Piracetam Therapy Does Not Enhance Cognitive Functioning in Children With Down Syndrome

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Background: Piracetam is widely used as a purported means of improving cognitive function in children with Down syndrome. Its efficacy, however, has not been rigorously assessed.

Objective: To determine whether 4 months of piracetam therapy (80-100 mg/kg per day) enhances cognitive function in children with Down syndrome.

Design: A randomized, double-blind, placebo-controlled crossover study.

Participants and Methods: Twenty-five children with Down syndrome (aged 6.5-13 years) and their caregivers participated. After undergoing a baseline cognitive assessment, children were randomly assigned to 1 of 2 treatment groups: piracetam-placebo or placebo-piracetam.

Main Outcome Measure: The difference in performance while taking piracetam vs while taking placebo on tests assessing a wide range of cognitive functions, including attention, learning, and memory.

Results: Eighteen children completed the study, 4 withdrew, and 3 were excluded at baseline. Piracetam therapy did not significantly improve cognitive performance over placebo use but was associated with central nervous system stimulatory effects in 7 children: aggressiveness (n=4), agitation or irritability (n=2), sexual arousal (n=2), poor sleep (n=1), and decreased appetite (n=1).

Conclusion: Piracetam therapy did not enhance cognition or behavior but was associated with adverse effects.


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Piracetam is a member of the class of drugs known as nootropics, which are generally thought to enhance cognitive function in instances of brain dysfunction. Putative mechanisms of action differ depending on the disease process being modeled and include enhanced membrane fluidity, increased neurotransmitter release (eg, dopamine), protective effects on specific receptors (eg, glutamate), increased blood flow, enhanced corticosteroid function, and effects on calcium channel function. Piracetam has been administered to patients with diverse clinical conditions such as stroke, Alzheimer disease, and developmental dyslexia. However, research on the efficacy of piracetam and related compounds to ameliorate cognitive deficiencies in these populations, and in animal studies, has frequently produced small or inconsistent results.

Down syndrome is associated with developmental delay, and affected children generally attain mental and cognitive capacity in the range of mild to moderate mental retardation. Interest in using piracetam to improve cognitive function in children with Down syndrome surged in North America after the television program *Day One* was nationally broadcast on January 19, 1995. In this program, claims were made that piracetam therapy improved cognitive function in a child with Down syndrome. This was followed by television reports on December 20, 1996 (*Nightline*), and on August 21, 1997 (*48 Hours*), and widespread dissemination of anecdotal evidence through Internet newsgroups. For example, parents of a 6-year-old girl indicated that “...her concentration and awareness have improved. Her speech has improved to the point that she is finally saying phrases and sentences; improvement is slow but she is finally making some” (May 1995). An 11-year-old boy became “healthier, happier, has more energy, pays attention better, is growing like crazy... absolutely full of energy” (January 1999). Partially in response to
PARTICIPANTS AND METHODS

STUDY DESIGN

This study used a double-blind, placebo-controlled design consisting of a baseline assessment and two 4-month treatment arms (Figure 1). To control for maturation effects, 2 treatment orders were used. Children were randomly assigned to receive piracetam in phase 1 and placebo in phase 2 (piracetam-placebo) or placebo in phase 1 and piracetam in phase 2 (placebo-piracetam). Cognitive evaluations were conducted at the end of each phase while the children were in school. Baseline assessments were conducted at the end of the 1996-1997 school year, phase 1 testing occurred at the end of the fall 1997 term, and phase 2 testing occurred near the end of the spring 1998 term. This study was approved by the research ethics board at The Hospital for Sick Children in Toronto, Ontario.

PARTICIPANTS

The target sample size ($N=25$) was chosen to allow detection of large performance differences (0.8 SD) between the piracetam and placebo phases with power of 80% and $\alpha = .05$. A large effect size was chosen because most reports in the popular press have indicated immediate and substantive effects of piracetam treatment in children with Down syndrome.

Moderate- to high-functioning children with Down syndrome (aged 6.5-13 years) were recruited through pediatricians and Down syndrome support groups throughout southern Ontario. Initial interviews with the child's parent(s) and teacher determined the child's general health and cognitive abilities. Exclusion criteria were hearing, vision, language, or other physical or cognitive limitations that would interfere with their ability to complete the test battery; known problems in swallowing capsules; use of piracetam during the previous 6 months; and concurrent use of megavitamins.

