Efficacy of Piracetam in the Treatment of Tardive Dyskinesia in Schizophrenic Patients: A Randomized, Double-Blind, Placebo-Controlled Crossover Study

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Background: Piracetam is a potent antioxidant, a cerebral neuroprotector, a neuronal metabolic enhancer, and a brain integrative agent. More than 20 years ago, an intravenous preparation of piracetam demonstrated an improvement in the symptoms of tardive dyskinesia. The aim of our study was to reexamine the efficacy of piracetam in the treatment of tardive dyskinesia using an oral preparation.

Method: The study was conducted at the Be'er Sheva Mental Health Center from May 2003 to December 2004 and involved a 9-week, double-blind, crossover, placebo-controlled trial assessing 40 DSM-IV schizophrenic and schizoaffective patients with DSM-IV-TR tardive dyskinesia. All study subjects received their usual antipsychotic treatment. Initially, subjects were randomly assigned to receive 4 weeks of treatment with either piracetam (4800 mg/day) or placebo. Thereafter, following a washout period of 1 week, they entered the crossover phase of the study for a further 4 weeks. The change in score of the Extrapyramidal Symptom Rating Scale from baseline to the study endpoint was the primary outcome measure.

Results: The mean decrease in score from baseline to endpoint in the clinical global impression subscale in patients treated with piracetam was 1.1 points compared to 0.1 points in the placebo group ($p = .004$). The mean decrease in the tardive parkinsonism subscale was 8.7 points in patients treated with piracetam and 0.6 points in those on placebo ($p = .001$). The mean decrease in the tardive dyskinesia subscale was 3.0 points in the piracetam group in contrast to deterioration of condition in the placebo group by –0.2 points ($p = .003$).

Conclusion: Piracetam appears to be effective in reducing symptoms of tardive dyskinesia. The specific mechanism by which piracetam may attenuate symptoms of tardive dyskinesia needs to be further evaluated.

Clinical Trials Registration: ClinicalTrials.gov identifier NCT00190008.

(J Clin Psychiatry 2007;68:1031–1037)

Received Aug. 15, 2006; accepted Nov. 22, 2006. From the Division of Psychiatry, Ministry of Health, Be'er Sheva Mental Health Center; and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Be'er-Sheva, Israel.

The study was supported by a Clinical Trials Grant from the Stanley Medical Research Institute, Bethesda, Md. (Dr. Vladimir Lerner, as Principal Investigator, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.)

The authors report no other financial or other relationship related to the subject of this article.

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Tardive dyskinesia is a common adverse effect generally resulting from the chronic use of conventional neuroleptics. The mechanism involved in the development of tardive dyskinesia is very complex and remains unclear and controversial.[1,2] Pathophysiologic theories have proposed mechanisms such as dopamine receptor supersensitivity,[1,3] the degeneration of cholinergic striatal interneurons,[4] a γ-aminobutyric acid (GABA) depletion,[5] and an excess of free radicals.[6] Many agents have been studied and reported to have a possible therapeutic benefit in this condition. Among them are a number of antioxidants,[7–9] cholinergic agents,[10,11] branched-chain amino acids,[12] monoamine depleters and dopamine receptor blockers,[13] and clonazepam.[14,15] Moreover, for the management of tardive dyskinesia it was proposed to use therapeutic strategies, such as changing from conventional to atypical antipsychotics,[16,17] discontinuing anticholinergic agents,[18,19] and switching to clozapine.[20] However, the problem may persist despite these approaches.

Piracetam (2-oxo-1-pyrrolidine-acetamide) is a nootropic drug structurally related to GABA. The main mode of action of this drug seems to be its beneficial influence on cell metabolism, including that of central neurons. According to several experimental and clinical studies,[21–24] piracetam has the potential to preserve, protect, and enhance brain synaptic membrane and receptor structure and plasticity, especially under detrimental conditions such as hypoxia, chemical toxicity, or impaired cerebral microcirculation. However, in a recent review[25] con-

cerning the effects of piracetam in acute ischemic stroke and the prevention of early death, the author concluded that the piracetam group of patients did not differ from the placebo group. Piracetam increases high-affinity choline uptake and elevates the density of frontal cortex acetylcholine receptors.[26,27] It also has effects on glutamate neurotransmission at the micromolar level.[23,28] In addition, piracetam potentiates potassium-induced release of glutamate from hippocampal nerves.[22] However, the mechanism of action in treating tardive dyskinesia remains unknown.

