0271-0749/87/0704-0230$02.00/0
Journal of Clinical Psychopharmacology

Vol. 7, No. 4
Printed in U.S.A.

Piracetam and Dyslexia: Effects on Reading Tests

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Previous research has suggested that dyslexics treated with piracetam have shown improvements in reading skills, verbal memory and verbal conceptualizing ability, feature analysis, and processing of letter-like stimuli. Two hundred twenty-five dyslexic children between the ages of 7 years 6 months and 12 years 11 months whose reading skills were significantly below their intellectual capacity were enrolled in a multicenter, 36-week, double-blind, placebo-controlled study. Children of below average intelligence, with abnormal findings on audiologic, ophthalmologic, neurologic, psychiatric, and physical examinations, who were emotionally disturbed or educationally deprived and who had recently been treated with psychoactive medication were excluded from the trial. Piracetam was well tolerated, with no serious adverse clinical or laboratory effects reported. Piracetam-treated children showed significant improvements in reading ability (Gray Oral Reading Test) and reading comprehension (Gilmore Oral Reading Test). Treatment effects were evident after 12 weeks and were sustained for the total period (36 weeks).
(J Clin Psychopharmacol 1987;7:230–237)

OVER the last 7 years there have been several reports that piracetam (2-oxo 1-pyrrolidine acetamide, trade names Nootropil, Nootropyl, Nootrop, Noostan, and Barcan) may be of use in treating children with learning difficulties. Piracetam is structurally related to gamma-aminobutyric acid (GABA) and is purported to selectively improve the efficiency of higher cognitive functions and to belong to a class of psychoactive drugs known as "nootropics."[1] An initial clinical study[2] involving 16 male dyslexic adolescents and 14 normal student volunteers in a 3-week double-blind trial gave encouraging results. Dyslexics (and normals) treated with piracetam showed a decrease in the number of trials required to reach criteria in a rote verbal learning task. After placebo both groups showed insignificant minor changes.

However, this initial report was followed by an inconclusive study. Simeon and co-workers[3] studied 14 "learning disordered" boys in a 4-week, double-blind, crossover study. Although they found a significant improvement in global evaluation of the equal IQ group (verbal and performance IQs being similar), they did not find any changes in learning or cognitive tasks. The lack of clinical effect may have been due to population heterogeneity, small numbers in each group, crossover effects, and the short duration of treatment. This same group reanalyzed their results in light of their EEG findings.[4, 5] They found that piracetam caused reductions in left-hemisphere Delta power, and that this was related to improvement on neuropsychological measures of verbal/sequential performance.

In a pilot study reported by DiIanni and colleagues,[6] 257 dyslexic boys were treated with piracetam or

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placebo for 12 weeks. Dyslexia was defined as a condition of specific written language difficulties in otherwise normal boys. These boys had average or above average IQs and good school, social and language opportunities; had no visual, auditory, neurological, or psychiatric disturbances; and were severe underachievers in reading. The results of the study showed that the piracetam-treated dyslexics increased their reading fluency without sacrificing accuracy, and those with poor short-term memory increased their digit span scores. During this 12-week trial, piracetam was well tolerated and the incidence of adverse effects was similar in both the drug and placebo groups.

A number of special studies were conducted within the study of DiIanni and colleagues.[6] Rudel and Helfgott[7] showed that dyslexics treated (double-blind) with piracetam increased their verbal memory on the Neimark Memorization Test and reduced the amount forgotten on a delayed recall trial. This same team[8] also reported a marked improvement on the WRAT reading test[9] for the piracetam-treated group. The results were not only statistically significant ($p < 0.005$) but also showed a meaningful gain of 6 months in this 12-week period. However, the authors did caution that such a result needed replication.

Wilsher and Milewski[10] reported the results of a 12-week study of dyslexics comparing piracetam and placebo on the similarities and vocabulary subtests of the WISC-R. They found that in this short treatment period, verbal conceptualizing ability (similarities) was enhanced by piracetam but word definitions (vocabulary) was not.

Chase and co-workers[12] reported a marked improvement in reading speed and writing accuracy in 28 dyslexics treated with piracetam (double-blind) compared to 27 treated with placebo. This group also analyzed their data to determine the effect of speed upon accuracy and comprehension of reading. Their combination of speed and accuracy, and speed and comprehension, produced what they termed "effective reading accuracy" and "effective reading comprehension." The results of this analysis showed significant piracetam effects upon "effective reading accuracy" ($p < 0.001$) and "effective reading comprehension" ($p < 0.003$). They interpreted this as showing that the placebo group slowed down to improve accuracy but the piracetam group increased in both speed and accuracy.

