Effects of Levetiracetam on Tardive Dyskinesia: A Randomized, Double-Blind, Placebo-Controlled Study

Scott W. Woods, M.D.; John R. Saksa, Psy.D.; C. Bruce Baker, M.D.; Shuki J. Cohen, Ph.D.; and Cenk Tek, M.D.

Objective: The goal of this study was to evaluate the efficacy and safety of levetiracetam versus placebo for tardive dyskinesia (TD).

Method: This double-blind, placebo-controlled, randomized study was conducted at the Connecticut Mental Health Center between September 2004 and April 2006. Antipsychotic-treated patients meeting Glazer-Morgenstern criteria for TD were assigned at random to receive levetiracetam 500 mg/day to 3000 mg/day or placebo for 12 weeks. After completion of 12 weeks, patients were permitted to receive open-label levetiracetam for a further 12 weeks. The principal efficacy outcome measure was improvement in the Abnormal Involuntary Movement Scale (AIMS) total score. Safety was assessed with an adverse event scale, psychiatric symptom rating scales, weight, and hematologic tests.

Results: A total of 50 patients were randomly assigned to treatment. AIMS total scores were moderate in severity at baseline. Mixed regression models revealed that AIMS total scores declined 43.5% from baseline in the levetiracetam group compared to 18.7% for placebo ($p = .022$). Patients continuing levetiracetam in the open-label phase continued to improve, and patients crossed over to open-label levetiracetam improved to a similar degree as those initially assigned. Levetiracetam was well tolerated.

Conclusion: Levetiracetam appeared effective for TD in this study. The mechanisms of its therapeutic effect are unclear but may involve reducing neuronal hypersynchrony in basal ganglia. Future studies should attempt to replicate the current results.

Trial Registration: clinicaltrials.gov Identifier: NCT00291213

(J Clin Psychiatry 2008;69:546–554)

Received April 24, 2007; accepted Aug. 27, 2007. From the Department of Psychiatry, Yale University, Connecticut Mental Health Center, New Haven.

This project was supported by a grant from UCB Pharma.

Dr. Woods discloses research grant support from Bristol Myers Squibb, Eli Lilly, Janssen, and UCB Pharma and advisory board membership for Otsuka. Drs. Saksa, Baker, Cohen, and Tek report no additional financial or other relationships relevant to the subject of this article.

Corresponding author and reprints: Scott W. Woods, M.D., Yale Department of Psychiatry, Connecticut Mental Health Center, 34 Park St., New Haven CT 06519 (e-mail: scott.woods@yale.edu).

Tardive dyskinesia (TD), an iatrogenic syndrome of involuntary movements, has been one of the most limiting adverse effects associated with antipsychotic medication. Some studies suggest that the newer atypical antipsychotics reduce the risk of tardive dyskinesia[1,2]; however, despite widespread use of the newer agents, TD unfortunately appears to continue to be a prevalent condition in current practice.[3–7] Tardive dyskinesia also remains an illness in need of satisfactory treatments.[8,9]

Levetiracetam, the levorotary stereoisomer of an ethylated congener of the commonly used European medication piracetam, is a U.S. Food and Drug Administration (FDA)–approved treatment for epilepsy. The mechanisms of action for levetiracetam are not fully known. Levetiracetam binds to a novel, specific binding site in CNS membranes[10] known as synaptic vesicle protein 2A (SV2A).[11] A number of clinical and preclinical studies suggest that levetiracetam may have efficacy for TD. Three prospective open-label trials[12–14] and a case report,[15] totaling to 42 patients, have all reported findings consistent with efficacy. In addition, an open study and case reports suggest levetiracetam may be helpful for levodopa-induced dyskinesia (LID) in Parkinson's disease,[16,17] although 2 more open studies found a lack of efficacy for this condition,[18,19] and all 4 studies indicate problematic sedation in this population. Levetiracetam also has decreased dyskinetic movements in an animal model of LID.[20–23] Other open studies and case reports suggest levetiracetam is helpful in humans with a variety of other dyskinetic or hyperkinetic movement disorders.[24–38] Case reports[39,40] have also suggested the possible efficacy of piracetam for TD.

Despite this variety of suggestive evidence, however, no placebo-controlled findings on the possible effects of levetiracetam for TD have yet been published. The overall goal of the present project was therefore to conduct such a trial.

