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Drug Therapy and Memory Training Programs: A Double-Blind Randomized Trial of General Practice Patients With Age-Associated Memory Impairment

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ABSTRACT. A double-blind randomized trial was performed involving 162 patients with age-associated memory impairment (AAMI) selected and followed by their general practitioners. Two intervention methods—a drug and a cognitive therapy—were assessed in combination. Three randomized parallel groups of 54 patients each, aged 55 years and over, were followed and treated for 3 months. After a placebo wash-out period of 10 days, one group received 2.4 g of piracetam, another group, 4.8g, and the third, a placebo. A total of 135 patients, 45 in each group, completed the study. Combined therapy was most effective in patients whose baseline performance on memory tests was lowest. The best results were observed with 4.8 g of piracetam, especially when training sessions began after 6 weeks of drug treatment. This result was confirmed by the global impression of the principal investigator.

Over the last decade, much research interest has focused on the aging process, normal forgetfulness, and the amnesic syndrome (Craik, 1977; Flicker et al., 1985; Fozard, 1985; Kral, 1962, 1966; Perlmutter & Mitchell, 1982; Poon, 1985; Poon et al., 1986). Therapeutic approaches to memory have been discussed in many studies and publications (Ferris et al., 1986; Flicker et al., 1986; Poon et al., 1978; Yesavage, 1985). In interpreting the results of these studies, one must distinguish between two kinds of therapeutic intervention. First, there is medical treatment, which is assumed to have a direct somatic impact on the cerebral function. Second, there is a memory training program (MTP), whose influence on memory activity and cognitive functioning is more indirect.

Our team has already performed several clinical trials during the last 4 years to determine when and how an interaction occurs between these two types of treatment (Israel et al., 1987a, 1987b, 1989a, 1989b). During the course of these studies, more than 400 patients have been examined and have undergone follow-

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up evaluation. These studies revealed that drugs and MTP had different effects and suggested that it would be interesting to experiment with a combination of these two therapies. The results reported here summarize the findings of a recent randomized double-blind placebo-controlled trial assessing the *combined effects* of drug treatment and memory training.

The drug used in this study is piracetam, a prototypical nootropic agent, i.e., a psychotropic drug that increases the efficiency of brain functions involved in the cognitive process without being sedative or psychostimulant. In the literature, different studies on the effects of piracetam report that it has a selective action on memory functioning and learning, cortical wakefulness, and behavior (Giurgea, 1976, 1979, 1986).

MTP develops basic mechanisms that underlie the memorization process and recall strategies: attention, association techniques, information processing, language, and spatial and temporal references. This method is based on the "learning transfer principle"; it postulates that such mechanisms, when developed by appropriate exercises, are transferred and reused in memory activities of everyday life. The efficacy of this kind of intervention has been the subject of much of our previous research (Israel, 1982, 1985, 1987, 1988b, 1989; Israel & Dejean de la Batie, 1985; Israel et al., 1982; Neyroud et al., 1988).

Experiments on animal models of induced amnesia have demonstrated piracetam's protective effect against hypoxia and various "aggressions" to the brain (Giurgea et al., 1971). These effects have been measured by their enhancement of retention and learning abilities (Bartus et al., 1981; Giurgea & Mouravieff-Lesuisse, 1972). More recent studies on age-related memory deficits in humans have led to similar results (Abuzzahab et al., 1977; Dorn, 1978; Ferris et al., 1982; Herrmann & Kern, 1987).

In describing their daily life activities to their general practitioners, the elderly complain most often of forgetfulness, which can be a distressing factor for them (Popkin et al., 1982). Forgetfulness can have many causes: disappearance of a trace, lack of consolidation, interference, or retrieval difficulties. Thus, it may be linked to the lability of the "mnesic trace" as well as to recall strategies. If piracetam has an effect on the underlying structures responsible for the maintenance of the "mnesic trace," and if an MTP were more specifically aimed at developing recall strategies, combined therapy should improve the global therapeutic effects. Thus, our basic hypothesis was that combined therapy would increase benefits for the patients. Accordingly, and considering the rationale of this study, the primary criterion we used to assess efficacy was forgetfulness.

PATIENTS AND METHOD

Study Population

Selection was based upon the criteria for age-associated memory impairment (AAMI). The term *AAMI*, adopted by the National Institute of Mental Health

Work Group (Crook et al., 1986), is applied to healthy persons over 50 years old who have experienced the onset of memory loss after early adulthood, but who are neither demented nor depressed. Although it has not yet gained international acceptance as a specific clinical entity, AAMI describes the age-linked memory decline of older patients in contrast to that of young adults (Blackford & La Rue, 1989; Crook et al., 1986).