BASELINE SCREENING ASSESSMENT

Twenty-five children passed the initial telephone screening and were invited to The Hospital for Sick Children for baseline physical and cognitive assessment. All children were assessed with the Stanford-Binet Intelligence Scale, 4th Edition, to establish mental age equivalents, and the cognitive test battery was also administered. Children were examined by a physician, and a medical history was obtained from the parents. Testing was divided into two 3- to 4-hour sessions, with a break for lunch and additional breaks as needed.

PRIMARY OUTCOME MEASURES: COGNITIVE TEST BATTERY

The 14 tests selected for this study were culled from a variety of standardized tests and experimental paradigms and broadly covered the following functional domains: attention, learning and memory, perceptual abilities, executive function, and fine motor and visuomotor skills. Additional criteria were that the tests be suitable for children with Down syndrome and show minimal or no learning or practice effects with repeated administration. Brief descriptions of the tasks are listed in Table 1, and full descriptions can be obtained from the authors. The standardized tests in the battery are typically used to assess children in the 3- to 5-year-old age range, and the remaining tests have been used in 3- to 5-year-old children (eg, see Johnson10) or patients with Down syndrome (eg, see Dalton19). The child's effort on each task was monitored by the tester using a 5-point rating scale (5 = fully compliant and 1 = noncompliant).

SECONDARY OUTCOME MEASURES: PARENT AND TEACHER QUESTIONNAIRES

Parents and teachers completed standardized questionnaires at each test phase (Table 2). Parent questionnaires provided 80 items that assessed activity levels, social behavior and well-being, stress, parenting and family issues, and the child's temperament. Teacher questionnaires provided 24 items that assessed activity levels, learning, and social behaviors in the school environment.
The cognitive battery was administered by the same tester (V.R.) at all visits to ensure the best possible rapport with the children. The 14 tests were divided into three 25-minute blocks. No more than one 15-minute task was in each block. To control for the order of test administration, 3 block orders were created and children were randomly assigned to 1 of the 6 possible combinations. Children received breaks between each block and as otherwise necessary. Parents sat in a nearby room and were brought into the test room only when poor compliance interfered with testing or the child’s verbal responses were not readily understood.

Baseline Performance

Children were generally compliant during testing, as seen in a mean effort rating of 4.2±0.2 across all tasks (range, 3.4–4.6). Performance on the standardized tests concurred with mental age equivalents determined from the Stanford-Binet Intelligence Scale. For example, on the McCarthy tests, the mean raw scores for Verbal Fluency (9.9±1.3), Verbal Memory (10.6±1.1), and Tapping (2.4±0.2) are typical for children aged 4.5, 3.5, and 4.0 years, respectively. There were no differences at baseline attributable to the randomization to treatment order, which was confirmed on the baseline data using between-group analysis of variance (SPSS version 10.0; SPSS Inc, Chicago, Ill; piracetam-placebo vs placebo-piracetam). The primary analyses were repeated-measures analyses of variance, with treatment phase (piracetam vs placebo) as the repeated measure. Cases with missing data were excluded on a test-by-test basis, which was necessary for only 5 tests (Go/No-Go, n=15; Stroop Color/Shape, n=16; Stroop Color/Word, n=10; Delayed Match-to-Sample, n=17; and Animal Pegs, n=17). Huynh-Feldt–adjusted probabilities were used to evaluate the significance of the repeated-measures factors. The strength of all statistical results is indicated by η², which indicates the proportion of total variability attributable to the factor.

