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Piracetam in Elderly Psychiatric Patients with Mild Diffuse Cerebral Impairment

G. Chouinard[1,2,3], L. Annable[1,2], A. Ross-Chouinard[2,4], M. Olivier[4], and F. Fontaine[3]

[1] Clinical Psychopharmacology Unit, Allan Memorial Institute, Royal Victoria Hospital, Montreal, Quebec H3A 1A1, Canada
[2] Department of Psychiatry, McGill University, Montreal, Canada
[3] Research Department, Hôpital Louis-H. Lafontaine, Montreal, Canada
[4] Hôpital Hôtel-Dieu de Montreal, Montreal, Canada

Abstract. In a 12-week double-blind study, piracetam at two dose levels (2.4 and 4.8 g/day) was compared to placebo in the treatment of 60 elderly psychiatric patients with mild diffuse cerebral impairment, but no signs of focal brain lesion. The psychiatric illness, schizophrenia or affective disorder, of patients selected was in remission at the time of the study. Monthly evaluations by the nurse revealed that piracetam improved overall functioning, particularly alertness, socialization, and cooperation, relative to the control group. Patients treated with 2.4 g/day piracetam also showed significant improvement in scores for the full IQ and the memory quotient on the Wechsler Adult Intelligence and Memory Scales; greater response was seen in those with lower initial scores. Piracetam at 4.8 g/day had a more rapid onset of action on behavioral variables than 2.4 g/day, but its therapeutic effect tended to diminish at 12 weeks, possibly as the result of overstimulation. Piracetam did not appear to interfere with concomitant psychotropic maintenance medication or affect the psychiatric illness itself.

Key words: Piracetam – Nootropic drugs – Psychotropic drugs – Geriatrics – Aging – Cognitive impairment – Senile dementia

Piracetam, 2-oxo-1-pyrrolidine acetamide, is a cyclic derivative of GABA without the usual GABA-like properties. In animal studies, piracetam was found to enhance learning and memory and to protect these functions against hypoxia (Giurgea et al. 1971). It has been proposed that the action of piracetam is due to its increasing adenosine triphosphate (ATP) formation (Pede et al. 1971) and enhancing protein synthesis (Burnotte et al. 1973) in cortical nerve cells, effects which may be of therapeutic value in the hypoxic aging brain. Studies in vitro suggest that piracetam has an effect on the cell membrane of platelets (Barnhart et al. 1979) and red blood cells (Nalbandian et al. 1978), and studies conducted in humans appear to confirm an effect on platelets (Bick and Skondia 1979). In addition, piracetam was shown to inhibit sickling of red cells containing sickle hemoglobin (Asakura et al. 1981) and to diminish the adherence of sickle erythrocytes to vascular endothelium (Nalbandian et al. 1981). Reports of a positive effect of piracetam in sickle-cell anemia (deMelo 1976; Targina deAraujo und Nero 1977) also suggest an effect on the red blood cell membrane. However, the clinical significance of these results needs to be established.

Offprint requests to: G. Chouinard, Allan Memorial Institute, 1025 Pine Avenue West, Montreal, Quebec, H3A 1A1

In studies conducted with volunteers, piracetam improved mental performance in normal aging individuals (Mindus et al. 1976) and increased verbal learning in students (Dimond and Brouwers 1976). In double-blind placebo-controlled studies, piracetam improved the level of post-operative consciousness in patients undergoing neurosurgery (Richardson and Bereen 1977), reduced the occurrence and severity of post-concussional symptoms (Hakkarainen and Hakamies 1978) and, in patients with artificial pacemakers, counteracted impairment of mental performance when the heart rate was reduced, possibly by a protective effect against hypoxia (Lagergren and Levander 1974). However, the results of studies on piracetam in geriatric patients with psycho-organic symptoms are inconsistent: three studies (Stegink 1972; Kretschmar and Kretschmar 1976; Dorn 1978) found piracetam to be superior to placebo on psychometric testing, whereas four others found no or little effect (Dencker and Lindberg 1977; Gustafson et al. 1978; Lloyd-Evans et al. 1979; Reisberg et al. 1982) and a fifth found piracetam better than placebo with respect to clinical improvement but not on psychometric testing (Abuzzahab et al. 1977). In schizophrenic patients piracetam had no significant effect on the disease process or state (Dimond et al. 1979; Pryce and Gray 1978), but improved performance on learning and memory tests (Dimond et al. 1979).