In our study, the patients had consulted their general practitioner because of memory problems that appeared gradually and were characterized by sporadic occurrence, lack of etiologic specificity, and isolation from any other cognitive context. Twenty-seven medical doctors each recruited and followed six patients. In total, 162 patients were included. As the AAMI criteria require, performances on psychometric tests were at least 1 *SD* less than the mean for young adults on Israel's test battery (Israel, 1988a; Israel et al., 1980). Because of the existing norms of this test battery, the patients selected were aged 55 or more years. All patients were aware of the purpose and methods of the study; written informed consent was obtained from each patient before inclusion. Patients with any of the following symptoms were excluded: mental deterioration or early dementia, as determined by a score equal to or less than 26 on Folstein's Mini-Mental State Exam (Folstein et al., 1975); depression, as determined by a score above 7 on Yesavage's Geriatric Depression Scale (Brink et al., 1982; Sheikh & Yesavage, 1986); alcoholism; and any organic or neurological disease likely to interfere with the clinical manifestations of the drug or its bioavailability (e.g., renal or hepatic failure). Treatment with the following drugs was not permitted during the study: antidepressants, neuroleptics, anticholinergics, levodopa, hypoglycemic sulphonamides, antiepileptics, lithium, centrally acting antihypertensive agents, long-acting benzodiazepines, as well as cerebral metabolic enhancers, oxygenators, and vasodilators.

The study included 162 patients (Table 1), 26 men and 136 women, with a mean age of 68.69 ± 7.8 years. The percentage of those who had not completed high school was 39.5%; 60.5% had at least a high-school diploma. They were characterized by an isolated memory impairment and displayed no signs of depression, as indicated by a mean score of 3.07 ± 2.68 (range 0-7) on Yesavage's Geriatric Depression Scale (Table 2). Their medical records showed 65 (40.5%) were free of any disease; 83 (51%) had one concurrent disease (mostly hypertension, arthritis, gastrointestinal disease, or angina pectoris); and 14 (8.5%) suffered from two concurrent diseases.

Study Design

The main purpose of the clinical trial was to compare the efficacy of MTP, when combined with piracetam at two different doses (2.4 g/day and 4.8 g/day) and when given to a group receiving a placebo medication. Therefore, three randomized parallel groups of 54 patients each were followed for 3 months (Figure 1). After a placebo wash-out period of 10 days, one group began receiving 2.4 g of piracetam, the second group 4.8 g, and the third a placebo. Piracetam and

TABLE 1. Population Sample: Sociocultural Parameters

	Placebo $N = 54$	Piracetam 2.4 g $N = 54$	Piracetam 4.8 g $N = 54$	Total $N = 162$	Percentage
Sex					
Number of males	6	6	14	26	16.0%
Number of females	48	48	40	136	84.0%
Educational level					
Grade school	26	17	21	64	39.5%
High school diploma or beyond	28	37	33	98	60.5%
Family status					
Living alone	21	28	20	69	42.5%
Not living alone	33	26	34	93	57.5%
Age					
Mean	68.25	68.57	69.07	68.69	
SD	±7.01	±8.17	±7.66	±7.80	
Number of subjects					
≤60	8	10	8	26	16.0%
61–65	11	10	11	32	19.8%
66–70	15	16	12	43	26.5%
71–75	12	7	11	30	18.5%
±76	8	11	12	31	19.2%

placebo were identical in appearance and taste. The 90-minute MTP sessions were conducted once a week at the University Geriatric Center, in Grenoble, France, for groups of 8 to 10 participants. To determine the best therapeutic sequence, we randomly subdivided each main group into two subgroups, one of which started the 6-week (D0 - D45) MTP immediately; the second group began the training 6 weeks later (D45 - D90). Thus, for the group taking 2.4 g of piracetam, half followed MTP in addition to drug treatment during the first half of the trial period, and the other half of the group started MTP in the second half of drug therapy. The same procedure was used for the groups treated with 4.8 g and with the placebo.

Follow-Up Assessment

Forgetfulness, as the principal target variable for measuring outcome, was assessed by free recall memory tests. So that a learning retest effect might be avoided, psychometric performances were assessed at D0 and D90 only by Israel's parallel forms of Memory Battery for older people (Israel, 1988a), whereas Rey's Word Repetition Test (Israel & Ohlmann, 1980; Rey, 1970) was administered at D0, D45, and D90. For exploratory purposes, patients' complaints were assessed by the Memory Functioning Questionnaire (MFQ) devised by Zelinski and colleagues (Gilewski & Zelinski, 1986; Zelinski et al., 1980), at the D0 baseline testing, at D45, and at D90. Subjects rated their