Treatment Effects

The children also worked well at the tasks in the 2 test arms of the study. The mean effort ratings were identi-
in the piracetam-placebo group (9.8 ± 0.9; F1,16 = 11.61, P < .01, η2 = 0.42). In the comparison of piracetam and placebo scores, 6 items from the parent and teacher questionnaires reached or approached significance (Figure 2C). For parents, these indicated improvements in leadership (FACES III: F1,13 = 4.45, P < .055, η2 = 0.26), fewer thought problems (Child Behavior Checklist: F1,15 = 4.93, P < .04, η2 = 0.25), and poorer attention while taking piracetam (Children's Behavior Questionnaire: F1,15 = 5.43, P < .03, η2 = 0.27). Teachers indicated that the children seemed happier (Teacher's Report Form: F1,11 = 8.04, P < .02, η2 = 0.42), had fewer internalizing problems (Teacher's Report Form: F1,13 = 8.65, P < .01, η2 = 0.40), and had fewer total problems while taking piracetam (F1,13 = 5.01, P < .04, η2 = 0.28). We note, however, that all of these differences, although statistically significant, were small from a clinical perspective. For example, on the parent questionnaire, thought problem scores below 67 are not considered clinically significant. Changes of the magnitude found here would not be interpreted by health care professionals as indicative of either improvement or decrease on the factor. Scores while taking piracetam and placebo were within the reference range, at 56.3 ± 1.5 and 60.1 ± 1.6, respectively. Similarly, for teachers, the total problem scores were in the clinically relevant range (≥60) at 62.1 ± 2.7 for the piracetam arm and 64.4 ± 2.6 for the placebo arm.

ADDITIONAL ANALYSES

Age at Baseline

To ensure that age-related beneficial effects of piracetam therapy were not being masked in the primary analysis, we examined the data for the younger and older children separately. Significant treatment × age group interactions were found for only 3 measures. Older children had better performance while taking placebo on 2
measures (Tapping and perseverations in Verbal Learning, \( P < .05 \)), whereas younger children showed no differences while taking piracetam vs placebo. On the first trial to correct reversal in the Go/No-Go task, young children were better while taking placebo (4.3 trials) and older children were better while taking piracetam (3.9 trials; \( P < .05 \) for both).

**Perceived Cognitive Improvement**

Analysis of the remarks made during telephone interviews indicated that 11 parents made some comment of improved cognition or attention during the piracetam arm. The data for these children were analyzed separately (mean±SD age, 10.3±0.6 years; range, 7.0-12.4 years). None of the cognitive measures reached or approached significance in this subsample.

**Individual Cases**

Inspection of performance on a case-by-case basis indicated that occasionally individual children showed meaningful changes in performance (improved or worsened relative to baseline) on 1 or 2 measures while taking piracetam. However, these effects were not consistent across children of similar ages or across tasks within a child.

**ADVERSE EFFECTS**

Adverse effects during the piracetam phase reported by caregivers were mostly associated with central nervous system stimulatory effects and were seen in 7 children: aggressiveness or violent behavior (n=4), agitation or irritability (n=2), sexual arousal (n=1), and decreased appetite (n=1). In 1 boy (aged 10.6 years at baseline), previously noted inappropriate sexual and aggressive behaviors increased during piracetam use and were especially disruptive at home and at school. No such effects were reported in the placebo arm. To ensure that the adverse effects were not overshadowing possible beneficial effects of piracetam treatment, performance was analyzed separately for the 11 children not showing behavioral problems. No beneficial effects of piracetam were identified, and the 2 groups did not differ from each other on any measure.

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**Table 2. Secondary Outcome Measures: Parent and Teacher Questionnaires**

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Completed Questionnaires, No.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parents</td>
<td></td>
</tr>
<tr>
<td>The Conners’ Parent Rating Scale[^24]</td>
<td>13</td>
</tr>
<tr>
<td>Child Behavior Check List[^{25}]</td>
<td>14</td>
</tr>
<tr>
<td>Parental Stress Inventory[^{29}]</td>
<td>15</td>
</tr>
<tr>
<td>FACES III[^{27}]</td>
<td>14</td>
</tr>
<tr>
<td>Temperament: Children’s Behavior Questionnaire</td>
<td>16</td>
</tr>
<tr>
<td>Teachers</td>
<td></td>
</tr>
<tr>
<td>The Conners’ Teacher Rating Scale[^23]</td>
<td>9</td>
</tr>
<tr>
<td>Teacher’s Report Form[^{23}]</td>
<td>12</td>
</tr>
</tbody>
</table>

* Only fully completed questionnaires for all 3 test periods were analyzed.