The present double-blind placebo-controlled study examines the effect of piracetam on behavioral variables and cognitive functioning in elderly psychiatric patients with mild diffuse cerebral impairment, but no evidence of focal brain lesion. In order to evaluate the dose-response relationship, piracetam was given for 12 weeks at two dosage levels (2.4 and 4.8 g/day).

Materials and methods

Sixty elderly psychiatric patients (54–80 years of age) with mild diffuse cerebral impairment were selected from inpatient wards and foster homes of Louis-H. Lafontaine Hospital, Montreal, for inclusion in the trial. The psychiatric illness of each patient selected was in remission at the time of the study. Twenty subjects were randomly assigned to 12 weeks of treatment with each of placebo, 2.4 g/day piracetam and 4.8 g/day piracetam. The dosages of psychotropic maintenance medication (if any) received by the patients were kept constant during the trial. Patients were evaluated on behavioural rating scales at monthly intervals and IQ and memory tests were carried out before and after treatment. Extrapyramidal symptoms were also rated before and after treatment.

Table 1. Patient characteristics

	Placebo	Piracetam (2.4 g)	Piracetam (4.8 g)
No. patients	20	20	20
Men/women	11/9	5/15	6/14
Age (years)	54–80	54–79	54–72
Mean age	67	61	63
Affective/schizophrenic disorders	7/13	8/11	9/10
Neuroleptics			
No. patients receiving neuroleptics	14	15	18
Dosage (mg/day) range chlorpromazine equivalents (median)[a]	50–825 (350)	25–600 (150)	25–1600 (305)
Antidepressants[b]			
Patients receiving antidepressants	3	4	8
Dosage (mg/day) range (median)	50–150 (100)	40–150 (77.5)	25–100 (62.5)
Lithium			
No. patients receiving lithium	0	2	1
Dosage (mg/day)		600, 900	1200

[a] Conversion to chlorpromazine equivalents based on estimates given by Davis and Cole (1975)
[b] Antidepressants received were amitriptyline, imipramine, doxepin or trimipramine

Subject population. The 60 elderly psychiatric patients were diagnosed as having schizophrenia ($N = 34$), affective disorder ($N = 24$) or mild organic brain syndrome ($N = 2$), according to the Research Diagnostic Criteria (Spitzer et al. 1978). Each patient included in the study satisfied psychiatric, neurological and medical criteria.

Psychiatric examination. Subjects were examined by the research psychiatrist (G. Chouinard) and only those whose psychiatric illness was in remission were included in the study. Dosages of psychotropic medication (Table 1) were kept constant during the trial.

Neurological examination. Patients were examined by a neurologist (A. Ross-Chouinard) who excluded those with major cerebral impairment or focal cerebral lesion, and included only those with mild diffuse cerebral impairment defined as a mild but definite abnormality on at least two of the nine tests of higher intellectual functions. The examination consisted of (1) a standard neurological examination, i.e. cranial nerves, sensory examination (primary and discriminative; two-point discrimination, extinction, graphesthesia, stereognosia), reflexes (DTR, plantar reflex, palmo-mental, grasp, snout, glabella, etc.), muscle strength, coordination and cerebellar tests; (2) neurological tests of higher intellectual functions, i.e. orientation (time, place and person), memory (immediate, recent and remote), attention and concentration, judgement, apraxia (bucco-facial, ideomotor, ideational and construction), visual agnosia (Poppelreuter drawings and color), left-right confusion, simple arithmetic and aphasia [Lecours' abbreviated protocol (Lecours and Lhermitte (1979), consisting of tests of spontaneous language, repetition, denomination (ten objects), reading, oral comprehension (Marie's test) and writing].

