks.

In conclusion, SLT in chronic PSA can be optimized by memantine treatment combined with CIAT. The beneficial effects of memantine and CIAT on aphasia severity are maintained at long-term follow-up.

The study was supported by Lundbeck and the Ministerio de Educación y Ciencia, Spain (SEJ2007-67793).

We thank the aphasic patients and their relatives for participation in the study, and J. Barón-López for advice on statistical analysis.

References

1. Berthier ML. Poststroke aphasia: epidemiology, pathophysiology and treatment. Drugs Aging 2005;22:163–182.
2. Kertesz A. Recovery of aphasia. In: Feinberg TE, Farah MJ, eds. Behavioral neurology and neuropsychology. New York: McGraw-Hill, 1997:167–182.
3. Hillis AE. Aphasia: progress in the last quarter of a century. Neurology 2007;69:200–213.
4. Basso A. How intensive/prolonged should be an intensive/prolonged treatment be? Aphasiology 2005;19:975–984.
5. Robey RR. A meta-analysis of clinical outcomes in the treatment of aphasia. J Speech Lang Hear Res 1998;41:172–187.
6. Bhogal SK, Teasell R, Speechley M. Intensity of aphasia therapy, impact on recovery. Stroke 2003;34:987–993.
7. Pulvermüller F, Neininger B, Elbert T, et al. Constraint-induced therapy of chronic aphasia after stroke. Stroke 2001; 32:1621–1626.
8. Pulvermüller F, Hauk O, Zohsel K, et al. Therapy-related reorganization of language in both hemispheres of patients with chronic aphasia. Neuroimage 2005;28:481–489.
9. Meinzer M, Djundja D, Barthel G, et al. Long-term stability of improved language functions on chronic aphasia after constraint-induced aphasia therapy. Stroke 2005;36: 1462–1466.
10. Meinzer M, Flaisch T, Breitenstein C, et al. Functional re-recruitment of dysfunctional brain areas predicts language recovery in chronic aphasia. Neuroimage 2008;39:2038–2046.
11. Barthel G, Meinzer M, Djundja D, Rockstroh BB. Intensive language therapy in chronic aphasia: which aspects contribute most? Aphasiology 2008;22:408–421.
12. Maher LM, Kendall D, Swearengin JA, et al. A pilot study of use-dependent learning in the context of Constraint Induced Language Therapy. J Int Neuropsychol Soc 2006;12:843–852.
13. Szaflarski JP, Ball AL, Grether S, et al. Constraint-induced aphasia therapy stimulates language recovery in patients with chronic aphasia after ischemic stroke. Med Sci Monit 2008;14: CR243–CR250.
14. Pulvermüller F, Berthier ML. Aphasia therapy on a neuroscience basis. Aphasiology 2008;22:563–599.
15. Richter M, Miltner WHR, Straube T. Association between therapy outcome and right hemispheric activation in chronic aphasia. Brain 2008;131:1391–1401.
16. Small SL. A biological model of aphasia rehabilitation: pharmacological perspectives. Aphasiology 2004;18:473–492.
17. Kessler J, Thiel A, Karbe H, Heiss WD. Piracetam improves activated blood flow and facilitates rehabilitation of poststroke aphasia. Stroke 2001;31:2112–2116.
18. Walker-Batson D, Curtis S, Natarajan R, et al. A double-blind, placebo-controlled study of the use of amphetamine in the treatment of aphasia. Stroke 2001;32:2093–2098.
19. Berthier ML, Green C, Higueras C, et al. A randomized, placebo-controlled study of donepezil in post-stroke aphasia. Neurology 2006;67:1687–1689.
20. Cramer SC. Repairing the human brain after stroke. I. Mechanism of spontaneous recovery. Ann Neurol 2008;63:272–287.

21. Cramer SC. Repairing the human brain after stroke. II. Restorative therapies. Ann Neurol 2008;63:549–560.
22. Karbe H, Thiel A, Weber-Luxemburger G, et al. Brain plasticity in poststroke aphasia: what is the contribution of the right hemisphere? Brain Lang 1998;64:215–230.
23. Parsons CG, Stöffler A, Danysz W. Memantine: a NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system—too little activation is bad, too much is even worse. Neuropharmacology 2007;53:699–723.
24. Qü M, Mittmann T, Luhmann HJ, et al. Long term changes of ionotropic glutamate and GABA receptors after unilateral permanent focal cerebral ischemia in the mouse brain. Neuroscience 1998;85:29–43.
25. Parton A, Coulthard E, Husain M. Neuropharmacological modulation of cognitive deficits after damage. Curr Opin Neurol 2005;18:675–680.
26. Orgogozo J-M, Rigaud A-S, Stöffler A, et al. Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). Stroke 2002;33:1834–1839.
27. Wilcock G, Möbius H-J, Stöffler A, MMM 500 group. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). Int Clin Psychopharmacol 2002;17:297–305.
28. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–1364.
29. Kertesz A, Pascual-Leone Pascual A, Pascual-Leone García A. Batería de afasias "Western" (Western Aphasia Battery en versión y adaptación castellana). Valencia, Spain: Nau Llibres, 1990.
30. Sutcliffe LM, Lincoln NB. The assessment of depression in aphasic stroke patients: the development of the Stroke Aphasic Depression Questionnaire. Clin Rehabil 1998;12:506–513.
31. Memantine tablets. Summary of product characteristics (SPC). Copenhagen, Denmark: H. Lundbeck A/S, 2005.
32. Wilkinson D, Andersen HF. Analysis of the effect of memantine in reducing the worsening of clinical symptoms in patients with moderate to severe Alzheimer's disease. Dement Geriatr Cogn Disord 2007;24:138–145.
33. van Dick CH, Schmitt FA, Olin JT, Memantine MEM-MD-02 Study Group. A responder analysis of memantine treatment in patients with Alzheimer disease maintained on donepezil. Am J Geriatr Pyschiatry 2006;14:428–433.
34. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988.
35. Kim JH, Lee HW, Cohen LG, et al. Motor cortical excitability in patients with poststroke epilepsy. Epilepsia 2008;49:117–124.