Conners and associates[13, 14] have conducted two electrophysiological studies of the effect of piracetam on dyslexia. The first was a pilot study using visual event-related potentials of dyslexic boys after a 12-week, double-blind trial of piracetam. The paradigm was one in which the subjects carried out a continuous performance task that involved identifying letter pairs or shape pairs. The results of this pilot study were not conclusive (probably due to the small number of subjects), but they did demonstrate that piracetam had an effect on late potentials to letter hits (correctly detecting letters) in the left hemisphere. A second, much larger study used dyslexic children who had been treated (double-blind) for 32 weeks (the sample was in fact part of the present 36-week study). Using the same paradigm, the investigators reported significant drug effects on performance (enhancing letter detection) and on event-related potentials associated with letter hits. This led them to conclude that "piracetam may increase the efficiency of a left-hemisphere cortical processor intimately involved in letter recognition."

This report presents the results for reading measures in the collaborative multicenter study which was conducted over a 36-week period during an entire academic year.

Subjects and Methods

This study was conducted by five investigative teams following a common protocol. Two hundred twenty-five children with a primary diagnosis of Developmental Reading Disorder (DSM-III)[15] and between the ages of 7 years 6 months, and 12 years 11 months were entered into the study. English was the primary language of all children and the predominant language of the home. A WISC-R was administered to all patients, and those included in the study had either a verbal IQ or a performance IQ of 90 or greater, with the other score being at least 80.

A reading quotient (RQ) of 0.850 or less was required, with RQ being defined as: (3 × reading age) / (chronological age + [2 × mental age]).[16, 17] An RQ of 0.850, for example, represents a *minimum* retardation from expectancy of 1yr 2m for an 8-year-old and 2yr 0m for a 13-year-old. The reading age was obtained from the total passage score of the Gray Oral Reading Test, and the mental age was derived from the full scale IQ of the WISC-R. The patients' parents showed adequate motivation to seek help for their children and to comply with visit schedules. The children's schools were contacted to verify that their performance on tasks requiring reading skills was significantly below their intellectual capacity.

In addition, all patients had normal findings on audiologic, ophthalmologic, neurologic, and psychiatric (or clinical psychologist's) examinations prior to the study entry. Patients were excluded if they were hyperactive or had significant emotional problems (as defined by the psychiatrist or clinical psychologist and/or by a score of 2 standard deviations above the mean on the hyperactivity, anxiety, or conduct disorder factors of the

Conners Rating Scales for Parents[18]); if they had inadequate educational experience (defined as three or more school or teacher changes in the previous school year, a total of five school changes in their school career, or absenteeism of more than 20% in any one school year); and if they had a family environment not conducive to learning (defined as lack of reading material, inadequate space to study, etc.). Also excluded were those who had significant neurological disease, defined as classical neurological signs with functional impairment or any seizures at any time (except nonrecurring febrile convulsions of short duration); those who were not likely to attend school on a regular basis during the study; and those whose psychological or educational therapy was likely to undergo radical changes. In addition, patients who had been treated with psychostimulant medication within 6 months of the study or who required concomitant treatment with any psychoactive medication were excluded from the study. To screen for other developmental disabilities, a detailed developmental history was taken. The primary source of referral for this study was parents.

Patients who fulfilled the entry criteria were randomly assigned to 36 weeks of double-blind treatment with either piracetam or placebo during the 1983–4 school year. Patients visited the study centers every 4 weeks to be evaluated, for a total of 9 follow-up visits. Piracetam was supplied in solution containing 0.33 g of piracetam per ml. The daily dose was 5 ml twice a day for a total of 3.3 g of piracetam daily. Compliance was measured by recording the level of returned syrup and by drug assay on one blood sample at 36 weeks.

The primary assessments were the reading tests: the Gray Oral Reading Test,[19] the Gilmore Oral Reading Test,[20] and the Wide Range Achievement Test-Revised (WRAT-R, reading subtest).[21] In addition, an experimental reading acquisition task was performed using an adaptation of the Milliken Comprehension Power[22] computer package. This task was difficult both to administer consistently and for the children to perform adequately, and hence the data were uninterpretable.