Medical examination. An internist carried out a medical examination and any patient with a major physical illness was excluded from the study.

All patients and, where applicable, their legal guardians gave informed written consent after the purpose of the study and the possible side effects had been explained to them.

Patient characteristics. Table 1 shows details of the sex, age, psychiatric diagnosis and maintenance medication of the 20 patients allocated to each treatment group. The mean age of patients treated with placebo was greater than that of patients treated with piracetam, but not significantly ($P > 0.05$ analysis of variance). Two patients had no history of affective or schizophrenic disorders but were considered to have a mild organic brain syndrome, one related to arteriosclerosis and the other to alcoholism. Before treatment, the mean $\pm$ SD of the Wechsler IQ scores of the 60 patients was 85.1 ± 9.8 and that of the Wechsler memory quotient (MQ) was 86.1 ± 15.2. On the basis of their MQ, 36 of the 60 patients (60%) had memory deficits that could be classified as mild deficit (MQ 81–89 in 17 patients), moderate deficit (MQ 71–80 in ten patients), severe deficit (MQ 61–70 in seven patients) and very severe deficit (MQ 51–60 in two patients). In addition, 16 of these 36 patients had a significant dissociation (greater than 10) between Wechsler IQ and MQ.

Drug administration. Medications were administered at constant dosage under double-blind conditions for a period of 12 weeks. Patients treated with 2.4 g/day piracetam received one active piracetam tablet of 800 mg 3-×-day and one placebo tablet 3-×-day, those treated with 4.8 g/day received two tablets of piracetam 800 mg 3-×-day and those treated with placebo received two placebo tablets 3-×-day. Medication intake was supervised by a research nurse using a pill count procedure.

Assessment procedure. All evaluations were carried out under double-blind conditions. A single nurse evaluated all the patients throughout the trial. Patients were assessed by the nurse on entering the study and then at weeks 4, 8 and 12 using the Sandoz Clinical Assessment Geriatric Scale (SCAG, Shader et al. 1974) and the Crichton Geriatric Rating Scale (Guy 1976). At the end of the trial, the nurse also completed a 6-point Clinical Global Improvement (CGI) rating scale and rated which (if any) of the following three characteristics showed the most improvement during the trial: alertness; socialization; orientation. Patients were evaluated by the psychiatrist at weeks 0 and 12 on the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham 1962).

Patients were also evaluated by one of two experienced neuropsychologists at weeks 0 and 12 on a validated French-language version (Chagnon 1953, 1955) of the Wechsler Adult Intelligence Scale and the Wechsler Memory Scale (Wechsler 1955), and the Rey figure test of immediate and short-term memory (Rey 1941; Osterrieth 1945). Patients were evaluated by the same neuropsychologist on both occasions. Extrapyramidal symptoms were evaluated by the neurologist at weeks 0 and 12 on the basis of a standardized examination procedure using the Extrapyramidal Symptom Rating Scale of Chouinard and Ross-Chouinard (Chouinard et al. 1979, 1980).

Vital signs, including body temperature, respiration rate, blood pressure (systolic and diastolic) and pulse rate, were recorded in both standing and supine positions following a standard procedure, twice a week during weeks 1–3, once a week during weeks 4–6 and every 2 weeks thereafter. Laboratory tests (biochemistry, hematology, urinalysis), complete physical and neurological examinations, electrocardiograms and electroencephalograms were carried out before treatment and at week 12. Blood samples were taken at weeks 0 and 12 for measurement of plasma prolactin by homologous radioimmunoassay using a double-antibody technique (Sinha et al. 1973).

Results

Early termination. One patient left the trial after 10 weeks because of physical illness unrelated to the drug treatment. A complete evaluation was carried out at the time of exclusion and served as the final assessment for the statistical analysis of the results. All other patients completed the 12-week trial.