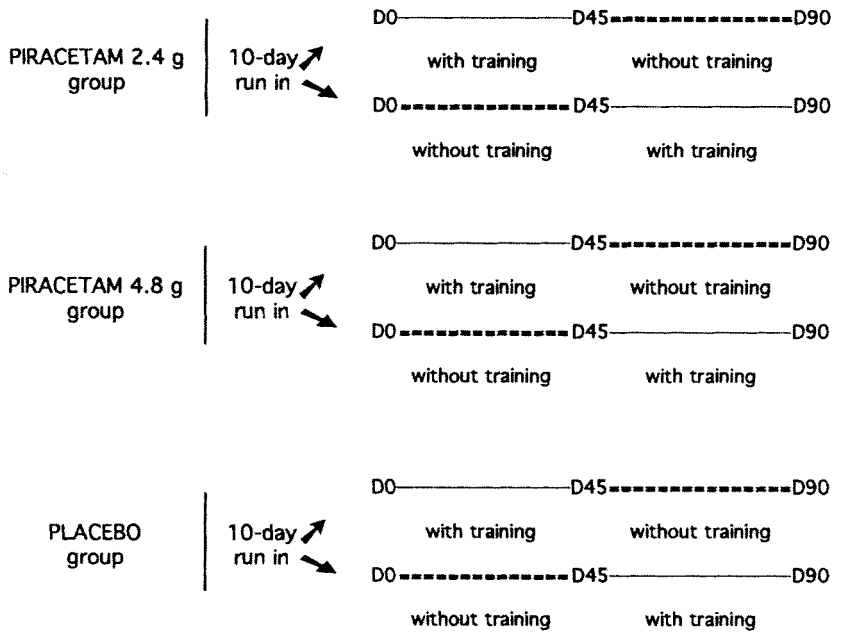


Figure 1. Study design: three randomized groups (piracetam 2.4g, piracetam 4.8g, placebo) randomly subdivided into six subgroups according to memory training sequence.

memory abilities on a 7-point Likert scale, with higher values assigned to more positive self-appraisal. Cognitive difficulties experienced in situations of everyday life were assessed by Mac Nair and Kahn's (1983) Cognitive Difficulties Scale (CDS) at D45 and D90. Finally, we obtained additional important information on the therapy's efficacy from the global evaluation, a 4-point rating scale scored by the principal investigator, the psychologist, at the final examination.

Statistical Analysis

Treatment groups were compared by a chi-square test for qualitative variables and by mean comparisons for quantitative variables. Global evaluations by the main investigator were also analyzed by a chi-square test. The results of psychometric tests were analyzed using the "repeated measurements" design analysis of variance (ANOVA) with the statistical software BMDP. In this method, the score of a given test is entered for each individual and for each repetition, e.g., the administration at baseline and at the study's end. We may thus investigate three effects:

- A "group" effect that tests whether there are significant differences between groups (pooling the two repetitions).
- A "time" effect that tests whether there are significant differences between the two repetitions (pooling three groups).
- A "time × group" effect that tests whether the evolution is significantly different for any group.

The CDS and MFQ scales were submitted to a main component analysis to detect factorial structures and then to paired ANOVA for the raw scores. We determined that the most relevant variable for identifying those who responded to drug treatment was the score on free recall tests. Clinically relevant values of improvement were determined before the study's start (Israel, 1988a) from normative data for the immediate and delayed recall tests (mean of delta ≥ 2.913; standard deviation of delta = 0.18). A comparison of percentages was performed to evaluate the number of improved patients in each group.

RESULTS

The homogeneity of the groups described in Tables 1 and 2 was checked at baseline for sociocultural (age, sex, educational background, marital status) and clinical (body weight, height, blood pressure, heart rate) parameters and for scores on rating scales. We found no statistical difference.

Withdrawals and Adverse Events

Twenty-seven patients withdrew from the study (9 patients per group, 16.6%): 10 patients during the first half, and 17 during the second half. At the end of the study, each group comprised 45 patients. Of the 27 withdrawals, 13 were related to side effects (7 on placebo and 6 on piracetam) and 14 for personal reasons. Neither the percentage nor the nature of the adverse reaction varied among the three groups. The most frequently reported adverse drug reactions were gastrointestinal; the next most common was dizziness (Table 3).

Performance on Psychometric Tests

Table 4 shows the results of the psychometric tests at baseline and at the study's end for the three groups. To determine if there were any trends regarding evolution of the different groups, we performed a two-way ANOVA with repeated measurement. The efficacy of the drug (time × group factor) and the effect of time (time factor) were assessed. For the time factor, statistically significant differences ($p<.01$–$p<.0001$) were observed for all variables, except the first administration of Rey's test. For the "time × group" factor, global and immediate free recall scores were statistically significant ($p<.01$ and $p<.002$, respectively). Immediate free recall remains significant when applying the Bonferroni correction to adjust the $\propto$ for correction of chance ($\propto = .05$, $\propto^* = .008$). Both piracetam groups showed greater improvements than the placebo group (Figure 2a). To consider the memory training sequence effect, an ANOVA with repeated measurements on the six subgroups was also performed. There was no significant difference between the two therapeutic sequences for the group taking the placebo and for the group taking 2.4 g of piracetam. Only the 4.8-g subgroup with training during the second period showed a greater trend of improvement than did the subgroup trained during the first half (Figure 2b).

TABLE 2. Homogeneity of the Population Sample for Clinical and Psychological Parameters: Means and Standard Deviations at Baseline

	Placebo $N = 54$		Piracetam 2.4 g $N = 54$		Piracetam 4.8 g $N = 54$		Total $N = 162$	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Clinical parameters								
Weight (kilos)	61.82	11.08	62.21	10.94	63.39	11.44	62.48	11.10
Height (cms)	159.53	6.67	161.45	7.11	164.77	7.14	166.88	7.26
Blood pressure syst.	140.7	13.30	133.58	16.77	137.31	14.16	137.23	15.0
Blood pressure diast.	79.63	6.9	78.30	10.87	77.88	8.0	78.62	8.75
Pulse rate	73.58	9.86	73.30	8.50	74.12	8.23	73.66	8.84
Psychological parameters:								
Scores on rating scales								
Yesavage Depression Scale	2.91	2.06	2.78	2.69	3.53	3.17	3.07	2.68
Mac Nair global score	37.22	12.54	36.50	10.05	41.46	12.70	38.41	12.00

The learning effect on Rey's test between D0 and D90 was measured on the R2/R1 ratio, i.e., recall after fifth repetition versus immediate recall. The differences, however, were not significant (Table 4).

