Piracetam as an Adjuvant to Language Therapy for Aphasia: A Randomized Double-Blind Placebo-Controlled Pilot Study

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ABSTRACT. Huber W, Willmes K, Poeck K, Van Vleymen B, Deberdt W. Piracetam as an adjuvant to language therapy for aphasia: a randomized double-blind placebo-controlled pilot study. Arch Phys Med Rehabil 1997;78:245-50.

Objective: To determine whether piracetam 4.8g/day together with intensive language therapy improved language function more than language therapy alone.

Design: Double-blind, placebo-controlled parallel group study.

Setting: Referral speech and language clinic of a university department of neurology.

Patients: Sixty-six inpatients with aphasia present between 4 weeks and 36 months.

Interventions: Intensive language therapy for 6 weeks in all patients. Thirty-two patients received piracetam 4.8g daily and 34 patients received placebo.

Main Outcome Measure: The Aachen Aphasia Test (AAT), a standardized procedure for evaluating the severity of aphasia, was performed at baseline and after 6 weeks' treatment.

Results: In 50 patients evaluated for efficacy, a trend toward improvement in the active group was observed in all subtests of the AAT. This trend was statistically significant for absolute differences in recovery of "written language" and "profile level."

Conclusion: Piracetam appears to have a positive adjuvant effect on the recovery of aphasia in patients receiving intensive language therapy.

IT HAS BEEN ESTIMATED that between 21% and 24% of stroke patients develop aphasia and that 10% to 18% of those who survive stroke have significant communication deficits.[1] The frequency of aphasia, and the fact that it causes long-lasting disability, indicates the need for effective medical treatment as an adjuvant to existing speech and language therapy. Pharmacotherapy might act by protecting brain function during the acute phase of stroke, by improving cerebral functional depression through modulation of neurotransmitter function, and/or by enhancement of learning.

The value of drug therapy in aphasia remains largely unknown because few agents with apparent therapeutic potential have been thoroughly examined in studies of adequate design.[2,3] Improvement has been described when catecholaminergic drugs such as bromocriptine[3] and amphetamine[4] have been added to language therapy and after treatment with levodopa,[5] although no placebo-controlled studies have been reported. We did a pilot study to investigate the effects of the nootropic agent piracetam in aphasic patients who were receiving language therapy.

Adequate demonstration of clinical benefit in aphasia is difficult.[6] The evaluation of any therapeutic measure must consider spontaneous recovery, the benefit from language therapy, and the selection of appropriate outcome measures.[7-10]

Discussions on whether speech treatment is effective have been published.[7,9,11-13] The preponderance of evidence suggests that speech treatment is efficacious, but debate continues about the optimal timing of language treatment in relation to the onset and duration of aphasia, as well as the type, intensity, and duration of such treatment.[9,11] Some investigators have claimed that language treatment by trained therapists has no more effect than nontreatment,[14] emotionally supportive counselling,[15] or therapy provided by untrained volunteers.[16,17]

Language therapy is, however, generally considered the treatment of choice for aphasic patients.[7,9,18,19] Basso et al[11] showed that speech therapy had a significant positive effect on all language skills and that improvement could occur even when therapy was undertaken months or years after the onset of the language disorder. In a well-designed and controlled study, Wertz et al[12] reported clinic treatment for 12 weeks to be efficacious and that deferral of treatment for 12 weeks did not preclude long-term response. After administration of intensive language treatment for 6 to 8 weeks, Poeck et al[7] found improvement greater than that to be expected from spontaneous recovery in about two thirds of patients with aphasia from 1 to 12 months.[7] Improvement of similar degree was also found in patients aphasic for more than 12 months in whom further spontaneous recovery was therefore unlikely.

Piracetam (Nootropil), a gamma-aminobutyric acid (GABA)–derivative devoid of GABA-like activity or antagonism, is a nootropic agent that improves cognitive functions such as learning and memory through facilitation of cholinergic and excitatory amine neurotransmission.[20] It has been shown to increase the fluidity of the neuronal membrane[21,22] and to protect the nerve cell against hypoxia.[23-26] These effects are not organ- or cell-specific, and piracetam exerts its effects not only at a neuronal level but also on the microcirculation through effects on platelets, red cells, and the vessel wall. Piracetam increases red cell deformability[27,28] and decreases platelet aggregation[29-32] and capillary vasospasm.[33] These properties lead to decreased plasma and whole blood viscosity,[30] to improvement in compromised cerebral blood flow,[34] and to increased cerebral perfusion.[33]