Statistical analysis. The scores for the nurse's CGI of improvement were submitted to analysis of variance. The scores on the other rating scales (SCAG, Crichton geriatric, BPRS, Wechsler Adult Intelligence and Memory Scales, extrapyramidal symptoms) were submitted to analysis of co-variance with initial scores as co-variate. In each analysis of co-variance the homogeneity of the within-treatment co-variance regression coefficients was tested (Winer 1971). We investigated the effect of age as a co-variate in the analysis of the nurse's CGI scores and as a second co-variate in the analysis of the other rating scale data, but regression of final scores on age was not significant ($P > 0.10$). Thus the difference between treatment groups with respect to mean age of subjects (Table 1) did not appear to have any effect on the results. Regression of final scores on initial scores, on the other hand, was highly significant ($P < 0.001$) in most cases, confirming that the analysis of co-variance utilized was appropriate. The adjusted mean scores for each dose of piracetam were compared with those for placebo on an a priori basis (Winer 1971).

Behavioral rating scales. Table 2 shows the mean scores for the nurse's CGI, and the initial and adjusted final (week 12) mean scores for the SCAG and Crichton geriatric rating scales and the BPRS. As may be seen, piracetam at either dose level (2.4 or 4.8 g/day) was significantly ($P < 0.001$) superior to placebo on the nurse's CGI and there was no significant ($P > 0.10$) difference between the two dose levels in this respect. The mean scores for the CGI represent mild to moderate improvement in piracetam-treated patients and no change in those treated with placebo. Among improved patients treated with piracetam, the nurse rated alertness to be

Table 2. Initial and adjusted final mean scores for nurse's Clinical Global Improvement (CGI), Sandoz Clinical Assessment-Geriatric (SCAG), Crichton Geriatric Rating Scale (CGRS), and Brief Psychiatric Rating Scale (BPRS): Items for which statistically significant treatment differences occurred are shown

	Placebo		Piracetam (2.4 g)		Piracetam (4.8 g)	
	Week 0	Week 12	Week 0	Week 12	Week 0	Week 12
Nurse's CGI (6-point)[a]		0.4		2.2***		2.6***
SCAG						
Total score	28.6	26.2	24.2	22.1†	25.8	23.8
Motivation-initiative	1.8	1.7	1.5	1.1*	1.2	1.1*
Indifference to surroundings	2.0	1.8	1.3	1.3†	1.7	1.4
Unsociability	2.5	2.3	1.3	1.4*	1.9	1.6*
Dizziness[b]	1.7	1.4	1.6	1.2	1.3	1.7
CGRS						
Total score	14.3	13.4	13.1	12.8	14.0	13.3
Orientation	1.3	1.2	1.2	1.1†	1.2	1.2
Cooperation	1.5	1.5	1.3	1.1*	1.5	1.2†
Sleep	1.9	1.3	1.6	1.1†	2.1	1.7
BPRS						
Total score	25.9	25.6	24.0	22.8†	25.0	24.0
Factors						
Hostile suspiciousness	1.2	1.3	1.2	1.1*	1.2	1.1**
Withdrawal retardation	1.4	1.5	1.3	1.2†	1.4	1.4
Thinking disturbance	1.2	1.4	1.1	1.1	1.2	1.2
Anxious depression	2.0	1.6	1.6	1.6	1.8	1.6

[a] Analysis of variance carried out on this measurement; unadjusted final mean scores shown

[b] Significant ($P < 0.001$) heterogeneity of co-variance regression coefficients; unadjusted final mean scores shown

Significantly different from adjusted final mean score for placebo-treated patients (analysis of co-variance) † $P < 0.10$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 3. Initial and adjusted final mean scores for Wechsler Adult Intelligence and Memory Scale and the Rey figure test