We also performed a two-by-two comparison between treatment groups for the free recall variables. These comparisons demonstrated:

- a significant difference for global ($F_{1,88} = 9.80, p < .002$), immediate ($F_{1,88} = 13.61, p < .0004$), and delayed recall ($F_{1,88} = 4.23, p < .04$) when comparing the group taking 4.8 g piracetam to that receiving placebo.
- a significant difference only for immediate recall ($F_{1,88} = 4.63, p < .03$) when the 2.4-g piracetam group was compared to that receiving placebo.
- no significant difference between the two groups receiving piracetam (2.4g and 4.8g).

TABLE 3. Reported Adverse Drug Side Effects

Side Effects	Placebo $N = 54$	Piracetam 2.4 g $N = 54$	Piracetam 4.8 g $N = 54$
Gastrointestinal effects	3	1	2
Nervousness	1	—	1
Sleep disturbances	—	—	3
Paresthesia	2	—	—
Weight gain	—	1	—
Dizziness	1	3	1
Lightheadedness	—	—	2
Edema	—	2	—
Total	7	7	9
Withdrawals related to side effects	7	4	2

Patient Complaints and Cognitive Difficulties in Activities of Daily Living

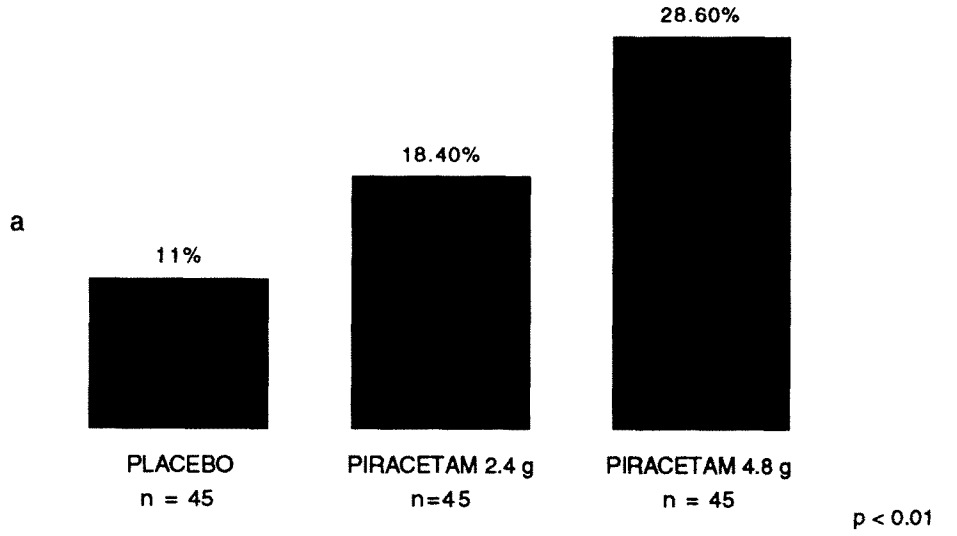
ANOVA on the MFQ failed to demonstrate any effect related to any aspect of the treatments tested (medication and sequence of training). For the CDS, we took into account the factorial structure after varimax rotation for the 135 patients who completed the study (Table 5). Four main components explained 55.5% of the variance: the first component measures data acquisition and the capacity to overcome interference; the second, third, and fourth components evaluate recall strategies related to the abilities to organize, retrieve, and process information. A significant difference between results at D0 and D90 was observed in all groups, but no significant difference among the three treatment groups was seen. The items measuring attention, immediate memory, and sensitivity to interferences (2, 5, 6, 8, 9, 12, 15) indicate improvement in data acquisition. Items 11, 3, and 1 ("check if door is locked or stove is turned off," "need a written list when doing errands to avoid forgetting things," "putting things down [keys, glasses, wallet] and having trouble finding them," respectively) suggest a lesser degree of forgetfulness. These two categories of items correspond respectively to the first (acquisition) and third (retrieval) components of the factorial analysis.

No correlation between the raw scores of psychometric tests, on the one hand, and the MFQ items and the CDS factorial scores, on the other, could be demonstrated. These findings are consistent with the conclusions of other investigators (Lott & Scogin, 1983; Popkin et al., 1982).