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Studies in stroke patients[35,36] have shown improvement in motor function, level of consciousness, and aphasia. Recent studies have confirmed the beneficial effect in aphasia.[37,38]

This pilot study evaluated whether piracetam, when administered to patients with chronic aphasia who were receiving intensive language treatment, led to greater improvement than language therapy alone. We performed a double-blind, randomized trial using a parallel group design with a piracetam and a placebo control group of inpatients in whom outcome was assessed by means of the Aachen Aphasia Test (AAT).[39,40]

PATIENTS AND METHODS

We studied consecutive patients admitted to the aphasia ward after referral to the speech and language clinic of our hospital's department of neurology. Each patient underwent extensive neurolinguistic and neuropsychological assessment. After admission, patients began intensive language therapy. They were randomized to treatment with piracetam 4.8g daily or placebo for 6 weeks in blocks from a computer-generated randomization list. Medication was administered as two 800-mg tablets of piracetam or matching placebo every 8 hours. Neither patients nor providers were asked to guess whether active treatment or placebo was given. All patients or their close relatives gave informed consent. The study protocol was approved by the ethics committee of the medical faculty and we performed the study according to European Community Guidelines for Good Clinical Practice.

Patients

The study population consisted of patients who had had aphasia for at least 4 weeks and no more than 36 months. Computed tomography (CT) had to show only a lesion of the left cerebral hemisphere related to ischemic or hemorrhagic stroke, brain injury, or brain surgery unrelated to a malignant tumor. Patients had to be right-handed, native speakers of German, and have no known mental deficit and no clinically relevant disturbance of sight or hearing after correction. Patients with mild aphasia, defined by a score above the 75th percentile in all AAT subtests, were excluded from the study. Patients with a recent myocardial infarct, severe and/or uncontrolled hypertension, or heart failure were ineligible, as were those with serious concomitant disorders, such as diabetes, renal insufficiency, and malignant disease. Patients receiving neuroleptic, antidepressant, cerebral vasodilator, nootropic, or psychostimulant drugs were excluded, but those previously receiving nootropic agents could be included after these agents had been withdrawn for 2 weeks. Patients on anticonvulsant therapy were included provided that their drug regimen remained unchanged from 1 week prior to entry until the end of the study.

Methods

Language therapy. Most patients received speech therapy of usual duration immediately after the onset of the disorder. For the 6-week study period all patients then received intensive language therapy with ten 60-minute sessions per week, five individual and five group sessions. The therapeutic approach in each patient was the result of a multidisciplinary group decision and consisted of both symptom-specific training and consolidation.[41,42] Individual symptom-specific training sessions were directed at the impaired linguistic abilities in a given patient. These involved relearning of degraded linguistic knowledge, reactivation of impaired linguistic modalities, and learning of compensatory strategies. Patients were indirectly made aware of lost linguistic units and regularities with the aim of inducing learning processes. Training included, for example, activities such as multimodal processing of phonemic and semantic word contrasts, sentence pattern expansion by using modal and auxiliary verbs, and discourse processing by focusing on story grammar, idioms, and key words. In group treatment, symptom-specific training was complemented by a phase of consolidation that aimed at the transfer of relearned linguistic skills to everyday speech.

Assessments. Baseline assessments consisted of an evaluation of factors that might influence the prognosis of and recovery from aphasia: age, sex, type and severity of aphasia, duration of aphasia, sensory and hearing acuity, medical history, and drug therapy.

We selected the AAT for the assessment of efficacy. The test was carried out at baseline and at the end of the 6-week treatment period by investigators unaware of which treatment a patient had received. The AAT[39,40] is a standardized procedure for evaluating the severity of aphasia developed and validated in the German language, subsequently translated into several European languages, and validated and standardized in Dutch and Italian. The presence and type of aphasia was established on entry using the ALLOC classification procedure, a nonparametric discriminant analysis computer program[39] using the normative data of the AAT.

The AAT consists of six rating scales for spontaneous speech and five subtests for the assessment of specific language impairments. The six aspects of spontaneous speech rated are communicative verbal behavior, articulation and prosody, automatized language, semantic structure, phonemic structure, and syntactic structure. Scores for each are defined by characteristic symptoms and their frequency.

The subtest Token Test of the AAT assesses the overall severity of the language disturbance. It is a modified version of the Italian original by De Renzi and Vignolo.[43] Scoring is dichotomous with errors ranging from 50-0, and a low score indicates a good result.