	Placebo		Piracetam (2.4 g)		Piracetam (4.8 g)	
	Week 0	Week 12	Week 0	Week 12	Week 0	Week 12
Wechsler intelligence						
Verbal IQ	94.8	95.2	91.6	96.7	96.0	93.7
Performance IQ	81.7	80.2	77.8	85.1*	78.2	82.6
Full IQ	87.0	86.3	82.3	90.3*	85.9	86.4
Wechsler memory						
Memory quotient	86.2	87.2	81.1	92.8*	91.1	88.2
Rey figure test						
Immediate memory[a]	7.0	6.2	5.4	8.1	5.6	8.5
Short-term memory[b]	7.4	6.8	5.0	8.1	4.8	8.1

* Significantly ($P < 0.05$) different from adjusted final mean score for placebo-treated patients (analysis of co-variance)

[a] One patient treated with placebo and two patients treated with piracetam 4.8 g would not cooperate for this test

[b] Five patients treated with placebo, one treated with piracetam (2.4 g) and three treated with piracetam (4.8 g) would not cooperate for this test

the most improved characteristic in 54% of patients, socialization in 34% and orientation in 12%. After the trial had terminated the nurse reported no carry-over or withdrawal effects, the patients returning to their original condition within 1 month.

On the SCAG and Crichton geriatric rating scales (Table 2), piracetam appeared to be superior to placebo and the lower dose (2.4 g/day) produced greater improvement than the higher dose (4.8 g/day). The items that were improved by piracetam treatment were motivation-initiative, indifference to surroundings, unsociability, orientation and cooperation. Piracetam did, however, cause some sleep disturbances, and the higher dose produced mild dizziness in some patients (Table 2). Analysis of the scores at weeks 4 and 8 showed that the response to 4.8 g/day piracetam occurred earlier than that to 2.4 g/day. Piracetam, at 4.8 g/day, was superior ($P < 0.05$) to placebo at week 4 with respect to disorientation and overall impression and, at week 8, with respect to uncooperativeness and impairment of recent memory on the SCAG. However, differences favouring the higher dose of piracetam tended to diminish at week 12. In contrast, the significant ($P < 0.05$) differences favouring 2.4 g/day piracetam over placebo did not appear until week 8. The initial scores for items on the SCAG and Crichton scales were low, and the reason for this is that the patients did not have severe symptoms of senility; it means, however, that these scales did not have a high degree of sensitivity for detecting behavioural changes.

Piracetam was also superior to placebo at week 12 for the BPRS total score (2.4 g/day, $P < 0.10$), the hostile-suspiciousness factor (2.4 and 4.8 g/day, $P < 0.05$) and the withdrawal-retardation factor (2.4 g/day, $P < 0.10$). The psychiatric illness of patients was considered to be in remission at the time of the study, so these changes were necessarily small. The BPRS assessment completed by the psychiatrist was therefore consistent with the ratings of the nurse.

Wechsler adult intelligence and memory scales. The mean scores for the Wechsler Adult Intelligence and Memory Scales are shown in Table 3. Patients treated with 2.4 g/day piracetam showed a significant ($P < 0.05$) improvement in mean IQ and memory scores compared to those treated with placebo; in contrast, those treated with 4.8 g/day showed no such improvement. The significant difference for the IQ tests occurred on the performance rather than the verbal subtests. Among the memory tests, associate learning was the most improved. It may be noted (Table 3) that, by chance, the patients treated with 2.4 g/day piracetam began the trial with lower mean scores for IQ and memory than the other treatment groups. We therefore investigated the relationship between initial scores and subsequent improvement. For patients treated with 2.4 g/day the Spearman rank-correlation coefficient between initial IQ score and improvement was -0.54 ($P < 0.01$) and that between initial MQ and improvement was -0.43 ($P < 0.05$), indicating that greater improvement tended to be made by patients with lower initial scores. The corresponding rank-correlation coefficients for patients who received 4.8 g/day piracetam were -0.10 ($P > 0.10$) and -0.45 ($P < 0.05$) respectively, suggesting a similar trend at least as regards the memory test.