METHOD

Patients

Participants were recruited from adult patients registered clinically at the Connecticut Mental Health Center (CMHC). The Yale Human Investigation Committee approved the study. Subject data were collected between

September 2004 and April 2006. Possible side effects were explained fully to each patient, and each patient gave written informed consent. Consenting patients underwent baseline evaluation, including evaluation of eligibility for randomization. In order to be eligible for randomization, patients must have (1) met Glazer-Morgenstern criteria[41] for a diagnosis of TD based on the Abnormal Involuntary Movement Scale (AIMS)[42] examination on 2 consecutive examinations separated by 1 week, (2) been sufficiently stable psychiatrically that their CMHC clinician indicated that changes in prescribed antipsychotic medication drug or dosage were not anticipated in the next 3 months, (3) been compliant with their prescribed medications, (4) had no unstable medical illness, (5) had no neurologic illness that might interfere with TD severity examinations, (6) had no history of renal insufficiency, (7) not been pregnant or breast feeding and been willing to use medically acceptable methods of contraception, (8) not initiated or increased the dosage of medication intended to treat TD within 4 weeks of enrollment, (9) not had leucopenia, neutropenia, or thrombocytopenia on baseline complete blood count with differential, and (10) not been known to be infected with human immunodeficiency virus or to be immunocompromised on another basis. Glazer-Morgenstern criteria for dyskinesia at a particular visit require that the total AIMS score be ≥ 3, with at least 1 body area rated ≥ 2. Baseline evaluation also included psychiatric and substance abuse diagnoses using the Structured Clinical Interview for DSM-IV,[43] duration of TD by history and medical record review, and urine toxicology screen.

Procedures

Eligible patients who gave written informed consent were assigned at random to receive levetiracetam versus matching placebo for 12 weeks. Each pill contained either levetiracetam 500 mg or placebo. Dosing was flexible, within the following guidelines. Dosage was initiated at 1 pill at bedtime for 1 week. Thereafter, side effects permitting and assuming lack of complete response, the dose was recommended to be escalated weekly by 500 mg/day to the maximum dose of 3000 mg/day, given in 2 divided doses. When the 2 daily doses were unequal, the larger dose was prescribed at bedtime. Patients continued in clinical treatment for their primary psychiatric disorders. Study visits during the double-blind phase occurred at baseline and at weeks 1, 2, 3, 4, 6, 9, and 12 after randomization. Medication adherence was assessed with pill counts.

After the double-blind phase, patients in the placebo group were offered the opportunity to receive open-label levetiracetam for a further 12 weeks. The blind from the former phase was maintained in the levetiracetam group, and levetiracetam was titrated (or retitrated) as per the schedule used in the double-blind phase. Thus, former placebo patients were crossed over to levetiracetam during this phase, and former double-blind levetiracetam-assigned patients continued levetiracetam during this phase. Study visits during the open-label phase occurred at weeks 13, 14, 15, 16, 18, 21, and 24 weeks after initial randomization.

At each study visit, patients were weighed and underwent an AIMS examination and symptom ratings using the Positive and Negative Syndrome Scale (PANSS),[44] Young Mania Rating Scale (YMRS),[45] Montgomery-Asberg Depression Rating Scale (MADRS),[46] and the Hamilton Rating Scale for Anxiety (HAM-A)[47] administered via a structured interview guide.[48] Adverse events were rated using the Systematic Assessment for Treatment Emergent Events, general inquiry method.[49] Complete blood counts were obtained at baseline and at 6, 12, 18, and 24 weeks. Quality of life was assessed using the Heinrichs-Carpenter Scale[50] at baseline.

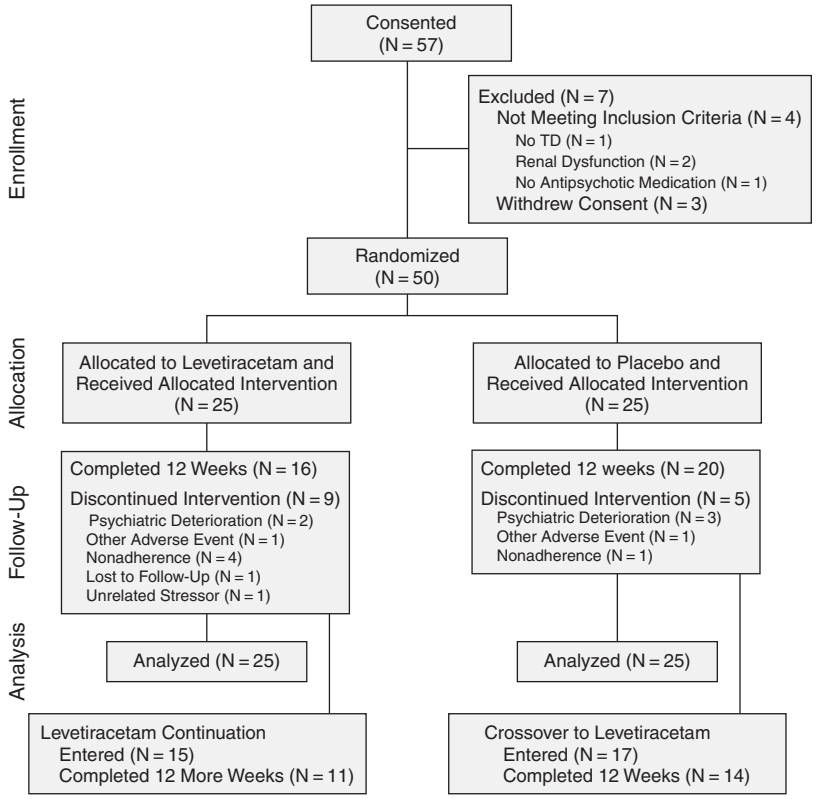
We converted all antipsychotic doses to chlorpromazine equivalents, using published equivalencies for oral conventional[51] and atypical[52] antipsychotics. We converted depot doses to oral doses using the manufacturers' recommended equivalents for haloperidol (15 mg/4 weeks intramuscularly equivalent to 1 mg/day orally), fluphenazine (12.5 mg/3 weeks intramuscularly equivalent to 10 mg/day orally), and risperidone (25 mg/2 weeks intramuscularly equivalent to 2 mg/day orally); these are generally supported by empirical studies.[53–55]