Three structural principles were observed in designing the four remaining linguistic subtests. Different linguistic modalities were considered: speech production with auditory input (subtest Repetition), language production with graphemic-phonemic/phonemic-graphemic transcoding (subtest Written Language), speech production on pictorial stimulation (subtest Naming on Confrontation), and matching auditory and graphemic stimuli to multiple choice sets of pictures (subtest Comprehension). In addition, different linguistic units were distinguished: phonemes, words, and sentences. Finally, the subtests were designed in such a way that different linguistic regularities were focused on in the various subtests. These four AAT subtests consist of 3 to 5 parts, each of which contains 10 items. Responses to individual items are scored on a 4-point scale, 3 indicating a correct response and 0 a complete deviation from the target or no response. The construct validity of this multiple facet design of the AAT was demonstrated empirically by Willmes et al.[44]

The percentile scores used for all five subtests express proficiency.[45] The reliability-weighted sum of the five subtest scores was used to determine the profile level, an overall and clinically relevant measure of the severity of aphasia expressed in T-score units.

Statistics. We compared the treatment groups at baseline for differences in age (t test), sex (chi-square test), and duration of aphasia (Mann-Whitney U test). We also compared baseline AAT scores in the two groups for spontaneous speech, for each subtest, and for the profile level.

Response to the combined effect of language and drug treatment was determined by comparing AAT scores, and the differences in scores from baseline, on entry, and after 6 weeks'

Table 1: Reasons for Exclusion From Efficacy Analysis

Withdrawal of consent to participate in study	4
Protocol deviations	
Interval between baseline and posttreatment AAT examination too long (>66 days)	5
Duration of aphasia too long (>36 months)	2
Aphasia not severe enough	2
Further stroke	1
Adverse event (nausea, in placebo group)	1
Dropout (premature discharge from hospital)	1
Total	16

treatment. We analyzed the five AAT subtest scores by multivariate analysis of variance (MANOVA) as well as by univariate analysis for each subtest. For the multivariate analysis, AAT subtest results were response variables, treatment and type of aphasia independent variables, and age was a covariate. Profile level was also analyzed by univariate analysis. Subtest results were analyzed throughout as percentile ranks rather than as raw scores. Because most scores were not normally distributed, items were ranked and normalized using the van der Waerden transformation.[46]

For each of the six ratings of spontaneous speech, the Mann-Whitney U test was used to compare the number of improvements in each treatment group. A gain of at least 2 rating scale points was the criterion for improvement, which takes into account the interrater variability determined during validation of the AAT.[39,44]

All tests were two-sided and the significance level was $\alpha = .05$. Analyses were performed with the SAS and StatXact statistical packages.

RESULTS

Patients

A total of 66 patients entered the study over a period of 4 years; 32 patients were randomized to piracetam and 34 to placebo. We were unable to evaluate efficacy in 16 patients, predominantly because of protocol deviations or withdrawal of patient consent. These were most often related to the stringent protocol entry criteria (table 1). Efficacy was thus assessed in 50 patients, 24 of whom received piracetam and 26 placebo.

The two groups were well matched with respect to prognostic factors: age, sex, etiology, and duration of aphasia (table 2). The type and severity of aphasia were also similar. All patients were right-handed. Baseline AAT scores were comparable for spontaneous speech ratings and for subtest scores, as well as for profile level. In addition, the distribution of scores within treatment groups was closely comparable (fig 1). Duration of language therapy and treatment with piracetam or placebo was between 30 to 42 days in all patients.

Outcome

Results of the AAT are presented in tables 3 and 4. Subtest scores after 6 weeks' treatment together with the differences in scores from baseline are shown in table 3 and figure 2.

The mean scores for all AAT subtests were higher with piracetam, indicating improvement compared with placebo. On univariate analysis of variance the difference between groups was significant for one test "written language" ($p < .05$) and approached significance for the Token Test ($p < 0.1$) (table 3, fig 2). The score for the profile level, the weighted average of all subtests reflecting overall severity of aphasia, was also significantly better on piracetam than on placebo ($p < .05$) (fig 3).

We found no statistically significant differences between the two treatment groups for any of the six scales of spontaneous speech, although the improvement in syntactic structure in piracetam-treated patients approached significance ($p = .07$). When the number of improvements by at least two scale points was considered (table 4), improvement was greater (approximately 30%) on piracetam, but this difference did not reach statistical significance because of large interindividual variability.