Both Forms C and D of the Gilmore Oral Reading Test were administered at baseline and after 36 weeks of treatment in order to gain a larger and more reliable sample of reading behavior on this test. Rate of reading was assessed at baseline according to the Gilmore manual (i.e., between basal and ceiling paragraphs), and at the 36-week assessment, rate of reading was again assessed across the same paragraphs. Equivalent forms of the Gray Oral Reading Test were given at baseline (Form A) and at the treatment intervals 12 weeks (Form B), 24 weeks (Form C), and 36 weeks (Form D). The same form of the WRAT-R reading subtest (level I) was administered at 12, 24, and 36 weeks. Raw scores were used in the data analysis.

The primary statistical analysis of efficacy was carried out using a parametric two-way analysis of covariance, with the baseline value as covariate and the change from baseline as the response variable. One-tailed probabilities are reported for analysis between piracetam and placebo groups (piracetam group hypothesized to show more improvement), and two-tailed probabilities are reported for comparison of baseline variables and interactions.

Results

Study population

Five investigators entered 225 children into the study, 112 of whom were treated with piracetam, while 113 were treated with a matching placebo. The piracetam group had a mean age of 10.1 years, was of average intelligence (full-scale IQ 104.9), and had an average reading quotient of 0.70. The placebo group had a mean age of 10.5 years, was of average intelligence (full-scale IQ 103.6), and had an average reading quotient of 0.69. Table 1 shows that both groups were comparable for most demographic factors except age, with the piracetam group being slightly younger ($p < 0.05$). As expected, unequal numbers of boys (153) and girls (72) were entered in the study.

The average reading grade level at baseline was 2.06 school grades (piracetam 1.96, placebo 2.16) based on the Gray Passage score, with a Gilmore Accuracy grade level of 2.67 (piracetam 2.52, placebo 2.81) and a

TABLE 1. Demographic and baseline characteristics: all patients

Parameter	Piracetam	Placebo	*p* value
No. of patients	112	113	
Sex (N)			
Male	79	74	0.421
Female	33	39	
Age (years)			
Mean	10.08	10.49	0.042
SD	1.62	1.37	
Race			
Black	4 (3.6%)	11 (9.7%)	
White	106 (94.6%)	99 (87.6%)	0.067
Other	2 (1.8%)	3 (2.7%)	
Full-scale IQ			
Mean	104.89	103.60	0.294
SD	10.95	10.40	
Performance IQ			
Mean	106.64	106.81	0.954
SD	11.45	11.54	
Verbal IQ			
Mean	102.73	100.55	0.135
SD	12.54	12.06	
Reading quotient			
Mean	0.70	0.69	0.561
SD	0.09	0.08	

TABLE 2. Patients prematurely discontinued

Primary reason	Piracetam (N = 112) No. %	Placebo (N = 113) No. %
Adverse reaction	3 (2.6)	4 (3.5)
Lost to follow-up	3 (2.6)	5 (4.4)
Protocol violation	3 (2.6)	2 (1.8)
Withdrew consent	0 (0)	4 (3.6)
Intercurrent illness	0 (0)	1 (0.9)
Total	9 (7.9)	16 (14.2)

Gilmore Comprehension grade of 4.00 (piracetam 3.70, placebo 4.30). Based on an average expected reading age of 10.6 years, 5.5 grade (expected reading age = (2 × mental age + chronological age)/3) this sample was an average of 3.4 school grades behind in reading proficiency (Gray Passage), 2.8 school grades behind in reading accuracy, and 1.5 school grades behind in reading comprehension. The average WRAT-R single word reading score was 76.8 standard scores (piracetam 75.7, placebo 77.9). As judged by the WRAT-R, the children were almost 2 standard deviations below the test norms for reading.

As shown in Table 2, a total of 25 patients were prematurely discontinued from the study: 9 from the piracetam group and 16 from the placebo group. The dropout rate of 11% is low for a study of such duration.

Comparison of baseline efficacy variables

Table 3 details the mean baseline values of the primary efficacy variables. It can be seen that there was an overall significant difference between treatments at baseline for Gray Comprehension, Gilmore Accuracy and Comprehension (and trends on the other variables). It can also be seen that only one investigator (#2) found significant differences between treatment groups at baseline, and all primary variables at that site showed the greatest differences between treatments. With investigator #2 excluded from the study, there were no longer any significant differences between differences at baseline (see Table 4).