Statistical Methods

Comparability of randomized groups at baseline was assessed using analysis of variance for continuous measures and Fisher exact test for categorical measures. The principal outcome measure was defined a priori as the AIMS total score. This and other continuous measures over time during the acute phase were analyzed using mixed-effects models,[56–58] including terms for treatment, time, baseline severity, and treatment-by-time interaction. All of these terms were considered fixed effects in the model, with the subjects term modeled as a random effect. The most parsimonious covariance matrix for within-patient error was specified, using Schwarz's Bayesian Criterion. Model-based least-squares means were tabulated by treatment and time. Analyses exploring possible quadratic effects of time were also explored; these models did not materially improve upon the simpler linear model and yielded similar results. Descriptive methods were used to assess results during the open-label phase. All hypotheses were tested at 2-sided $\alpha = .05$. Power calculations indicated that a sample size of 25 per group was required to have power greater than 0.80 to detect an average 3-point improvement in the AIMS total score in the levetiracetam group as statistically different from an average 1-point improvement in the placebo group.[59]

Review of the literature on double-blind, placebo-controlled studies did not identify strong a priori hy-

Figure 1. Study CONSORT Diagram



Abbreviation: TD = tardive dyskinesia.

potheses for possible moderators of drug versus placebo effects. One study suggested that the difference between ceruletide versus placebo was stronger among patients less than 60 years of age,[60] and another study reported that the effects of vitamin E were stronger versus placebo among the subgroup of patients who had had TD for fewer than 5 years.[61] Analyses to investigate whether baseline factors modified the treatment effect over time therefore tested effects of age and duration of TD and explored additional empirically selected variables: baseline AIMS total score, gender, and antipsychotic dose and type. These analyses were accomplished by adding 3-way interaction terms to separate models.

In addition to the principal analyses of the AIMS total score, we also investigated the relative rates at which subjects achieved remission, defined a priori as no longer meeting the Glazer-Morgenstern TD entry criteria. These analyses employed Cox regression or "survival" techniques.

RESULTS

Patients and Disposition

A total of 50 patients were randomly assigned: 25 assigned to placebo and 25 to levetiracetam (Figure 1). Most patients were middle-aged and were receiving atypical antipsychotics at baseline (Table 1). The treatment groups did not differ significantly on demographic or diagnostic measures at baseline, although there were trends for the levetiracetam group to be younger, less well-educated, and to be on lower chlorpromazine equivalent antipsychotic doses (Table 1). Completion rates (64% [N = 16] for the levetiracetam group and 80% [N = 20] for the placebo group, p = .345) and reasons for discontinuation (Figure 1) also did not differ significantly between treatment groups. The mean ± SD number of weeks patients participated in the acute phase was 8.4 ± 5.1 for the levetiracetam group and 10.2 ± 3.9 for the placebo group (F = 1.98, df = 49, p = .166).

Dosing and Concomitant Medication

Prescribed daily doses (mean ± SD) at the last visit during the randomized phase were 1900 ± 1099 mg/day for levetiracetam and 2460 ± 912 mg/day for placebo (F = 3.84, df = 1,48; p = .056). Pill count adherence was 98% for levetiracetam and 89% for placebo. Changes in the prescribed concomitant antipsychotic medications or their doses during the randomized phase occurred in 3 levetiracetam patients (12%) versus 5 placebo patients (20%, p = .702). Changes in the prescribed concomitant

Table 1. Baseline Characteristics of Randomized Groups of Patients With Tardive Dyskinesia (TD)