We evaluated all patients for adverse events, and none that

Table 2: Baseline Characteristics of Aphasic Patients Evaluable for Efficacy ($n = 50$)

	Piracetam ($n = 24$)	Placebo ($n = 26$)
Age (years)		
Mean (SD)	49.8 (13.0)	51.9 (12.2)
Range	26-76	26-69
Sex		
Men	17	20
Women	7	6
Etiology of aphasia		
Stroke (first stroke)	23	24
Head injury	1	2
Type of aphasia		
Global	12	12
Wernicke	7	7
Broca	5	6
Amnestic	0	1
Duration of aphasia (months)		
Mean (SD)	9 (8.4)	12 (13.5)
Range	1-29	1-36
Median	5	6.5
Severity of aphasia: means (SD)		
AAT scores for spontaneous speech scales (0-5 points each)		
Communicative behaviour	1.46 (0.88)	1.38 (1.06)
Articulation and prosody	3.50 (1.50)	3.42 (1.55)
Automatized language	2.54 (1.41)	2.46 (1.75)
Semantic structure	1.83 (1.40)	1.92 (1.44)
Phonemic structure	1.87 (1.57)	2.12 (1.56)
Syntactic structure	1.37 (1.35)	1.62 (1.47)
AAT subtest scores (percentiles)		
Token Test	39.96 (25.37)	37.65 (25.89)
Repetition	40.58 (21.87)	34.92 (26.66)
Written language	45.13 (24.07)	40.35 (23.21)
Confrontation naming	39.83 (25.76)	36.08 (20.91)
Comprehension	45.58 (21.66)	46.26 (22.83)
Profile level (T-score)	47.27 (6.38)	46.00 (6.68)

None of the differences between piracetam and placebo was statistically significant.

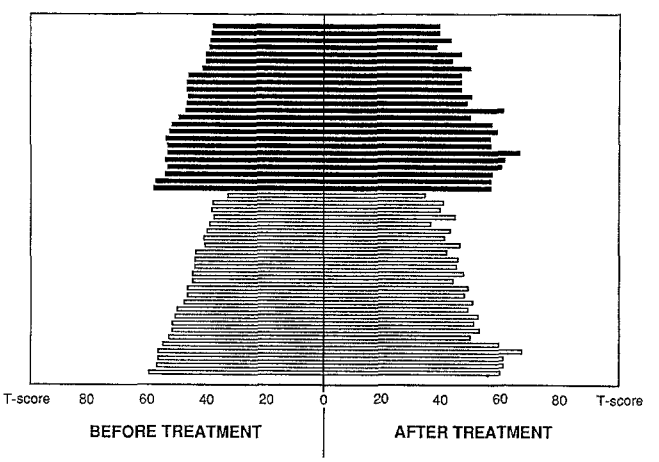

Fig 1. Distribution of individual T-scores for profile levels in piracetam (■) and placebo (□) groups before and after treatment. T-score distribution in the two groups before treatment was similar.

Table 3: AAT Subtest Scores (Percentiles) and Profile Level T-Scores and Differences in Scores From Baseline After 6 Weeks' Treatment

	AAT Scores After Treatment			Differences in Scores From Baseline		
AAT Subtest	Piracetam (n = 24)	Placebo (n = 26)	p Value	Piracetam (n = 24)	Placebo (n = 26)	p Value
Token Test	51.0 (29.2)	42.2 (29.6)	.07	11 (12.8)	6.5 (4.5)	.08
Repetition	51.7 (24.5)	41.5 (26.9)	NS	11.1 (13.9)	7.0 (6.6)	NS
Written language	58.3 (29.6)	45.5 (26.3)	.03	13.2 (14.2)	6.5 (5.2)	.05
Naming	55.0 (21.9)	46.5 (26.0)	NS	15.2 (17.6)	12.0 (10.4)	NS
Comprehension	58.3 (21.9)	55.2 (27.9)	NS	12.7 (15.2)	9.5 (8.3)	NS
Profile level	51.2 (8.0)	48.5 (8.0)	.04	3.95 (3.9)	2.52 (3.0)	NS

Values given as means (standard deviations).

could be considered possibly drug-related was reported with piracetam. One patient on placebo withdrew because of nausea.

DISCUSSION

In this pilot study we were able to show the effect of 6 weeks' treatment with piracetam relative to placebo in aphasic patients receiving intensive speech therapy. The results suggest that piracetam led to significant overall decrease in the severity of aphasia as assessed by AAT subtests. We found a significant difference in favor of piracetam in the profile level, a clinically relevant weighted average of subtest scores. In addition, there were improvements in individual subtests on piracetam that were generally almost twice as great as on placebo and that reached significance for written language. Although numeric differences between treatments in tests for spontaneous speech favored piracetam, the differences were not significant.