Rey figure test. The mean scores for the Rey figure test of immediate and short-term memory are shown in Table 3. There were no significant ($P > 0.10$) differences between piracetam and placebo on these tests, but directional trends favour piracetam treatment and are consistent with results on the other tests. The greater degree of difficulty of this test resulted in lack of cooperation in three patients for the immediate memory test and, in nine patients for the short-term memory test (Table 3). This reduced the power of the Rey tests for detecting statistically significant treatment differences.

Extrapyramidal symptoms. The examination by the neurologist using the Extrapyramidal Symptom Rating Scale revealed that 70% of the patients had parkinsonian-like symptoms, according to the criterion of presence of at least one symptom of moderate intensity, and that 52% showed signs of tardive dyskinesia, according to the research criteria suggested by Schooler and Kane (1982) which require presence of at least 'moderate' dyskinetic movements in one or more body areas or at least 'mild' dyskinetic movements in two or more body areas. Piracetam had no significant ($P > 0.10$) effect on mean total scores for parkinsonism or tardive dyskinesia, but patients treated with 2.4 g/day piracetam showed a significant ($P < 0.05$) decrease in expressive automatic parkinsonian movements compared to the placebo group and those treated with piracetam 4.8 g/day showed a

significant ($P < 0.05$) decrease in tardive dyskinetic movements of the jaw compared to placebo-treated patients. There was no evidence of piracetam exacerbating or inducing extrapyramidal symptoms.

Side effects. The only side effect of piracetam observed by the nurse, other than the insomnia and mild dizziness that were already noted, was overstimulation. This occurred to a moderate degree in one patient treated with 4.8 g/day and to a mild degree in one patient treated with 2.4 g/day and another treated with 4.8 g/day. A marked increase in sexual activity was also noted in one patient treated at each dose level. In addition, a patient with a history of cyclical psychotic episodes became psychotic during treatment with 4.8 g/day piracetam: the episode appeared similar to previous ones but with superimposed hypersexuality. This patient completed the study but, as the relationship of the psychosis to study medication was doubtful, it was decided to replace her before the code was broken. Apart from these few cases, our impression was that piracetam was well tolerated by most subjects. All side effects disappeared upon discontinuation of medication.

Hematocrit and hemoglobin. In patients treated with piracetam there was a small (less than 2%) but, in comparison with the placebo-treated group, statistically significant ($P < 0.05$) decline in mean hematocrit and hemoglobin values. The means $\pm$ SD (in parentheses) of the hematocrit (%) at weeks 0 and 12 respectively were placebo 43.5 (4.1) and 44.7 (4.5), 2.4 g piracetam 42.2 (3.4) and 41.8 (3.8) and 4.8 g piracetam 42.9 (3.6) and 42.1 (3.4). The corresponding values for hemoglobin (g/100 ml) were placebo 14.3 (1.5) and 14.7 (1.6), 2.4 g piracetam 13.8 (1.3) and 13.6 (1.4) and 4.8 g piracetam 14.0 (1.3) and 14.0 (1.3).

Plasma prolactin levels. Analysis of co-variance revealed no significant effect of piracetam on plasma prolactin.

Discussion

Our findings are that 12 weeks of piracetam treatment in elderly psychiatric patients with mild diffuse cerebral impairment produced mild to moderate improvement in both behavioural and cognitive variables. The nurse considered alertness to be the most improved characteristic in the majority (54%) of patients, followed by socialization (34%) and orientation (12%). Her ratings on the SCAG and Crichton geriatric scales also indicate increased motivation, initiative and cooperation and reduced indifference to surroundings. The psychiatrist's evaluations on the BPRS corroborate these findings.