Piracetam is excreted practically unchanged in the urine and is completely eliminated after 30 hours. The central nervous system half-life of 7.7 hours following an oral dose of 2 g in humans is greater than the 5-hour plasma half-life, thus resulting in some accumulation in the brain over time.[22,29] It should also be emphasized that this compound has limited side effects, even in relatively high doses (24 g daily),[22,30,31] and has no teratogenic effects.[30]

The current evidence-based treatment for tardive dyskinesia does not refer to the use of piracetam as a therapeutic option.[32–35] However, a number of clinical reports have suggested that piracetam may be effective in improving symptoms in a range of movement disorders, including that of acute neuroleptic-induced extrapyramidal symptoms and tardive dyskinesia.[36–43] In these reports, the dose of piracetam used for treating tardive dyskinesia varied from 800 mg/day to 24,000 mg/day.[38,39,43] To date there has been only 1 double-blind crossover study, performed more than 20 years ago, using intravenous piracetam in the treatment of tardive dyskinesia.[38] Although the findings of this study were impressive, they have not been reproduced since.

The aim of our study was to evaluate the efficacy of piracetam as an oral preparation in treating tardive dyskinesia in patients with schizophrenia and schizoaffective disorders.

METHOD

Subjects

Over a period of 20 months (May 2003–December 2004), we screened 53 schizophrenic and schizoaffective inpatients in the Be'er Sheva Mental Health Center (Israel) for tardive dyskinesia. A complete clinical evaluation, including medical and neurologic examination as well as laboratory tests, was performed prior to inclusion in the study. The study was approved by the institutional review board committee of the Soroka Medical Center, Be'er Sheva, Israel, and was conducted according to good clinical practice guidelines. Written informed consent was obtained from all participants prior to study entry following a detailed explanation of the nature of the study.

The subjects included those patients who fulfilled the following criteria: (1) DSM-IV diagnosis of schizophrenia or schizoaffective disorder; (2) a diagnosis of tardive dyskinesia (according to DSM-IV-TR research criteria[44]), confirmed independently by 2 specialist psychiatrists who were experienced in the diagnosis and treatment of movement disorders; (3) a score on the clinical global impression (CGI) subscale of the Extrapyramidal Symptom Rating Scale (ESRS)[45,46] of moderate or marked degree; (4) duration of tardive dyskinesia for at least 1 year; (5) a stable psychotropic regimen for at least 1 month prior to entry into the study; and (6) hospitalization of the patient.

Exclusion criteria included the following: (1) a concurrent medical or neurologic illness possibly causing a movement disorder, such as Huntington's chorea, tics, or Parkinson's disease; (2) a score on the CGI subscale of the ESRS of mild severity; and (3) the use of drugs or alcohol.

Of the 53 screened patients, 8 patients refused to participate, and 5 were discharged from hospital prior to the commencement of the study and were lost to follow-up. Thus 40 eligible subjects provided their written informed consent to participate in this study. The mean ± SD age of the patients (26 men and 14 women) was 47 ± 12 years (range, 24–69 years). Twenty-four patients suffered from schizophrenia and 16 from schizoaffective disorder. All patients had been hospitalized for a period of 1 to 3 years. The majority was smokers, and most had suffered from tardive dyskinesia for less than 3 years. The demographic characteristics of the patients are presented in Table 1.

At the time of the study, 24 patients were receiving conventional psychotropics (chlorpromazine equivalent 100–950 mg/day, mean ± SD = 337.5 ± 176.5). Thirteen patients received atypical antipsychotics: 7 received olanzapine 5–20 mg/day (mean ± SD = 16.4 ± 6.3), 3 received ziprasidone 120–200 mg/day (mean ± SD = 173.3 ± 46.2), a further 3 received clozapine 100–300 mg/day (mean ± SD = 233.3 ± 115.5), 2 received risperidone 2–4 mg/day (mean ± SD = 3.0 ± 1.4), and 1 received quetiapine 400 mg/day. Three patients were treated with a combination of neuroleptics: 2 patients with typical-atypical and 1 patient with atypical-atypical combinations. Twenty-four patients received various mood stabilizers (lithium, carbamazepine, or valproate) in combination with antipsychotic agents.