TABLE 4. Baseline comparison of primary efficacy variables (raw scores) excluding investigator #2

Variable	Piracetam (N = 81 to 84): mean	Placebo (N = 78 to 85): mean	Between baseline difference[a]: *p* value
Gray			
Passage	14.8	17.1	0.18
Comprehension	17.4	19.1	0.12
Gilmore			
Comprehension	20.6	22.4	0.13
Rate (wpm)	72.5	77.7	0.35
Accuracy	16.0	18.0	0.23
WRAT-R			
Reading	54.1	56.4	0.26

[a]Two-tailed test.

Analysis of primary efficacy variables

Due to the difficulties inherent in assessing results for which baselines are different, the results of the pooled data will be presented both with and without investigator #2's sample. Tables 5 and 6 display the results of the efficacy analysis with and without investigator #2, respectively. In addition, since data are covaried for baseline scores, between-treatment effects are freed of initial pretreatment level differences.

Treatment effects

The results for the total sample (including investigator #2) revealed significant differences in favor of pi-

TABLE 3. Baseline comparison by investigator: primary efficacy variables—mean raw scores[a]

Variable	Investigator 1		2		3		4		5		Total		*p*
	PR	PL	PR	PL	PR	PL	PR	PL	PR	PL	PR	PL	
n =	19	19–20	21–24	19–20	20–21	21–24	16–17	15–18	26–27	23	102–108	97–105	
Gray													
Passage	15.0	19.4	16.8	21.8	13.5	17.3	18.9	18.8	13.0	13.7	15.2	18.0	0.06
Comprehension	19.8	21.1	17.0	21.1*	15.7	17.4	19.5	19.9	15.6	18.6	17.3	19.5	0.02*
Gilmore													
Comprehension	21.5	23.9	21.0	24.3	18.7	20.7	23.6	22.9	19.6	22.7	20.7	22.8	0.05*
Rate (wpm)	83.4	82.7	78.4	93.1	71.9	84.6	83.4	82.0	56.8	64.5	73.7	80.7	0.15
Accuracy	16.2	20.6	16.3	23.4*	14.0	17.0	20.3	19.6	14.7	15.8	16.1	19.1	0.04*
WRAT-R													
Reading	56.0	58.0	52.8	59.3	52.1	54.9	59.5	58.2	50.9	55.4	53.8	57.0	0.07

[a]PR = piracetam, PL = placebo. Underlining denotes mean values differing most at baseline in each center.
*$p < 0.05$, two-tailed test.

TABLE 5. Analysis of efficacy variables—raw scores for all patients

Variable	Piracetam				Placebo				Between baseline significance (p)	TXI[b] (p)	Between treatment significance[c] (p)
	N	Mean	Adj. diff.[a]	(SE)	N	Mean	Adj. diff.[a]	(SE)			
Gray Oral Reading Test											
Total Passage (raw score)											
Baseline	108	15.2	—[d]	—	105	18.0	—	—	0.060	0.729	
Wk 12	102	17.3	2.5	(0.53)	101	19.0	1.4	(0.52)		0.018*	0.072
Wk 24	105	20.9	6.0	(0.57)	94	22.8	4.6	(0.60)		0.007**	0.045*
Wk 36	101	23.0	7.5	(0.60)	96	24.0	6.0	(0.62)		0.149	0.043*
Total Comprehension (raw score)											
Baseline	108	17.3	—	—	105	19.5	—	—	0.021*	0.716	
Wk 12	102	20.7	3.4	(0.37)	101	21.9	2.6	(0.37)		0.259	0.056
Wk 24	105	20.9	3.4	(0.41)	95	22.3	3.1	(0.43)		0.874	0.322
Wk 36	101	20.5	2.8	(0.41)	96	21.2	1.9	(0.42)		0.146	0.061
Gilmore Oral Reading Test											
Rate (wpm)											
Baseline	102	73.7	—	—	97	80.7	—	—	0.147	0.729	
Wk 36	101	92.4	18.3	(1.81)	96	98.3	18.0	(1.69)		0.752	0.442
Accuracy (raw score)											
Baseline	108	16.1	—	—	103	19.1	—	—	0.039*	0.494	
Wk 36	101	23.1	6.7	(0.55)	96	25.0	6.0	(0.57)		0.688	0.204
Comprehension (raw score)											
Baseline	108	20.7	—	—	103	22.8	—	—	0.046*	0.778	
Wk 36	101	25.4	4.3	(0.46)	96	25.3	2.7	(0.48)		0.133	0.009**
WRAT-R											
Reading (raw score)											
Baseline	108	53.8	—	—	105	57.0	—	—	0.072	0.646	
Wk 12	102	55.9	2.6	(0.39)	101	59.0	2.4	(0.39)		0.499	0.398
Wk 24	105	58.5	5.0	(0.42)	94	60.9	4.2	(0.44)		0.252	0.090
Wk 36	101	60.4	6.2	(0.43)	96	62.7	5.9	(0.44)		0.211	0.272