TABLE 4. Comparative Evolution of the Psychometric Test Results in the Three Groups: Means and Standard Deviations at Baseline (D0) and Final (D90)

		Placebo $N = 45$		Piracetam 2.4 g $N = 45$		Piracetam 4.8 g $N = 45$		F (ANOVA)		Significance	
		D0	D90	D0	D90	D0	D90	Time	Time x group	Time	Time x group
Matched pictures	*M*	11.51	14.20	11.33	14.06	10.13	12.40	35.42	0.10	$p < .001$*	*NS*
	SD	4.1	3.1	5.1	3.0	5.1	4.3				
Immediate recall	*M*	12.71	13.80	11.77	14.00	10.46	13.62	87.74	6.68	$p < .001$*	$p < .002$*
	SD	2.8	2.3	2.9	2.6	3.1	2.3				
Delayed recall	*M*	12.11	13.75	11.77	13.88	10.60	13.44	83.97	2.10	$p < .001$*	*NS*
	SD	3.1	2.3	3.0	2.1	3.3	2.6				
Global recall	*M*	12.41	13.77	11.77	13.94	10.53	13.53	103.19	4.80	$p < .001$*	$p < .01$
	SD	2.7	2.2	2.8	2.2	3.1	2.3				
Rey 1st repetition	*M*	5.26	5.51	5.42	5.52	5.31	5.15	0.10	0.64	*NS*	*NS*
	SD	1.2	1.4	1.5	1.4	1.2	1.5				
Rey 2/Rey 1	*M*	2.35	2.45	2.19	2.34	2.18	2.4	5.78	0.49	$p < .01$	*NS*
	SD	0.6	0.6	0.5	0.5	0.5	0.8				

NS = nonsignificant
* = significant after Bonferroni correction



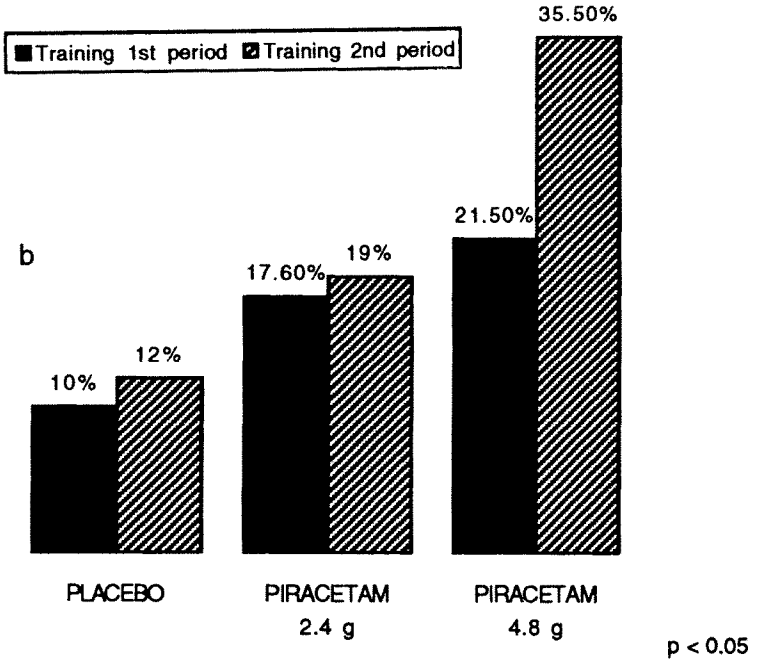


Figure 2. Evaluation of forgetfulness through global recall expressed on percentage of improvement as determined by ratio: delta/baseline. a. Results for the three treatment groups; b. Results for the six subgroups.

TABLE 5. Factorial Analysis in Principal Components (Mac Nair Rating Scale; N = 135, Total Explained Variance: 55.5%)

Items	Factors 1	2	3	4
1	–0.00275	0.01791	0.55819	0.56299
2*	0.59824	0.02425	–0.00480	0.37741
3	0.07550	0.39574	0.55460	–0.01653
4	0.33040	–0.10409	0.61011	0.25794
5*	0.65516	0.33013	0.20510	0.11700
6*	0.64002	0.26144	0.22181	0.06578
7	0.33039	0.19468	0.70283	–0.00544
8*	0.67947	–0.04035	0.16792	0.20772
9*	0.60038	0.26655	0.37822	0.05944
10	0.34744	0.19574	0.14675	0.57995
11	0.11160	0.26630	0.51484	0.20999
12*	0.76248	0.24402	0.12285	–0.02269
13	0.43115	0.47876	0.23748	0.16434
14	0.04337	0.15906	0.06557	0.72912
15*	0.61579	0.39605	0.12342	0.21117
16	0.28359	0.30446	0.12468	0.60709
17	0.42339	0.58164	0.11255	0.17220
18	–0.01043	0.73957	0.04342	0.23922
19	0.26479	0.63145	0.24386	0.20952
20	0.31436	0.63972	0.16643	0.02913
% of variance explained for each factor	3.95 35.5%	2.82 25.5%	2.24 20.2%	2.07 18.7%
	Data acquisition	Recall strategies		
	Impression ↓ Attention Ability to overcome interference	Expression Organization	Retrieval	Information processing

*2- When interrupted while reading, I have trouble finding my place again.
5- I find it hard to keep my mind on a task or job.
6- I have trouble describing a program I just watched on television.
8- I forget names of people soon after being introduced.
9- I lose my train of thought as I listen to somebody else.
12- I cannot keep my mind on one thing.
15- I forget right away what people say to me.

Global Evaluation of Treatment Effects

The evaluation by the principal investigator was carried out by blind interviews of the patients at D45 and D90. Results were rated "very good" or "good" when clear-cut improvements were noted; "slight" when the improvement was slight and/or irregular during one phase and no improvement was observed during the other one; and "none" when no improvement or deterioration was seen for either

phase. When "very good" and "good" were pooled together, clear improvements were achieved by 93.5% in the 4.8-g group and 82% in the 2.4-g group versus 22% in the placebo group. Significant differences (chi-square = 58.69, $p < .001$) in the distribution of the results were obtained.