Results on the Wechsler Adult Intelligence and Memory Scales reveal that only the group receiving the lower dose of piracetam (2.4 g/day) improved relative to the placebo group. Also, greater improvement tended to be seen in those with lower initial IQ and MQ, as evidenced by the negative rank-correlation coefficients ($r = 0.54$ and -0.43 respectively) between initial score and improvement. This suggests that piracetam tended to have a greater effect on the cognitive functioning of those with greater initial impairment. By chance, the group treated with 2.4 g/day piracetam began the trial with lower mean scores on the intelligence and memory tests than those treated with 4.8 g/day piracetam, and this may explain why a positive effect was seen only in those treated with the lower dose. Another possibility is that the higher dose of piracetam may have had an effect on these tests earlier in the treatment, as the behavioural ratings would tend to suggest, but that the effect diminished at week 12, possibly as a result of overstimulation. Improvement on the Wechsler Adult Intelligence Scale was on performance IQ rather than verbal IQ, and this may also be related to the tendency for patients to have lower scores on the performance than the verbal subtests. During aging, performance IQ usually declines to a greater extent than verbal IQ and consequently may be more amenable to drug treatment. Similarly, memory tends to show a greater decline in the elderly than other cognitive functions and also appeared to respond well to piracetam. The finding that improvement was most pronounced on associate learning is consistent with predictions from animal studies (Giurgea 1973).

The time course of the effects on the behavioural rating scales reveals that the high dose of piracetam tended to have a more rapid effect than the low dose, producing significant improvement relative to placebo at weeks 4 and 8, which then diminished at week 12. The effect of the lower dose, on the other hand, was more gradual and significant differences compared to placebo did not appear until week 8 and were at their peak when the trial ended at week 12. The high dose of piracetam produced mild dizziness, sleep disturbances and overstimulation in some patients, and this may have interfered with its therapeutic effect at week 12.

Previous studies of piracetam in geriatric patients with impaired cognitive functioning show inconsistent results, some reporting a positive effect (Stegink 1972; Kretschmar and Kretschmar 1976; Dorn 1978) and others little or none (Abuzzahab et al. 1977; Dencker and Lindberg 1977; Gustafson et al. 1978; Lloyd-Evans et al. 1979; Reisberg et al. 1982). There are various factors that could account for these discrepancies etc.: (1) differences in the type of patient tested and the degree of cognitive or cerebral impairment; (2) differences in measurement criteria; (3) differences in the dosage of piracetam used; (4) differences in the duration of the study; (5) differences in the number of patients included, which affects the statistical power of the study to detect significant treatment differences. The results of our own study suggest that a dose of 4.8 g/day may be too high for prolonged treatment of some elderly patients and that a flexible dosage regimen would be advantageous, yet all studies to date appear to have used a fixed dose. With 20 subjects per group, 2.4 g/day piracetam did not produce a significant difference compared to the control group until week 8, whereas 4.8 g/day had a more rapid effect. This may explain why studies of shorter duration (4–8 weeks) which have used the low dose (2.4 g/day) found no or little significant effect (Abuzzahab et al. 1977; Kretschmar and Kretschmar 1976; Dencker and Lindberg 1977), but those using 4.8 g/day did find an effect (Kretschmar and Kretschmar 1976; Dorn 1978). However, Reisberg et al. (1982), in a placebo-controlled cross-over study, reported that 4 weeks of treatment with 7.2 g/day piracetam produced a significant ($P < 0.05$) improvement in only three of 43 psychometric measures. Using a sample size of 196 patients, Stegink (1972) did, however, find a significant effect of 2.4 g/day piracetam in an 8-week placebo-controlled study. Gustafson et al. (1978), on the other hand, found no effect of piracetam with 4.8 g/day or 9.6 g/day, but eight subjects per group was probably insufficient to detect anything but a very large difference. The difficulties of assessing cognitive and be-

haviourial changes in geriatric patients with standard measuring instruments were discussed by Abuzzahab et al. (1977) in their study of piracetam. Likewise, we found that the Crichton and Sandoz geriatric scales also lacked sensitivity for measuring behavioural changes in these patients, and that the Rey figure memory tests were too difficult for some patients to be able to cooperate. As in the study of Abuzzahab et al. (1977), the highly significant effect of piracetam on the CGI was poorly reproduced on the other behavioural rating scales.