Characteristic	Levetiracetam (N = 25)[a]	Placebo (N = 25)[a]	p
Male, N (%)[b]	16 (64)	13 (52)	.567
White, N (%)[b]	9 (36)	10 (40)	.999
Age, mean ± SD, y[b]	45.1 ± 10.0	49.8 ± 9.3	.091
Education, mean ± SD, y[b]	11.5 ± 2.9[c]	12.2 ± 2.6[d]	.081
Weight, mean ± SD, kg	84.9 ± 19.4[d]	92.3 ± 20.1[d]	.199
Antipsychotic dose, mean ± SD[e]	455 ± 334	800 ± 958	.099
Prior[b] antipsychotic dose, mean ± SD[e]	455 ± 346	807 ± 949	.091
Anticholinergic use, N (%)	13 (52)	12 (48)	.999
AIMS total score, mean ± SD	9.4 ± 3.4	8.0 ± 3.1	.157
Principal psychiatric diagnosis, N (%)			.333
Schizophrenia/schizoaffective	24 (96)	21 (84)	
Affective disorder	1 (4)	3 (12)	
Other	0 (0)	1 (4)	
Substance abuse or dependence, N (%)	10 (40)	9 (36)	.999
Duration of TD, mean ± SD, y	7.5 ± 8.4	9.0 ± 7.3	.501
Antipsychotic type, N (%)			.416
Atypical only	13 (52)	16 (64)	
Conventional only	8 (32)	4 (16)	
Atypical and conventional	4 (16)	5 (20)	
PANSS total score, mean ± SD	72.3 ± 10.3[d]	76.2 ± 15.9	.311
MADRS total score, mean ± SD	7.7 ± 7.0[d]	9.2 ± 8.5	.486
YMRS total score, mean ± SD	2.1 ± 2.1[d]	3.3 ± 4.2[d]	.215
HAM-A total score, mean ± SD	9.4 ± 7.2[c]	10.0 ± 6.9	.765
Heinrichs-Carpenter total score, mean ± SD	64.0 ± 14.9[d]	59.4 ± 19.0	.347

[a]Sample sizes: N = 25, except where indicated.
[b]3 months prior to baseline.
[c]N = 23.
[d]N = 24.
[e]Chlorpromazine equivalents.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, HAM-A = Hamilton Rating Scale for Anxiety, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, YMRS = Young Mania Rating Scale.

anticholinergic medications or their doses during the randomized phase occurred in 0 levetiracetam patients (0%) versus 2 placebo patients (8%, p = .490).

Efficacy During Double-Blind Phase

Since there was a small difference between randomized groups on AIMS total score at baseline (Table 1), and baseline AIMS scores were significantly correlated with subsequent scores, the mixed-effects model for the AIMS total score included a term for baseline as well as terms for treatment and time. In addition to the treatment-by-time interaction term, baseline-by-time, baseline-by-treatment, and baseline-by-treatment-by-time interaction terms were initially included as well. Since none of the interactions with baseline were statistically significant, these terms were eliminated from the model. Further analyses revealed that the small age difference at baseline did not confound the levetiracetam treatment effect, nor did the small baseline differences in years of education, antipsychotic chlorpromazine equivalent dose, antipsychotic type at baseline (only atypical vs. any conventional), or gender. Other analyses including 3-way interaction terms suggested that the levetiracetam treatment effect was not modified by age, duration of TD, gender, or antipsychotic dose or type. Thus none of these terms were included in the final model, which was restricted to terms for treatment, time, baseline, and treatment-by-time interaction.

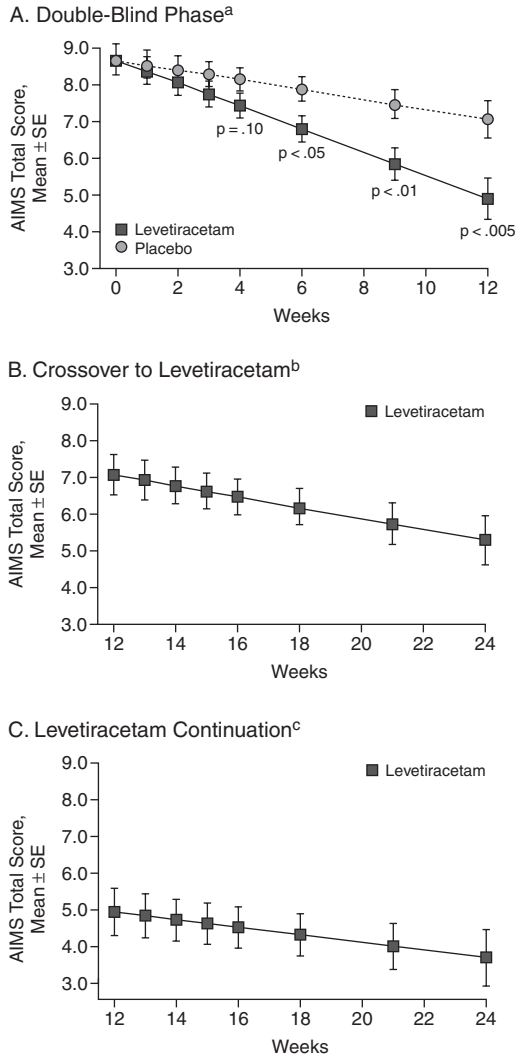
In the final mixed-effects model, the treatment-by-time interaction for the AIMS total score during the first 12 weeks (Figure 2A) was statistically significant (F = 5.35, df = 1,236; p = .022). The levetiracetam-placebo difference reached a trend level by week 4 and was statistically significant at weeks 6, 9, and 12 (Figure 2A). At week 12, the AIMS total score model-estimated marginal mean in the levetiracetam group dropped 43.5% from baseline, and the placebo group estimated mean fell 18.7%.