[a]Adjusted mean difference from baseline.
[b]Treatment by investigator interaction.
[c]p values based on two-way analysis of covariance using pretreatment value as covariate.
[d]— indicates not applicable.
*$p < 0.05$, **$p < 0.01$.

racetam in the following variables: Gray Oral Total Passage Score at 24 and 36 weeks ($p < 0.05$), and Gilmore Oral Reading Test Comprehension Score at 36 weeks ($p < 0.009$). However, there were significant differences between groups at baseline, and many of the variables also exhibited a significant treatment-by-investigator interaction. The results of the analysis of the more homogeneous sample with equal baselines (i.e., excluding the investigator with unequal baselines, Table 6) showed significant treatment effects favoring piracetam for the following variables: Gray Oral Total Passage Score at 12, 24, and 36 weeks ($p < 0.009$); Gray Oral Total Comprehension Score at 12 and 36 weeks ($p < 0.05$); Gilmore Oral Reading Test Comprehension Score at 36 weeks ($p < 0.001$); and WRAT-R Reading Score at 24 weeks ($p < 0.04$).

Safety

There were no serious or life-threatening adverse effects reported during this 36-week study. A total of seven patients (three piracetam and four placebo) were prematurely discontinued from the study due to adverse effects. Two piracetam patients (1.8%) dropped out because of nervousness, and one patient (0.9%) was discontinued because of slight elevation of liver function tests. Two patients (1.8%) treated with placebo withdrew because of behavior problems; one (0.9%) because of leukopenia and one (0.9%) because of gastrointestinal disorders.

Each investigator was required to record all reported and observed adverse signs and symptoms throughout the study. These reports included infections and viruses (such as the common cold), and hence 104 (92.9%) of piracetam-treated patients and 101 (89.4%) of placebo-treated patients reported one or more adverse effect. When reactions considered by the physician to be possibly or probably related to study medication were tabulated (Table 7), 31 of the 112 (27.7%) piracetam patients reported 42 adverse effects and 31 of the 113 (27.4%) placebo patients reported 48 adverse effects. As can be

TABLE 6. Analysis of efficacy variables—raw scores for total sample minus investigator #2

Variable	Piracetam				Placebo				Between baseline significance (p)	TXI[b] (p)	Between treatment significance[c] (p)
	N	Mean	Adj. diff.[a]	(SE)	N	Mean	Adj. diff.[a]	(SE)			
Gray Oral Reading Test											
Total Passage (raw score)											
Baseline	84	14.8	—[d]	—	85	17.1	—	—	0.179	0.697	
Wk 12	79	17.1	2.7	(0.59)	81	17.4	0.7	(0.58)		0.163	0.009**
Wk 24	82	21.2	6.7	(0.64)	76	21.2	4.2	(0.67)		0.085	0.004**
Wk 36	81	22.9	8.1	(0.67)	77	22.5	5.6	(0.69)		0.809	0.005**
Total Comprehension (raw score)											
Baseline	84	17.4	—	—	85	19.1	—	—	0.116	0.822	
Wk 12	79	20.6	3.3	(0.42)	81	21.1	2.2	(0.41)		0.212	0.032*
Wk 24	82	21.0	3.5	(0.46)	77	21.8	3.0	(0.48)		0.879	0.257
Wk 36	81	20.4	2.8	(0.45)	77	20.7	1.7	(0.47)		0.081	0.048*
Gilmore Oral Reading Test											
Rate (wpm)											
Baseline	84	72.5	—	—	83	77.7	—	—	0.348	0.702	
Wk 36	81	93.4	20.5	(2.03)	78	96.1	18.7	(1.89)		0.872	0.257
Accuracy (raw score)											
Baseline	84	16.0	—	—	83	18.0	—	—	0.225	0.724	
Wk 36	81	22.9	6.9	(0.61)	77	23.8	6.0	(0.63)		0.528	0.166
Comprehension (raw score)											
Baseline	84	20.6	—	—	83	22.4	—	—	0.133	0.694	
Wk 36	81	25.3	4.6	(0.51)	77	24.5	2.2	(0.52)		0.444	0.001***
WRAT-R											
Reading (raw score)											
Baseline	84	54.1	—	—	85	56.4	—	—	0.263	0.714	
Wk 12	79	56.4	2.8	(0.44)	81	58.2	2.2	(0.44)		0.866	0.181
Wk 24	82	59.0	5.2	(0.48)	76	60.3	4.0	(0.49)		0.306	0.040*
Wk 36	81	60.4	6.3	(0.48)	77	61.9	5.7	(0.50)		0.161	0.206