As in most treatment studies in aphasia, we were not able to control all variables influencing response to treatment. The duration of aphasia before therapy was variable, and because of the small numbers studied, stratification according to duration of aphasia was not possible. In addition, we made no attempt to control the site and size of lesion as demonstrated on CT.

The two treatment groups were well matched for most prognostic factors, however, an important point in considering whether piracetam is effective as add-on therapy in the rehabilitation of aphasic patients. Age, sex, etiology, and type and severity of aphasia were similar in the two groups. All patients were right-handed. The mean and median durations of aphasia prior to piracetam and language therapy were also comparable. All patients entered the study after the acute stage of stroke (ie, at least 1 month after onset), and the median duration was about 6 months. The amount (10 hours/week), methods, and content of language therapy were specified in a prescribed treatment protocol, resulting in closely similar management of all patients.

Both groups improved on treatment. The improvement in profile level of 2.5 T-scores in the placebo group, ie, those who received only language treatment, was similar to that in a previous study of similar design in our department in which patients, 4 to 12 months after suffering a stroke, received 10 hours of language treatment weekly for 6 to 8 weeks.[7]

The addition of piracetam to language therapy led to greater improvement than language therapy alone. In addition to a significant difference in favor of piracetam in profile level, we found improvements on piracetam in all individual subtests that were approximately twice as great as on placebo and which, for written language, reached significance.

That these findings are valid and probably clinically relevant is supported by the results of Enderby et al,[37] who also reported a double-blind, placebo-controlled pilot study in which aphasia was assessed using the AAT. They found significant overall improvement in AAT subtests and a pattern of improvement, including changes in written language that approached significance, closely similar to the results we report here.

The mean improvement in AAT profile level in favor of piracetam was 1.43 T-scores. This exceeds the critical difference of 1.1 profile level T-scores that is considered a standard criterion of statistically significant improvement in an individual patient according to the psychometric single case analysis approach of Huber.[45,47] The improvement was due mainly to a marked increase in profile level, in excess of 4.4 T-scores (ie, 4 × critical difference), in twice as many patients treated with piracetam (10/24; 41.6%) as with placebo (5/26; 19.2%). This group of responders to piracetam accounts for the greater variability of response in the active group. Although the number of patients was too small to allow conclusions, response appeared to be more frequent in patients with aphasia of Wernicke and Broca types than in those with global aphasia.

An improvement of at least 2 scale points in spontaneous speech is a strict criterion and one which indicates a marked improvement in spontaneous speech. We found improvement of this degree in 19 items in piracetam-treated patients and in 12 items in those receiving placebo. Although this difference is not statistically significant, communicative ability showed the same pattern of improvement as the linguistic abilities assessed by AAT subtests.

The mechanism by which piracetam acts to improve aphasia is not well understood. In the acute stage after stroke or brain injury, the aim of language treatment is to enhance improvement of temporarily impaired language functions. The additional effect of piracetam might be due to its neuroprotective properties of enhanced cell metabolism and neurotransmission in the presence of hypoxia.[23,24]

In this context, preservation of metabolic function in viable neurones in the peri-infarct zone has been shown in positron emission tomography (PET) studies to be an important predictive factor in recovery from aphasia.[48] Such studies in patients given piracetam after an acute stroke have shown restoration of impaired blood flow in ischemic tissue at the periphery of cerebral infarcts together with increase in regional oxygen extraction and impaired regional glucose metabolism.[34,49] The fact that cerebral metabolic rates for glucose in speech-relevant brain regions, including the contralateral mirror region of the infarcted area, measured early after stroke are also a predictor of long-term outcome in aphasia[48] may also be relevant to the

Table 4: AAT Spontaneous Speech Scales: No. of Improvements of ≥2 Scale Points

	Piracetam (n = 24)	Placebo (n = 26)
Communicative behaviour	3 (13%)	2 (8%)
Articulation and prosody	1 (4%)	4 (15%)
Automatized language	2 (8%)	1 (4%)
Semantic structure	3 (13%)	2 (8%)
Phonemic structure	6 (25%)	3 (12%)
Syntatic structure	4 (17%)	0
Total number of improvements ≥2 scale points	19	12