Procedure and Outcome Measures

The crossover design of the study included an initial period of 4 weeks (phase I) where subjects were randomized to receive either piracetam or placebo. After a washout period of 1 week, a further 4-week period (phase II) of the crossover design was commenced where those subjects who had previously received piracetam now received placebo, and those initially in the placebo arm now received the study drug. Both patients and raters were blinded to group allocation. Piracetam or placebo was administered in addition to the patient's regular antipsychotic medication schedule. A crossover design was used

as an appropriate design for chronic patients in stable condition in an attempt to reduce variance and increase the effective sample size.

Each subject received 3 capsules of piracetam (each containing 800 mg) twice a day (total dose, 4800 mg/day) or 3 capsules of placebo twice per day, depending on the phase of the crossover design, at 8 a.m. and 8 p.m.

Clinical Ratings

The ESRS was chosen to assess the severity of tardive dyskinesia. This scale was developed for epidemiologic studies of tardive dyskinesia in schizophrenic patients and was designed to rate 4 types of drug-induced movement disorders: parkinsonism, akathisia, dystonia, and tardive dyskinesia. Each variable in this scale can be scored from normal (0 points) to extremely severe (6 points). Its sensitivity and validity were established through several clinical trials.[45,46] In addition, ESRS also includes a CGI subscale.

The safety and tolerability of piracetam were evaluated by assessing both the incidence and severity of adverse events in each phase of the study for all subjects who had received at least 1 dose of medication. All patients were assessed by the same investigators (I.L. and V.L.) who underwent pretrial training in the assessment tool. The κ for inter-rater reliability on the tardive parkinsonism subscale was 0.93, and on the tardive dyskinesia and CGI subscales it was 0.90. The assessment was performed at baseline; at weeks 1, 2, 3, and 4 (end of phase I); at week 5 (end of washout period); and at weeks 6, 7, 8, and 9 (end of phase II). All assessments were made at the same time in the morning (10 a.m. ± 1:00 hour) in order to rule out diurnal fluctuations that may influence tardive dyskinesia symptoms.[47] All study and routine medications were taken by the participants under the supervision of the nursing staff, thus ensuring compliance.

We considered a reduction of up to 20% from baseline in CGI subscale of ESRS scores to represent no response; any improvement greater than 20% was considered to be clinically significant.[9]

Statistical Analysis

All statistical analyses were performed using Statistica 7 for Windows.[48] Differences between groups in the demographic and baseline clinical data were compared by the Pearson χ^2 test, and baseline scores were analyzed with Student t test. Two-period crossover design for analysis of variance (ANOVA) was performed.[49] We used absolute values for the ESRS subscales in those subjects completing the entire study (N = 31) (Table 2). For dependent variables, 5 points of time were used as within effect. Treatment (piracetam/placebo) and treatment order (for evaluating carryover effect) were used as independent factors, and analysis for specific effects and interactions was performed. According to this trial design, a separate post hoc analysis of phase I alone was performed. In this analysis, we included all those subjects who completed the first phase of the study (N = 35). Two-way ANOVA with repeated measures was performed relating to changes in scores from baseline (Table 3).

Table 1. Demographic Data and Clinical Characteristics of Schizophrenic and Schizoaffective Patients With Tardive Movement Disorders at Baseline[a]

Characteristic	All Patients (N = 40)	Piracetam (N = 21)	Placebo (N = 19)
Gender, N			
Female	16	7	9
Male	24	14	10
Age, y			
Mean ± SD	47.4 ± 11.6	44.9 ± 12.4	50.1 ± 10.2
Range	24–69	26–69	24–69
Smoker, N	31	17	14
Nonsmoker, N	9	4	5
DSM-IV diagnosis, N			
Schizophrenia	24	10	14
Schizoaffective disorder	16	11	5
Duration of illness, y			
Mean ± SD	21.4 ± 11.2	22.6 ± 12.3	20.1 ± 10.0
Range	3–45	3–45	6–39
Duration of tardive dyskinesia, N			
< 3 y	25	12	13
3–5 y	8	5	3
> 5 y	7	4	3
ESRS baseline scores, mean ± SD			
Tardive parkinsonism	21.3 ± 10.6	22.8 ± 11.7	19.5 ± 9.2
Tardive dyskinesia	7.8 ± 5.2	8.7 ± 6.4	6.8 ± 3.3
CGI	3.8 ± 0.8	3.8 ± 0.9	3.9 ± 0.8

[a]There were no significant differences between the 2 groups.
Abbreviations: CGI = clinical global impression, ESRS = Extrapyramidal Symptom Rating Scale.