Recently, the combination of piracetam with acetylcholine precursors has been investigated (Bartus 1981). In behavioural retention tests in aged rats the combination of piracetam and choline produced a much greater effect than piracetam alone, and repeated administration over 1 week was superior to acute administration (Bartus et al. 1981). A clinical trial of the combination of piracetam (4.8 g/day) and choline (9 g/day) in ten patients with senile dementia of the Alzheimer's type found small nonsignificant improvements in cognitive measures for the entire group and clinical improvement in three patients who had significantly greater increases in both plasma and erythrocyte choline levels compared to non-responders (Friedman et al. 1981; Ferris et al. 1982): responders were all subjects with moderate rather than mild impairment, which is consistent with the findings of the present study. The same group of authors failed to find such marked clinical improvement in previous studies with piracetam treatment alone (Reisberg et al. 1982) or choline treatment alone.

Piracetam had no effect on the psychiatric illness, either schizophrenia (57%) or affective disorder (40%), of our patients, although this was considered to be in remission at the time of the study. Furthermore, piracetam did not appear to interfere with the maintenance psychotropic treatment received by the patients. Dimond et al. (1979) and Pryce and Gray (1978) also found no effect of piracetam on schizophrenia.

Piracetam did not exacerbate pre-existing parkinsonian symptoms or tardive dyskinesia induced by neuroleptic drug treatment. In some patients piracetam appeared to alleviate the parkinsonian facial mask, but this may be due to increased alertness rather than true antiparkinsonian action. Even though it has generally been accepted that piracetam has no GABA activity, a recent study found that piracetam potentiated haloperidol-induced catalepsy (Balsara et al. 1980). This suggests that piracetam at high doses might mask tardive dyskinesia by an increased inhibitory effect of GABA neurons on nigrostriatal dopamine neurons.

Although its mechanism of action is not fully understood, piracetam appears to act as a cell-membrane stabilizer and to have little effect under normal physiological conditions (Nickolson and Wolthuis 1976). However, its effects are significant in conditions which modify cell-membrane equilibrium such as ischemia, anoxia and intoxication. Piracetam has been shown to enhance ^{32}P incorporation into brain phospholipids (Rochus and Reuse 1972; Woelk 1979) and, more recently, to decrease the non-esterified free fatty acid brain tissue response to stress (Sklenovsky and Chmela 1980). Thus by activating re-synthesis of membrane phospholipids it may enhance membrane stability and resistance to adverse cellular effects such as anoxia. It is unlikely that its effect on the CNS results from its action on the red blood cell or platelets because of the excitation seen in some patients. Another argument against an indirect effect is that, in a power-spectral analysis of EEG changes, piracetam was reported to decrease slow frequencies and increase both α and β activity (Bente et al. 1978; Volavka et al. 1981). These changes suggest an increase in alertness, which is compatible with our results. Itil et al. (1982) found 1.2 g piracetam to produce a similar, but not identical, computer EEG profile to that of 15 mg dextroamphetamine, and classified both drugs as 'vigilance enhancing'. In our study no effect of piracetam was found on prolactin secretion. This is in accord with the finding that piracetam failed to antagonize apomorphine stereotypy in rats, ruling out the possibility of its possessing dopamine receptor blocking activity (Balsera et al. 1980). Increased prolactin secretion occurred in rats at a dose of 5 g/kg piracetam, but not at a dose of 0.5 g/kg (Nyback et al. 1979).

Thus our results suggest that piracetam had a beneficial effect in remitted elderly psychiatric patients with cerebral impairment by improving alertness, socialization and cognitive functioning. On the cognitive measures (IQ and memory) piracetam appeared to be of greater value in patients with greater impairment, although none of the patients included in our trial were severely senile. The results also suggest that a dose of 4.8 g/day produced more rapid improvement than 2.4 g/day, but that this dose may need to be decreased in some patients to avoid overstimulation, sleep disturbances and dizziness, which could interfere with the drug's therapeutic effect. It would appear that long-term studies of piracetam of more than 3-month duration in the treatment of elderly patients with cerebral impairment are warranted.

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