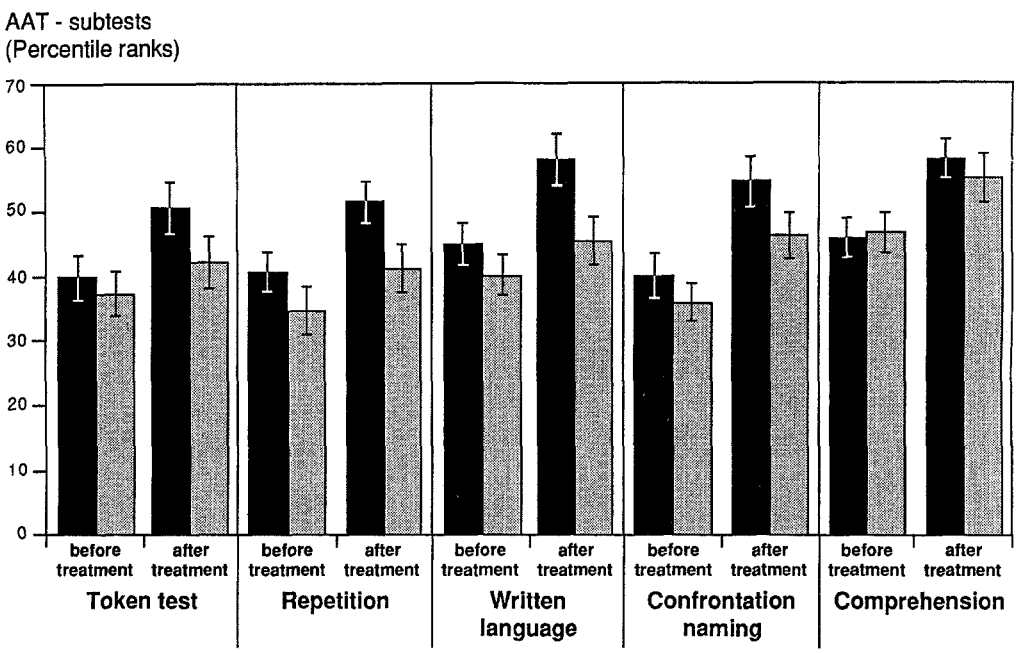

Fig 2. Scores for Aachen Aphasia Test subtests at baseline and after 6 weeks of treatment (means and SE): ■, piracetam; □, placebo.

effects of piracetam on neurotransmission: piracetam has been shown to improve communication between the two brain hemispheres by facilitating transcallosal transfer.[50,51]

In a recent PET activation study,[52] patients fully recovered from Wernicke's aphasia despite a persisting lesion of the left posterior language zone demonstrated, during lexical processing, increased activity of intact Broca's area and, when semantic processing generation was required, also of the dorsolateral prefrontal cortex. In addition, right hemisphere areas homotopic to Broca's and Wernicke's area were significantly more activated than in normal controls. Thus, redistribution of activity within a preexisting, parallel processing, and bilateral network might be the central mechanisms in functional reorganization of the language system after stroke.

In the later stages of rehabilitation, relearning of degraded linguistic knowledge[41,42] and learning of compensatory strategies might be facilitated by the well-documented effects of piracetam on learning and memory[20] and by facilitating transcallosal transfer.[50,51]

The potential implications of these preliminary results with piracetam are considerable. If further well-designed studies confirm the findings, the question of whether piracetam should be broadly used as an adjuvant to language treatment of aphasia will need serious consideration. Further studies might also help define potential responders and the probable degree of response, and indicate whether beneficial effects are maintained with long-term treatment.

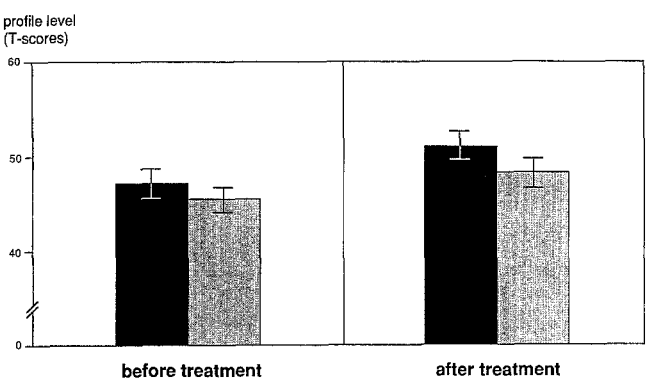

Fig 3. Scores for Aachen Aphasia Test profile level at baseline and after 6 weeks of treatment (means and SE): ■, piracetam; □, placebo.

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