RESULTS

After breaking the code following the database lock, it was found that 21 patients (14 men and 7 women, mean ± SD age was equal to 44.9 ± 12.4 years) commenced treatment with piracetam and 19 patients (10 men and 9 women, mean ± SD age was 50.1 ± 10.2 years) received placebo initially. No significant demographic or clinical differences were found between the piracetam and placebo groups (Table 1). Piracetam was well tolerated by all patients without any side effects, and all of them were able to receive the dose of 4800 mg/day.

Of the 40 randomly assigned patients, 5 subjects (4 taking placebo and 1 taking piracetam) did not comply with the treatment regimen following the first 2 weeks of the study and were not included in the statistical analysis. Therefore, 35 patients completed phase I, and, of these, 4 patients (2 receiving placebo and 2 receiving piracetam) did not agree to continue to phase II, resulting in 31 patients completing both phases of the crossover protocol. The main reason for patient dropout was the large size and number of the capsules that they were required to take.

Table 2. Efficacy of Piracetam Versus Placebo in 31 Schizophrenic and Schizoaffective Patients With Tardive Movement Disorders Completing All Phases of the Crossover Study (ESRS subscales analysis, mean ± SEM, N = 31)

							Treatment × Time (df = 4,116)	
ESRS Subscale	Treatment	Baseline	Week 1	Week 2	Week 3	Week 4	F	p
Tardive parkinsonism	Piracetam	19.7 ± 2.2	14.1 ± 1.9	13.2 ± 1.6	11.9 ± 1.5	11.0 ± 1.5	4.9	.001[a]
	Placebo	16.1 ± 1.7	16.3 ± 2.2	15.2 ± 2.2	15.6 ± 2.1	15.5 ± 2.2		
Tardive dyskinesia	Piracetam	7.7 ± 0.9	6.5 ± 1.0	6.1 ± 0.9	5.5 ± 0.9	4.7 ± 0.8	4.3	.003[b]
	Placebo	5.8 ± 1.0	5.6 ± 0.9	5.7 ± 0.8	6.0 ± 1.1	6.0 ± 0.9		
CGI	Piracetam	3.5 ± 0.2	3.1 ± 0.2	2.9 ± 0.2	2.6 ± 0.2	2.4 ± 0.2	4.1	.004[c]
	Placebo	3.0 ± 0.2	3.0 ± 0.2	2.9 ± 0.2	2.9 ± 0.3	2.9 ± 0.2		

[a]Order × time F = 0.6 (df = 4,116), p = .7; order × treatment × time F = 0.5 (df = 4,116), p = .8.
[b]Order × time F = 0.9 (df = 4,116), p = .4; order × treatment × time F = 0.8 (df = 4,116), p = .5.
[c]Order × time F = 0.8 (df = 4,116), p = .5; order × treatment × time F = 0.3 (df = 4,116), p = .9.
Abbreviations: CGI = clinical global impression, ESRS = Extrapyramidal Symptom Rating Scale.

The efficacy of piracetam versus placebo in those 31 patients completing both phases of the crossover study is presented in Table 2. There was no carryover effect in all ESRS subscales (time-order and time-order-treatment interactions, p > .5). The effect of piracetam on the tardive parkinsonism subscale was significantly superior (time-treatment interaction: F = 4.9; df = 4,116; p = .001). During piracetam treatment, the mean ± SEM symptom score on the tardive parkinsonism subscale decreased by 8.7 points, from 19.7 ± 2.2 (baseline) to 11.0 ± 1.5 (endpoint), whereas for placebo this score decreased by only 0.6 points: from 16.1 ± 1.7 initially to 15.5 ± 2.2 at the end of the study.

Symptoms of tardive dyskinesia during piracetam treatment improved, decreasing by 3 points, from a mean ± SEM score of 7.7 ± 0.9 (baseline) to 4.7 ± 0.8 (endpoint), while in the placebo group the symptoms actually deteriorated by 0.2 points, increasing from 5.8 ± 1.0 to 6.0 ± 0.9 (time-treatment interaction: F = 4.3; df = 4,116; p = .003).

On the CGI subscale, the mean ± SEM score decreased during piracetam treatment by 1.1 points, from 3.5 ± 0.2 (baseline) to 2.4 ± 0.2 (endpoint), and for placebo the decrease was only 0.1 point, from 3.0 ± 0.2 to 2.9 ± 0.2 (time-treatment interaction: F = 4.1; df = 4,116; p = .004).