Cox regression analyses of time-to-remission employed the baseline AIMS total score as a covariate. Group differences did not achieve statistical significance.

Efficacy During Open-Label Crossover to Levetiracetam

Among 20 patients completing acute treatment who had been assigned to placebo, 17 entered the open-label phase. Of these, 14 completed 12 weeks (82%). Prescribed daily doses (mean ± SD) at the last visit were 2350 ± 860 mg/day. Only 2 of these patients underwent antipsychotic medication or dosage adjustments. After 12 weeks of open-label levetiracetam, the AIMS total score estimated mean dropped 25.1% from the end of placebo and a total of 39.1% from the original baseline (Figure 2B).

Figure 2. Abnormal Involuntary Movement Scale (AIMS) Total Scores Over Time With Levetiracetam and Placebo



[a]Estimated marginal means and standard errors from mixed regression model for AIMS total scores during double-blind treatment in patients randomly assigned to levetiracetam versus placebo. Time is shown as weeks since randomization. Model contained terms for assignment, baseline score, time, and the assignment-by-time interaction. These terms were modeled as fixed effects with the subjects term modeled as a random effect. Values are adjusted to the grand baseline mean. Indicated p values are for levetiracetam versus placebo at indicated time point with a 2-tailed test.
[b]Effects of open-label levetiracetam treatment in the former placebo group.
[c]Effects of open-label continuation treatment in the group previously randomized to levetiracetam.

Efficacy During Open-Label Levetiracetam Continuation

Among 16 patients completing acute treatment who had been assigned to levetiracetam, 15 entered the open-label phase. Of these, 11 completed the 12 continuation weeks (73%). Prescribed daily doses (mean ± SD) at the last visit were 2156 ± 1028 mg/day. Only 1 of these patients underwent antipsychotic medication or dosage adjustments during this phase. Figure 2C shows that AIMS total scores continued to improve in these patients. At week 24, the AIMS total score estimated marginal mean dropped 25.1% from week 12 and a total of 57.7% from the original baseline.

Table 2. Patients Reporting Any Increase From Baseline at Any Time, According to Systematic Assessment for Treatment Emergent Events, General Inquiry Method (SAFTEE-GI)

SAFTEE-GI Term[a]	Levetiracetam (N = 25), N (%)	Placebo (N = 25), N (%)	p
Sedation	10 (40)	9 (36)	.999
Excitement/nervousness	3 (12)	1 (4)	.609
Headache	3 (12)	1 (4)	.609
Nasal congestion	3 (12)	2 (8)	.674
Irritability	2 (8)	0 (0)	.490
Ataxia	2 (8)	0 (0)	.490
Appetite decrease	2 (8)	0 (0)	.490
Fatigue	2 (8)	1 (4)	.999
Dry mouth	2 (8)	1 (4)	.999

[a]All SAFTEE-GI terms with > 2 emergent complaints in the levetiracetam group.

Poststudy Treatment Selection

Of the 25 subjects completing the open-label phase, 12 (48%) continued levetiracetam on a clinical basis after the protocol ended.

Safety

Adverse events leading to treatment discontinuation are shown in Figure 1. The 2 cases of psychiatric deterioration in patients receiving levetiracetam were for recurrence of suicidality in a patient with comorbid borderline personality disorder and for relapse to substance abuse. The 3 cases of psychiatric deterioration in patients receiving placebo were for agitated and psychotic behavior, for suicidal behavior, and for general clinical deterioration. The other adverse event leading to discontinuation was sedation in 1 patient receiving levetiracetam and aspiration pneumonia of unknown cause in 1 patient receiving placebo. In the 4 patients discontinuing levetiracetam because of protocol- or medication-nonadherence, 2 no longer had time for study visits (1 new job, 1 with marital problems), 1 became concerned about the theoretical potential for adverse effects and withdrew consent, and 1 decided to discontinue psychiatric treatment.