Characteristics of the Responders

Drug responders were identified by free recall, as measured by the psychometric test. We considered as clinically relevant the improvement of patients whose score difference in later tests was equal to or greater than the standard deviation of the mean score at baseline; based on the standard previously established (Israel, 1988a), the score difference should be equal to or greater than 2.91. We identified the patients whose score difference equaled or exceeded this threshold and compared the percentages of such patients in each group: 53.5% of the patients improved in the group taking 4.8 g piracetam, 38% in the group taking 2.4 g, and 22% in the placebo group (chi-square = 9.26, $p < .01$).

To distinguish these responders from the nonresponders, we computed the mean score values of the psychometric tests at D0 for all 135 patients (Table 6). Responders and nonresponders differed essentially in their baseline performances on the memory test. All responders had initially lower scores than the mean of the total population tested for retention and topographic memory. Their scores on tests measuring other cognitive functions were equivalent to those of nonresponders and always higher than their memory performance. Patients whose level of mnemonic performance was initially lower improved more than those with a higher level at baseline. Is this a therapeutic effect, a phenomenon of regression to the mean, or a consequence of the variability among the patients?

TABLE 6. Comparison of Responders and Nonresponders (Figures Indicate Mean Scores of Psychometric Tests at Baseline)

	Whole Population	Nonresponders ($\Delta < 3$) $N = 84$			Responders ($\Delta \geq 3$) $N = 51$		
Memory Tests (Target variables)	$N = 135$	Placebo $N = 35$	2.4 g $N = 28$	4.8 g $N = 21$	Placebo $N = 10$	2.4 g $N = 17$	4.8 g $N = 24$
Matched pictures	10.99	11.84	11.64	10.70	8.20	9.64	9.33
Immediate recall	11.65	12.77	12.24	11.63	10.80	9.82	9.50
Delayed recall	11.49	12.00	12.43	11.83	9.80	9.52	9.45
Global recall	11.57	12.38	12.33	11.73	10.30	9.67	9.47
Rey 2/Rey 1	2.24	2.40	2.22	2.20	2.05	2.27	2.17
Other Tests (Exploratory variables)							
Crossing digits	49.03	50.68	49.00	48.23	49.20	45.58	48.79
Digits symbol	35.91	35.22	36.67	34.00	35.39	35.82	35.33
Field dependency	8.67	8.38	8.62	8.80	8.47	8.47	9.41

DISCUSSION

In discussing the findings of this trial, we limit ourselves to the pragmatic aspects of effectiveness: efficacy of the combined therapy and best therapeutic sequence.

Comparison of results for the three groups for the principal evaluation criterion, which measures efficacy, showed a difference in favor of the groups taking piracetam. Their improvement exceeds that of those in the placebo group. No significant difference, however, appeared between the two piracetam groups. Does this mean that the effectiveness of the two dosages is equivalent? Or are there other reasons for the lack of differences?

The fact that only immediate recall improved for the group receiving 2.4 g of piracetam, whereas immediate, delayed, and global recall improved for the group on 4.8 g, may suggest that the residue of the fixative effects of the two doses is dissimilar. They might, for example, have a different impact on the persistency of the mnemonic trace. In further studies, the effect of piracetam on the duration of retention should be evaluated more precisely for each dose, to verify this hypothesis. Combining the two types of therapy appears beneficial: All subjects showed a global improvement between D0 and D90 on the time factor (Table 4). This result suggests that memory training affected all variables (except Rey's first repetition, which remained stable over time). Because drug treatment improved only free recall tests, we may presume that the training influence is more diffuse, whereas drug impact is more focused on recall performances.

A comparison of the two therapeutic sequences on psychometric tests showed a difference between the two periods only for the group receiving 4.8 g piracetam. Improvement was more significant when training started on D45. The difference was no longer obvious, however, when we considered the percentage of subjects who improved for each of the therapeutic sequences (MTP first period: 52.5%; MTP second period: 54%). Such discrepancies might be due to a sequence effect, or to the patients' variability. Nevertheless, the question remains: Which method of evaluating change is most reliable—assessment by a psychometric variable or by percentage of improved patients?

This trial has proved to be an interesting illustration of the use of AAMI criteria and an original design that includes the participation of general practitioners. The psychotherapeutic relationship developed during the course of MTP appeared essential to its success. To achieve this relationship, the psychologist must work in close collaboration with the physician.

In conclusion, our basic hypothesis was not confirmed as expected. Nonetheless, some positive results of drug treatment, combined with MTPs, were revealed in our population of AAMI patients over 55 years. The best results were observed when patients started MTP after a previous 45-day piracetam treatment at a dose of 4.8 g/day, and in patients presenting an initial mnemonic performance on free recall tests lower than the mean score for their age group. Finally, and most important, this study shows that the patients with AAMI

whom general practitioners routinely encounter in their practices can improve memory performance through combined intervention methods.