During the week-long washout period, there was no change in the scores on any of the subscales for either the piracetam or the placebo group.

The effect of those patients receiving piracetam (N = 20) versus placebo (N = 15) (mean changes from baseline in each of the ESRS subscale scores) in phase I only is presented in Table 3. The analysis of the mean Δ ± SEM baseline scores of the tardive parkinsonism, tardive dyskinesia, and CGI subscales did not reveal any significant difference between the piracetam and placebo groups: 22.4 ± 2.4 and 19.9 ± 2.8 (t = –0.7; df = 1,33; p = .51), 7.7 ± 0.9 and 8.4 ± 1.6 (t = 0.4; df = 1,33; p = .69), and 3.9 ± 0.2 and 3.7 ± 0.2 (t = –0.6; df = 1,33; p = .53), respectively. At the end of phase I, those subjects treated with piracetam demonstrated a significant improvement on the tardive dyskinesia and CGI subscales compared to those receiving placebo (time-treatment interaction: F = 6.3; df = 3,99; p < .044 and F = 5.2; df = 3,99; p < .002, respectively). On the tardive parkinsonism subscale, the patients treated with piracetam demonstrated a trend towards improvement, but this was not significant (time-treatment interaction: F = 0.5; df = 3,99; p < .7).

In order to evaluate the treatment effect, we calculated the percentage of responders, including all patients who completed at least 1 phase of the study. Twenty patients were treated with piracetam during the first phase and 13 were treated with it during the second phase (N = 33). Fifteen patients received placebo during the first phase and 18 received it during the second phase (N = 33). There was a clinically significant improvement in 67% of patients receiving piracetam treatment. Of note is that in 27% there was no clinical change, and a further 6% deteriorated on piracetam treatment. In contrast to these findings, during treatment with placebo, 24% of patients improved, the condition of a further 43% remained unchanged, and 33% deteriorated ($\chi^2 = 15.12$, df = 3, p = .0017).

DISCUSSION

The treatment of tardive dyskinesia includes a variety of medications. Recently, the most popular therapeutic approach has been vitamin E, but, although there is evidence that it may prevent the deterioration of tardive dyskinesia, it does not improve symptoms.[7] Apart from vitamin E, there are some reports of a beneficial effect of vitamin B_6 on tardive dyskinesia.[9,50–53]

Earlier studies have reported an improvement in the symptoms of tardive dyskinesia in patients with schizophrenia treated with piracetam.[37–39,43] Much of these data was based on uncontrolled studies or on case reports,[37,39,43] with only 1 double-blind, placebo-controlled study being published some decades ago.[38] Yet in spite of these poten-

Table 3. Efficacy of Piracetam Versus Placebo in Schizophrenic Patients With Tardive Movement Disorders Completing Phase I (ESRS subscales analysis, mean Δ ± SEM, N = 35)[a]

							Treatment Effect (df = 1,33)		Time (df = 3,99)		Time-Treatment Interaction (df = 3,99)	
ESRS Subscale	Treatment[b]	Baseline[c]	Week 1 (Δ)	Week 2 (Δ)	Week 3 (Δ)	Week 4 (Δ)	F	p	F	p	F	p
Tardive parkinsonism	Piracetam	22.4 ± 2.4	4.5 ± 1.8	6.1 ± 1.6	6.2 ± 2.1	7.2 ± 2.2	3.1	< .09	2.3	< .1	0.5	< .7
	Placebo	19.9 ± 2.8	–0.3 ± 2.1	2.9 ± 1.9	0.8 ± 2.4	1.5 ± 2.5						
Tardive dyskinesia	Piracetam	7.7 ± 0.9	0.9 ± 1.0	1.2 ± 0.9	1.6 ± 1.2	2.9 ± 0.9	0.8	.38	1.4	< .25	6.3	< .044
	Placebo	8.4 ± 1.6	0.9 ± 1.2	0.8 ± 1.0	–0.5 ± 1.3	0.3 ± 1.0						
CGI	Piracetam	3.9 ± 0.2	0.3 ± 0.2	0.5 ± 0.2	0.8 ± 0.3	1.0 ± 0.3	2.9	< .1	1.2	< .3	5.2	< .002
	Placebo	3.7 ± 0.2	0.2 ± 0.3	0.2 ± 0.3	–0.1 ± 0.3	0.0 ± 0.3						

[a]Table 3 presents the mean changes (Δ) from baseline in each of the ESRS subscale scores for the 2 groups on weeks 1 to 4 of treatment.
[b]Piracetam, N = 20; placebo, N = 15.
[c]No difference between groups at baseline (t test, p > .05).
Abbreviations: CGI = clinical global impression, ESRS = Extrapyramidal Symptom Rating Scale.

tially positive results, this therapeutic option has received little attention.