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**Table 3. Baseline Demographics and Stanford–Binet Intelligence Scale Results\[^a\]**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Study Children (n = 18)</th>
<th>Children Who Withdrew (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronological age</td>
<td>9.8 ± 2.0</td>
<td>9.3 ± 2.1</td>
</tr>
<tr>
<td>at baseline (range), y</td>
<td>(6.9-12.9)</td>
<td>(7.6-12.3)</td>
</tr>
<tr>
<td>Stanford-Binet age equivalents, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal reasoning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocabulary</td>
<td>4.8 ± 1.4</td>
<td>4.4 ± 1.0</td>
</tr>
<tr>
<td>Comprehension</td>
<td>4.0 ± 1.1</td>
<td>3.4 ± 1.1</td>
</tr>
<tr>
<td>Absurdities</td>
<td>4.5 ± 1.2</td>
<td>3.7 ± 1.1</td>
</tr>
<tr>
<td>Abstract/visual reasoning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pattern analysis</td>
<td>4.6 ± 0.9</td>
<td>4.2 ± 0.9</td>
</tr>
<tr>
<td>Copying</td>
<td>3.8 ± 1.1</td>
<td>3.9 ± 1.5</td>
</tr>
<tr>
<td>Quantitative reasoning</td>
<td>4.9 ± 1.0</td>
<td>4.1 ± 0.6</td>
</tr>
<tr>
<td>Short-term memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Read memory</td>
<td>3.6 ± 0.4</td>
<td>3.8 ± 0.8</td>
</tr>
<tr>
<td>Memory for sentences</td>
<td>3.4 ± 0.8</td>
<td>2.9 ± 0.4</td>
</tr>
</tbody>
</table>

\[^a\] Data are given as mean ± SD.

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Piracetam has received significant attention in the media for its purported beneficial effects on cognition in children with Down syndrome. Because enhancement has been reported on several cognitive functions, we explicitly designed the present study to capture a wide range of cognitive functions and behaviors. Thus, our primary outcome measure incorporated tests of sustained and short-term attention and memory; tests that assess processing in the visual and auditory domains; tests that examine verbal abilities, such as word fluency and learning and remembering new words; and basic fine motor and perceptual motor skills. The study is strengthened by the addition of a set of standardized parent and teacher questionnaires to evaluate behavior, temperament, and social and academic performance. The 2 test sessions of primary importance (piracetam and placebo) were conducted within a single school year, and well within each school term, providing a degree of stability to our measurements. It also strengthens the teacher reports, as the same teacher conducted both assessments. Because of the inherent difficulties in assessing changes in cognitive function in cognitively impaired individuals, we were careful to include tasks that children with Down syndrome could complete. In addition, our screening measures ensured that the participating children would have sufficient capacity to understand and perform all tasks. These goals were met for most measurements.

The results of this study indicate no consistent or pervasive beneficial effects of piracetam therapy over placebo use in these children. Across 3 analyses of the formal test battery, 2 measures indicated better performance while taking piracetam and 2 indicated better performance while taking placebo. For the parent and teacher reports, all detected changes were either within the reference range or remained in a clinically relevant range. Given the small number of significant effects and the mixed nature of the findings, we conclude that there is no strong evidence to indicate that piracetam use im-
proved cognition in these children, either in the formal test battery or from parent and teacher reports.

As is typical in clinical trials, some children were lost to the study. Because this reduced our sample size below that needed to detect large effects of the drug, we were careful to examine multiple aspects of the data, including relaxing the threshold for statistical significance, to ensure that positive effects of piracetam treatment were not being masked. We did not identify even a single case that would suggest the possibility that piracetam therapy generally improved cognition. Most telling, perhaps, is that although 11 parents noted that cognitive function seemed to be better when children were taking piracetam, this did not translate into measurable beneficial effects of piracetam over placebo.

The dose of piracetam used by us was within the range used in adults and in children with dyslexia. Despite this, potentially serious adverse effects were experienced by 7 of the 18 children while taking piracetam. This finding excludes the option of dose escalation.

The results of this study are strikingly different from the anecdotal testimonials presented in the popular press. One possibility that might partially account for the perceived beneficial effects of piracetam therapy might lie in the stimulatory effects of this medication. This type of behavioral stimulation could easily be confused with...
actual cognitive improvement in the absence of objective measures. Especially relevant to parent observations of alertness and better focus, none of our attention tasks revealed enhanced performance while taking piracetam over placebo on any measure. In conclusion, the results of this study indicate that piracetam treatment is associated with adverse effects and does not substantially enhance cognition or behavior.

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REFERENCES