[a]Adjusted mean difference from baseline.
[b]Treatment by investigator interaction.
[c]p values based on two-way analysis of covariance using pretreatment value as covariate.
[d]— indicates not applicable.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

seen from Table 7, three piracetam-treated children (2.7%) reported nervousness or irritability.

No systematic change in laboratory parameters (hematology, blood chemistry, and urinalysis) was observed for either the piracetam or the placebo group. The investigators evaluated each laboratory value that was outside the normal range for clinical significance. The distribution of laboratory "abnormalities" that were considered to be clinically significant was generally similar in both treatment groups.

No clinically meaningful changes in weight, temperature, pulse, respiration, or blood pressure were observed.

Investigators rated each patient at the end of treatment for overall tolerance of the medication (1 = excellent, 2 = good, 3 = fair, 4 = poor). There was no significant difference between treatment groups, with most patients' tolerance being assessed as excellent or good (mean piracetam rating: 1.27, placebo: 1.36).

Discussion

The demanding schedule of this ambitious protocol was well adhered to, with 225 dyslexic children being screened and entered between July and October, such that 200 children completed the 36-week, double-blind treatment by the end of the school year. Although medication was randomized and allocated under double-blind conditions, the analysis of the data revealed that the piracetam group was slightly younger. There was also a difference between treatments at baseline for three of the efficacy measures. It was found that only one investigator had significant differences between treatments at baseline (Table 3), and that the removal of this investigator equalized the baselines of the combination of the remaining four investigators' samples (Table 4). It should also be noted that with the total sample (including investigator #2), there was a significant treatment-by-investigator interaction (TXI) on sev-

TABLE 7. Adverse reactions considered to be possibly or probably related to study drug

Adverse effect	Piracetam (N = 112) No. of patients	(%)	Placebo (N = 113) No. of patients	(%)
Hyperkinesia	3	(2.7)	2	(1.8)
Nervousness	3	(2.7)	0	(0.0)
Personality disorder	3	(2.7)	4	(3.5)
Abnormal dreams	1	(0.9)	0	(0.0)
Emotional lability	1	(0.9)	0	(0.0)
Insomnia	1	(0.9)	4	(3.5)
Somnambulance	1	(0.9)	0	(0.0)
Tremor	1	(0.9)	0	(0.0)
Incoordination	0	(0.0)	1	(0.9)
Dizziness	0	(0.0)	1	(0.9)
Thinking abnormal	0	(0.0)	1	(0.9)
Gastrointestinal disorder	2	(1.8)	3	(2.7)
Nausea	2	(1.8)	2	(1.8)
Increased appetite	1	(0.9)	0	(0.0)
Constipation	1	(0.9)	0	(0.0)
Diarrhea	1	(0.9)	1	(0.9)
Liver function tests abnormal	1	(0.9)	0	(0.0)
Decreased appetite	0	(0.0)	1	(0.9)
Vomiting	0	(0.0)	1	(0.9)
Rhinitis	6	(5.4)	4	(3.5)
Pharyngitis	1	(0.9)	0	(0.0)
Abdominal pain	4	(3.6)	1	(0.9)
Headache	0	(0.0)	3	(2.7)
Throat pain	0	(0.0)	2	(1.8)
Rash	4	(3.6)	4	(3.5)
Allergic dermatitis	0	(0.0)	1	(0.9)
Eczema	0	(0.0)	1	(0.9)
Seborrhea	0	(0.0)	1	(0.9)
Dry skin	0	(0.0)	1	(0.9)
Leukopenia	1	(0.9)	1	(0.9)
Lymphadenopathy	1	(0.9)	0	(0.0)
Weight gain	2	(1.8)	1	(0.9)
Bilirubinemia	0	(0.0)	1	(0.9)
Edema lips	0	(0.0)	1	(0.9)
Weight loss	0	(0.0)	1	(0.9)
Periorbital edema	1	(0.9)	0	(0.0)
Eye disorder	0	(0.0)	3	(2.7)
Eye pain	0	(0.0)	1	(0.9)
Total number of adverse effects reported	42		48	
Total number of patients with one or more adverse effects	31	(27.7)	31	(27.4)

eral of the efficacy variables (Table 5). Removal of investigator #2 eliminated this interaction.