Adverse events overall were similar in levetiracetam- and placebo-treated groups during double-blind treatment (Table 2). Emergent ataxia/impaired coordination was observed in 2 patients receiving levetiracetam, in both cases rated as moderate. In one case, the complaint resolved with continued treatment. In the other case, ataxia emerged at the last visit of the double-blind phase, whereupon the patient decided not to continue on to the open-label phase.

Rating scale data similarly showed little evidence of psychiatric deterioration. In the mixed-effects analysis, the treatment-by-time interaction for the PANSS total score actually suggested a significant improvement ($F = 6.19$, $df = 1,131$; $p = .014$). Post hoc analyses revealed that the levetiracetam-placebo differences were small but statistically significant by week 6. At week 12, levetiracetam-treated patients had improved from baseline by 2.0 points, compared to a 0.2 point decline in the placebo group. The p values for the treatment-by-time interaction for the YMRS, MADRS, and HAM-A were not statistically significant.

During the open-label phase, 3 former placebo patients complained of newly emergent sedation, and 1 complained of dizziness. Three patients during open-label levetiracetam continuation complained of newly-emergent sedation, 2 of irritability, 2 of dizziness, and 1 of ataxia.

The treatment-by-time interaction for weight during the double-blind phase was not statistically significant, and there was no meaningful change in weight during the open-label phase, either in the crossover to levetiracetam group or the levetiracetam continuation group. Analyses on white blood cell (WBC) count, absolute neutrophil count (ANC), hemoglobin, hematocrit, and platelet count outcomes similarly showed no significant treatment-by-time interaction. In no patient did the WBC count fall below 2.8×10^9/L, the ANC fall below 1.0×10^9/L, or the platelet count fall below 75×10^9/L.

DISCUSSION

The principal finding of the present study is that the severity of TD movements in patients randomly assigned to levetiracetam improved significantly more than in those assigned to placebo over 12 weeks, as measured by the AIMS total score. The levetiracetam treatment effect did not appear to be modified by age, gender, baseline antipsychotic medication type or dose, or baseline TD severity. Open-label phase findings also supported levetiracetam efficacy. Rates of behavioral adverse events in this chronically ill group of psychiatric patients were low overall and similar in the randomized groups.

The degree of improvement observed during 12 weeks of blinded levetiracetam appears clinically meaningful (43.5% intent-to-treat average reduction in the AIMS total score). The average improvement from baseline of 57.7% at 24 weeks in the group continuing levetiracetam continuation appears clinically robust. Nearly half of patients completing the protocol chose to continue levetiracetam after the study ended on a clinical basis, confirming that the benefit patients received was clinically important in many cases.

The study design featured several strengths that increase confidence in the findings. Tardive dyskinesia efficacy studies have historically featured small sample sizes; we are aware of only 4 larger than ours.[62–65] Inclusion of placebo as the control treatment increases confidence in efficacy of levetiracetam. Modest to moderate improvement in TD with placebo in the range that we observed has been reported previously.[66–72] Treatment duration was relatively long-term compared to many previous TD efficacy studies, and the parallel design addresses concerns about possible carryover effects with the crossover design that has historically been frequently used in TD treatment studies. Finally, the study was conducted at only 1 site with only 2 raters, who were very experienced and had established excellent interrater reliability in a previous study.[7] The single-site design confers a strength in terms of minimizing measurement error, although it also imposes a limitation in terms of generalizability.

In addition to the limitation imposed by the single-site design, a second limitation of the trial is that analyses of time to remission did not distinguish between levetiracetam and placebo, even though analyses of the principal outcome (the continuous AIMS total score measure) were statistically significant, as outlined above. The reasons for nonsignificance in the time to remission analyses are not clear. One possibility is the limited sample size. Categorical outcomes are inherently less statistically powerful than the AIMS total score continuous outcome on which we based sample size calculations. Another possibility is that the levetiracetam treatment effect is sufficiently robust to improve the severity of tardive dyskinesia but not sufficiently robust to achieve remission. Further explorations of alternate categorical outcomes were promising but are not reported here due to their post hoc character. Future studies could test such hypotheses a priori.

Another potential limitation is that TD severity was only moderate on average in our sample, raising questions as to whether levetiracetam would be effective in more severely affected patients. This is a question requiring further empirical study; however, the levetiracetam-placebo difference did not vary significantly across the range of severity present in our subjects. Interestingly, in the 3 previously-reported prospective open-label trials,[12–14] TD movements were approximately twice as severe as those in our patients, and improvement from baseline to the final time point was more pronounced than in our patients, in the context of trial durations that were similar,[14] shorter,[12] or longer,[13] and average levetiracetam doses that were similar[13,14] or lower.[12] Lastly, the blind was maintained in patients who had been randomly assigned to levetiracetam as they entered continuation, so we needed to retitrate levetiracetam doses in this group. This retitration may have reduced efficacy during continuation.