REFERENCES

Abuzzahab, F. S., Merwin, G. E., Zimmerman, R. L., & Sherman, M. C. (1977). A double blind investigation of piracetam (Nootropil) vs placebo in geriatric memory. *Pharmakopsychiatry, 10*, 49-56.

Bartus, R. T., Dean, R. L., Scherman, K. A., Friedman, E., & Beer, B. (1981). Profound effects of combining choline and piracetam on memory enhancement and cholinergic function in aged rats. *Neurobiology of Aging, 2*, 105-111.

Blackford, R. C., & La Rue, A. (1989). Criteria for diagnosing age-associated memory impairment: Proposed improvements from the field. *Developmental Neuropsychology, 5*, 295-306.

Brink, T. L., Yesavage, J. A., Lum, O., Heersema, P. H., Adey, M., et al. (1982). Screening tests for geriatric depression. *Clinical Gerontologist, 1*, 37-43.

Craik, F. I. M. (1977). Age differences in human memory. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging* (pp. 384-414). New York: Van Nostrand Reinhold.

Crook, T., Bartus, R. T., Ferris, S. H., Whitehouse, P., Cohen, G. D., et al. (1986). Age-associated memory impairment: Proposed diagnostic criteria and measures of clinical change. Report of a National Institute of Mental Health Work Group. *Developmental Neuropsychology, 2*, 261-276.

Dorn, M. (1978). Piracetam in premature biological aging: A double-blind study following medicamental preselection. *Fortschritte der Therapie, 96*, 1525-1530.

Ferris, S. H., Reisberg, B., Crook, T., Friedman, E., Schneck, M. K., et al. (1982). Pharmacologic treatment of senile dementia: Choline, l-dopa, piracetam, and choline plus piracetam. In S. Corkin, K. L. Davis, J. H. Growdon, E. Usdin, & R. J. Wurtman (Eds.), *Alzheimer's disease: A report of progress in research* (pp.475-481). New York: Raven Press.

Ferris, S. H., Crook, T., Flicker, C., Reisberg, B., & Bartus, R. T. (1986). Assessing cognitive impairment and evaluating treatment effects: Psychometric performance tests. In L. W. Poon, T. Crook, K. L. Davis, C. Eisdorfer, B. J. Gurland, et al. (Eds.), *Handbook for clinical memory assessment of older adults* (pp. 139-148). Washington, DC: American Psychological Association.

Flicker, C., Ferris, S. H., Crook, T., & Bartus, R. T. (1985). Cognitive function in normal aging and early dementia. In J. Traber & W. H. Gispen (Eds.), *Senile dementia of the Alzheimer type* (pp. 2-17). New York: Springer-Verlag.

Flicker, C., Ferris, S. H., Crook, T., Bartus, R. T., & Reisberg, B. (1986). Cognitive decline in advanced age: Future directions for psychometric differentiation of normal and pathological age changes in cognitive function. *Developmental Neuropsychology, 2*, 309-322.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189-198.

Fozard, J. L. (1985). Psychology of aging—Normal and pathological age differences in memory. In J. C. Brocklehurst (Ed.), *Textbook of geriatric medicine and gerontology* (pp. 122-144). Edinburgh: Churchill Livingstone.

Gilewski, M. J., & Zelinski, E. M. (1986). Questionnaire assessment of memory complaints. In L. W. Poon (Ed.), *Handbook for clinical memory assessment of older adults* (pp. 93-107). Washington, DC: American Psychological Association.

Giurgea, C. (1976). Piracetam: Nootropic pharmacology of neurointegrative activity. *Current Developments in Psychopharmacology, 3,* 223-273.

Giurgea, C. (1979). Nootropic and related drugs interacting with the integrative activity of the brain. In J. Obiols, C. Ballus, E. Gonzalez Monclus, & J. Pujol (Eds.), *Biological psychiatry today* (Vol. B-2, pp. 876-881). Amsterdam: Elsevier.

Giurgea, C. (1986). The nootropic concept and the pharmacologic originality of piracetam. *Essentialia, 15,* 1-16.

Giurgea, C., Lefevre, D., Lescrenier, C., & David-Remacle, M. (1971). Pharmacological protection against hypoxia-induced amnesia in rats. *Psychopharmacologia, 20,* 160-168.

Giurgea, C., & Mouravieff-Lesuisse, F. (1972). Multitrial learning facilitation in the rat by piracetam. *Journal of Pharmacology, 3,* 17-30.

Herrmann, W. M., & Kern, U. (1987). Nootropic drugs. Effects and therapeutic efficacy: A phase III study with piracetam as a model. *Nervenartz, 58,* 358-364.

Israel, L. (1982). Means of prevention of mental disability in the elderly through memory stimulation. In World Health Organization, Regional Office for Europe, *Preventing disability in the elderly: Report of a WHO working group at Cologne, November 16-19, 1981* (Reports and Studies 65) (26-28). Copenhagen: World Health Organization.

Israel, L. (1985). Memory and mental stimulation: Assessment in clinical trials. In C. J. Brainerd & V. F. Reyna (Eds.), *Developmental psychology* (pp. 9-17). Amsterdam: Elsevier.

Israel, L. (1987, March 9-10). *Entraînement de la mémoire et/ou "pilule mémoire."* Paper presented at the Gedachtnistraining Gottlieb Duttweiler Institut Symposium, Zurich.