The results of our double-blind, placebo-controlled, crossover study suggest that oral piracetam at a dose of 4800 mg/day may be an effective and safe treatment for tardive dyskinesia. A beneficial clinical therapeutic effect was seen in all the ESRS subscales, with this effect becoming more marked over time. We also found that the therapeutic effect of piracetam was maintained after stopping treatment. It should be noted that the improvement of symptoms was clearly temporally related to piracetam treatment, which may suggest that continuing treatment for a longer period of time may lead to a greater clinical benefit. Thus, studies with longer periods of follow-up are needed.

The design of our study included those patients whose antipsychotic medication schedule was not altered in order to prevent a "masking" tardive dyskinesia effect of atypical antipsychotics. Clinically, we did not find any difference between the various atypical antipsychotics and conventional neuroleptics regarding their influence on the symptoms of tardive dyskinesia.

Previous studies have shown a beneficial effect of piracetam not only on tardive movement disorders but also on acute extrapyramidal side effects (EPS). Piracetam was found to be effective in the treatment of EPS (akathisia, tremor, muscle rigidity, dyskinesia) at a dose of 4000 mg/day, having an onset of action of 30 to 60 min after intravenous administration.[37] Compared to its use in the treatment of acute movement disturbances, the therapeutic dose of piracetam in tardive dyskinesia was higher and symptoms took longer to improve,[38] disappearing 3 to 7 days following the daily intravenous administration of 8000 mg of piracetam. In that study,[38] the authors treated 32 patients and evaluated the effect using the CGI scale. In contrast to those results, our findings demonstrate a significant improvement in tardive dyskinesia only by the end of the fourth week of oral piracetam treatment, yet at a lower dose. This discrepancy may be explained by the difference in the route of administration and in the doses of the drug.[31] Our study supports previous reports that piracetam may be a useful agent in the treatment of drug-induced tardive dyskinesia.

Although the mechanism of action of piracetam is not known, we may postulate as to theoretical possibilities. Since the loss of striatal cholinergic neurons may be a basis for the development of tardive dyskinesia,[4] one explanation relates to the ability of piracetam to elevate the density of acetylcholine receptors in the brain.[26,27] Another explanation is derived from the theory that free radicals are neurotoxic and that the antioxidant properties of piracetam[54] may neutralize this damaging effect.

The prevalence of tardive dyskinesia is significantly higher among smokers than nonsmokers. Nicotine increases the synthesis and release of dopamine in the

nigrostriatal pathway of animals. Such mechanism may contribute to the higher prevalence of tardive dyskinesia among smokers.[55] Some researchers concluded that patients who smoke received significantly higher doses of neuroleptics but did not have significantly more severe tardive dyskinesia or parkinsonism.[56] Our results demonstrate that both smokers and nonsmokers had a positive effect of piracetam on tardive dyskinesia.

Our study has a number of limitations, mostly related to the fairly small sample size and the relatively short duration of follow-up. In order to examine its long-term treatment effect, an extended period of drug administration and follow-up is needed. Another limitation is the lack of the use of a psychopathologic rating scale in order to examine the possibility of a relationship between the amelioration of tardive dyskinesia and the presence of psychotic symptoms. Nevertheless, we must emphasize that only schizophrenic patients who had been on a stable psychotropic regimen for at least 1 month prior to entry into the study took part in this trial and that no patients were excluded from follow-up due to worsening psychotic symptoms. Also, no subjects required an alteration in their dose of psychotropic medications during the study.

There is as yet no consensus regarding the definitive treatment of tardive dyskinesia. This study is the first report of a randomized, double-blind, crossover trial using oral piracetam in schizophrenic and schizoaffective patients suffering from tardive dyskinesia. In the light of our findings, we propose that piracetam be considered as a potential therapeutic option for tardive dyskinesia and that large, randomized controlled studies be performed to further evaluate and confirm the effect of piracetam on tardive dyskinesia.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine, Sonazine, and others), clonazepam (Klonopin and others), clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa and others), quetiapine (Seroquel), ziprasidone (Geodon).

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