Behavioral toxicity was not a limiting adverse effect of levetiracetam in our chronic psychiatric population. Levetiracetam treatment has been labeled with a warning from the FDA due to infrequent emergence of psychotic symptoms, suicidality, and other behavioral symptoms in the

epilepsy registration trials.[73] In other patient groups, analyses of placebo-controlled studies of levetiracetam suggested that these concerns did not extend to the trials investigating cognitive enhancement or antianxiety properties.[74] The current study is the first of which we are aware in chronic psychiatric patients, and discontinuations for behavioral adverse events or effects on rating scales with levetiracetam did not exceed placebo effects. Caution is still indicated nevertheless in using levetiracetam with psychiatric patients, because the current sample size is far too small to detect rare events.

Levetiracetam is also labeled with warnings from the FDA resulting from rates of somnolence and ataxia in the epilepsy trials that exceeded rates with placebo.[73] For example, in the epilepsy trials, about 3% of levetiracetam-treated patients discontinued treatment due to somnolence versus 0.7% for placebo, and 3.4% versus 1.6% experienced coordination problems. Somnolence and ataxia findings in our small group of chronically psychotic patients receiving other potentially sedating medications appeared similar to the experience with epilepsy patients. In the double-blind phase, 1 subject (4%) discontinued levetiracetam due to somnolence, and 2 subjects (8%) experienced emergence of ataxia/impaired coordination rated as moderate. Across all phases, the total number of patients complaining of newly emergent sedation at any time with levetiracetam was 16, among 42 patients (38%) receiving active drug for up to 24 weeks.

Levetiracetam is labeled with a precaution from the FDA for hematologic abnormalities. In the adult epilepsy registration trials, in which subjects took levetiracetam for up to 16–18 weeks, the WBC count fell below 2.8×10^9/L at some time in 3.2% of levetiracetam patients and in 1.8% of placebo patients. The ANC fell below 1.0×10^9/L at some time in 2.4% of levetiracetam patients and in 1.4% of placebo patients. No patient was discontinued from treatment for low ANC, and, in all cases but 1, ANC rose with continued treatment.[73] In a summary of adverse events on 3347 patients exposed to levetiracetam for as long as 3 years or more, the incidence of WBC drop was lower in the first month and then relatively constant across exposure duration thereafter.[75] In postmarketing reports, there have been infrequent complaints of leucopenia, neutropenia, pancytopenia, and thrombocytopenia in patients receiving levetiracetam. Although we did not observe any important effects of levetiracetam on hematologic parameters, our sample has very low power to detect infrequent events.

The pathophysiology of tardive dyskinesia remains relatively obscure, and the mechanisms of action of levetiracetam similarly remain to be fully elucidated. Consequently, we can only speculate about mechanisms of the observed treatment effect. We initiated the current study based largely on reports of clinical experience with levetiracetam[12–15] and piracetam.[39,40] Clinical use of levetiracetam in TD had been undertaken based on clinical studies of levetiracetam in LID in Parkinsonian patients.[16,17] These LID clinical studies had been based on levetiracetam performance in an animal model of LID,[20–23] which in turn had been suggested by basal ganglia electrophysiologic hypersynchrony in an animal Parkinsonism model[76,77] (and recently in the LID animal model[78] and in LID patients[79] as well) and by levetiracetam's ability to reduce hypersynchrony in epilepsy models.[80–82] Basal ganglia hypersynchrony has not to our knowledge been investigated in TD patients or TD animal models.

Levetiracetam does have other reported properties that could interact with γ-aminobutyric acid (GABA),[83] glutamate,[84] and/or free radical/oxidative[85] mechanisms implicated in TD. Postmortem TD patient studies and rodent and primate models of TD have observed GABA system dysregulation in subthalamic nucleus and other basal ganglia sites,[86–92] possibly consequent to neuronal loss and/or ultrastructural pathology in striatum,[93] which in turn may be due to excitatory and oxidative toxicity initiated by blockade of dopamine D2 receptor located on corticostriatal glutamate terminals.[84] Levetiracetam's reported ability to alter GABA turnover in striatum and substantia nigra[94] and/or its reported ability to enhance nitric oxide production[95] could potentially have contributed to the therapeutic effect we observed. Lastly, effects of levetiracetam at its SV2A synaptic vesicle site[11] could potentially relate to TD efficacy.