The treatment effects found that were common to both analyses were significant drug-related improvements in the Gray Oral Total Passage score and the Gilmore Oral Comprehension score. In addition, three investigators had significant drug-related improvements in their own samples for these two variables, and for one of them (Gray Oral Total Passage score) one investigator found a trend ($p = 0.09$, at 36 weeks) in favor of placebo. This latter result is very puzzling because of the extraordinary improvement of the placebo group at this one site. When this center's placebo improvement ($n = 19$) was compared to the other sites' placebo change ($n = 80$), a highly significant difference was found ($p = 0.0009$, two-tailed). For the other reading tests, one investigator found superior piracetam performance on the Gray Oral Comprehension score, another investigator found significant drug effects on WRAT-R reading score, and one other investigator found significant piracetam improvement on one form of the Gilmore Oral Reading Test Accuracy score.

The improvement in the Gray Oral Total Passage score represents a global improvement in ability that combines reading accuracy and speed. This is very similar to that reported by Chase and co-workers[12] and Wilsher.[23] However, in contrast to this finding, there was no improvement in speed or accuracy (except for one investigator) on the Gilmore Oral Reading Test. It must be emphasized that the Gray and the Gilmore are very different passage reading tests that produce different scores: the Gray Total Passage score combines both speed and accuracy for each paragraph at each stage of difficulty, while the Gilmore keeps these scores separate. There are also different scoring conventions, i.e., punctuation, hesitation, and self-correction errors are not scored on the Gray.

There was a consistent improvement in reading comprehension in the piracetam group, shown by the significant effects upon both Gray ($p < 0.05$) and Gilmore Comprehension scores ($p < 0.001$). The Gray Comprehension score is merely a checklist of questions to each paragraph; this portion of the Gray has not been standardized, unlike the Gilmore. These results show that as well as demonstrating improvements in their combined reading accuracy and speed (Gray Oral Total Passage score), children treated with piracetam had also improved their ability to comprehend what they had read. The objective of teaching children to read is clearly for them to understand the material that is presented. Reading more without concomitant understanding would be futile.

Piracetam was found to be well tolerated throughout this long-term study, and no serious or unusual adverse clinical or laboratory effects were reported.

Conclusion

Children with Developmental Reading Disorder (dyslexia) who were treated with piracetam showed im-

provement in reading ability (Gray Oral Total Passage score) and reading comprehension (Gray and Gilmore Comprehension scores). These improvements were evident over a 36-week period, which is one of the longest controlled trials of its kind. The medication was well tolerated.

Acknowledgments

This research was supported by a grant from UCB Pharmaceutical Sector, Brussels, Belgium. We thank G. H. Besselaar Associates, Princeton, New Jersey, who organized and monitored the study and performed the statistical analysis of the data; all the study co-ordinators and assistants at each site; Mrs. Jenny Taylor for compilation/typing; and all the children and their parents who participated.

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More Trivia and a Perspective

Nineteen eighty-seven marks the 100th anniversary of the death of Dorothea Lynde Dix. No individual has contributed more than she to the development of an improved public mental health system. In her 1843 address to the Massachusetts Legislature, she said, "I proceed, Gentlemen, briefly to call your attention to the present state of Insane Persons confined within this Commonwealth, in cages, closets, cellars, stalls, pens! Chained, naked, beaten with rods, and lashed into obedience. . . . " She directly influenced the building of 30 state mental hospitals in the United States, concluding that if the "insane" were treated in medically run institutions under state control, a better quality of care would be obtained. We are in need of the spirit of Dorothea Dix today as we deal with the ravages of deinstitutionalization, which has resulted in a return to conditions of neglect and abandonment rather than the hoped-for freedom for patients. The chronically mentally ill are now excluded from the very institutions created to ease their plight.

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