Israel, L. (1988a). *Batterie de fluidité pour les personnes âgées.* Paris: Editions du Centre de Psychologie Appliquée.

Israel, L. (1988b). *Entraîner sa mémoire. Guide à l'intention des moniteurs.* Paris: Editions du Centre de Psychologie Appliquée.

Israel, L. (1989). Memory training program as a reference to the clinical evaluation of drugs in memory disorders. *Archives of Gerontology and Geriatrics* (Suppl. 1), 223-230.

Israel, L., & Dejean de la Batie, M. A. (1985). Mémoire et stimulation mentale. *Gérontologie et Société, 32,* 15-26.

Israel, L., Dell'Accio, E., & Hugonot, R. (1989a). Action combinée du praxiléne et exercices d'entraînement mental sur les troubles de la mémoire de sujets âgées. *Psychologie Médicale, 21,* 1219-1234.

Israel, L., Dell'Accio, E., & Hugonot, R. (1989b). Arcalion 200 et entrainement mental. *Journal de Médecine Pratique, 16* (Suppl.), 19-24.

Israel, L., Dell'Accio, E., Martin, G., & Hugonot, R. (1987a). Extrait de Ginko Biloba 761 et exercices d'entraînement de la mémoire. Evaluation comparative chez les personnes âgées ambulatoires. *Psychologie Médicale, 19,* 1431-1439.

Israel, L., Kozarevic, D., & Orgogozo, J. M. (1987b). Subjective and objective health in aging: Problems of assessment. In S. Govoni & F. Battaini (Eds.), *Modification of cell to cell signals during normal and pathological aging* (pp. 261-285) (NATO ASI Series, Vol. H9). Berlin: Springer-Verlag.

Israel, L., & Ohlmann, T. (1980). Structure factorielle de la mémoire appréciée à travers une batterie d'épreuves psychologiques chez des personnes âgées ambulatoires. *L'Encéphale, 6,* 181-195.

Israel, L., Ohlmann, T., & Chappaz, M. (1980). Batterie psychométrique à l'usage du médecin généraliste pour apprécier les conduites intellectuelles des personnes âgées. *Psychologie Médicale, 12,* 921-938.

Israel, L., Rotrou, J.(de), & Chappaz, M. (1982). Une thérapeutique non médicamenteuse nouvelle: La stimulation de la mémoire chez les personnes âgées. *La Revue de Gériatrie, 7,* 387-390.

Kral, V. A. (1962). Senescent forgetfulness: Benign and malignant. *Journal of Canadian Medical Association, 86,* 257-260.

Kral, V. A. (1966). Memory loss in the aged. *Diseases of the Nervous System, 27* (Suppl. 1), 51-54.

Lott, C. L., & Scogin, F. (1983, November). *Relationship of memory complaint and memory performance.* Paper presented at the meeting of the Gerontological Society of America, San Francisco.

Mac Nair, D. M., & Kahn, R. J. (1983). Self assessment of cognitive deficits. In T. Crook, S. Ferris, & R. Bartus (Eds.), *Assessment in geriatric psychopharmacology* (pp. 137-143). New Canaan, CT: Mark Powley Associates Inc.

Neyroud, J., Israel, L., Raymond, L., & Jeanneret, O. (1988). Randomized trial on memory training in the over 60's. *(Lancet, April, 23)* 932.

Perlmutter, M., & Mitchell, D. B. (1982). The appearance and disappearance of age differences in adult memory. In F. I .M. Craik & S. Trehub (Eds.), *Aging and cognitive processes* (Vol. 8, pp. 127-144). New York: Plenum.

Poon, L. W. (1985). Differences in human memory with aging: Nature, causes, and clinical implications. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging* (2nd ed., pp. 427-462). New York: Van Nostrand Reinhold.

Poon, L. W., Crook, T., Davis, K. L., Eisdorfer, C., Gurland, B. J., et al. (Eds.). (1986). *Handbook for clinical memory assessment of older adults.* Washington, DC: American Psychological Association.

Poon, L. W., Fozard, J. L., & Treat, N. J. (1978). From clinical and research findings on memory to intervention programs. *Experimental Aging Research, 4,* 235-253.

Popkin, S. J., Gallagher, D., Thompson, L. W., & Moore, M. (1982). Memory complaint and performance in normal and depressed older adults. *Experimental Aging Research, 8,* 141-145.

Rey, A. (1970). *L'examen clinique en psychologie.* Paris: Presses Universitaires de Paris.

Sheikh, J. Y., & Yesavage, J. A. (1986). Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clinical Gerontologist, 5,* 165-174.

Yesavage, J. A. (1985). Nonpharmacologic treatment for memory losses with normal aging. *American Journal of Psychiatry, 142,* 600-605.

Zelinski, E. M., Gilewski, M. J., & Thompson, L. W. (1980). Do laboratory tests relate to self-assessment of memory ability in the young and old? In L. W. Poon, J. L. Fozard, L. S. Germak, D. Arenberg, & L. W. Thompson (Eds.), *New directions in memory and aging: Proceedings of the George A. Talland Memorial Conference* (pp. 519-544). Hillsdale, NJ: Erlbaum.

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