Recently, we became aware of another placebo-controlled study of levetiracetam for TD, as yet unpublished (J. Gerlach, M.D., data on file, UCB Pharma, Brussels, Belgium, 2006). In this study, 70 TD patients at 15 sites in Belgium, Bulgaria, Germany, Hungary, and Poland were assigned at random to levetiracetam versus placebo for 8 weeks. Mean stable doses achieved were 2642 mg/day for levetiracetam and 2520 mg/day for placebo. Interpretation of the St. Hans TD severity ratings[96] was compromised by substantial differences between treating psychiatrist ratings and ratings conducted by a single neurologist at a central site from videotaped examinations. The central St. Hans ratings were approximately one third of site St. Hans ratings. No significant differences in efficacy emerged between levetiracetam and placebo, however, on either set of ratings. It is difficult to account for the different outcomes between this study and ours. Doses achieved were similar to ours, and the sample was somewhat larger. Although our study lasted 12 weeks instead of 8 weeks, in our sample, levetiracetam was significantly superior to placebo by week 6. The central ratings suggested that baseline TD severity may have been mild, rather than moderate as in our study.

In summary, levetiracetam was well tolerated and appeared effective in this placebo-controlled treatment trial for TD. In view of the uncertain mechanism of the observed therapeutic effect and a previous negative unpub-

lished study, however, further study and replication is warranted. Readers are reminded that levetiracetam is not FDA-approved for the treatment of TD, and that caution is warranted given its various potential adverse effects, perhaps particularly in psychiatric patients.

Drug names: haloperidol (Haldol and others), levetiracetam (Keppra), risperidone (Risperdal).

REFERENCES

1. Beasley CM, Dellva MA, Tamura RN, et al. Randomised double-blind comparison of the incidence of tardive dyskinesia in patients with schizophrenia during long-term treatment with olanzapine or haloperidol. Br J Psychiatry 1999;174:23–30
2. Jeste DV, Lacro JP, Bailey A, et al. Lower incidence of tardive dyskinesia with risperidone compared with haloperidol in older patients. J Am Geriatrics Soc 1999;47:716–719
3. Modestin J, Stephan PL, Erni T, et al. Prevalence of extrapyramidal syndromes in psychiatric inpatients and the relationship of clozapine treatment to tardive dyskinesia. Schizophr Res 2000;42:223–230
4. Halliday J, Farrington S, MacDonald S, et al. Nithsdale Schizophrenia Surveys 23: movement disorders: 20 year review. Br J Psychiatry 2002; 181:422–427
5. Miller DD, McEvoy JP, Davis SM, et al. Clinical correlates of tardive dyskinesia in schizophrenia: baseline data from the CATIE schizophrenia trial. Schizophr Res 2005;80:33–43
6. Ross DE, Thomas M, Booth M, et al. Rate of tardive dyskinesia in hospitalized patients [letter]. Am J Psychiatry 2005;162:816
7. Woods SW. Tardive dyskinesia: dead or alive? [poster]. Presented at the 57th Institute on Psychiatric Services; Oct 5–9, 2005; San Diego, Calif
8. Emsley R, Turner HJ, Schronen J, et al. A single-blind, randomized trial comparing quetiapine and haloperidol in the treatment of tardive dyskinesia. J Clin Psychiatry 2004;65:696–701
9. Kinon BJ, Jeste DV, Kollack-Walker S, et al. Olanzapine treatment for tardive dyskinesia in schizophrenia patients: a prospective clinical trial with patients randomized to blinded dose reduction periods. Prog Neuropsychopharmacol Biol Psychiatry 2004;28:985–996
10. Noyer M, Gillard M, Matagne A, et al. The novel antiepileptic drug levetiracetam (ucb L059) appears to act via a specific binding site in CNS membranes. Eur J Pharmacol 1995;286:137–146
11. Lynch BA, Lambeng N, Nocka K, et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. Proc Natl Acad Sci U S A 2004;101:9861–9866
12. Konitsiotis S, Pappa S, Mantas C, et al. Levetiracetam in tardive dyskinesia: an open-label study. Mov Disord 2006;21:1219–1221
13. Bona JR. Treatment of neuroleptic-induced tardive dyskinesia with levetiracetam: a case series. J Clin Psychopharmacol 2006;26:215–216
14. Meco G, Fabrizio E, Epifanio A, et al. Levetiracetam in tardive dyskinesia. Clin Neuropharmacol 2006;29:265–268
15. McGavin CL, John V, Musser WS. Levetiracetam as a treatment for tardive dyskinesia: a case report. Neurology 2003;61:419–420
16. Tousi B, Subramanian T. The effect of levetiracetam on levodopa-induced dyskinesia in patients with Parkinson's disease. Parkinsonism Relat Disord 2005;11:333–334
17. Zesiewicz TA, Sullivan KL, Maldonado JL, et al. Open-label pilot study of levetiracetam (Keppra) for the treatment of levodopa-induced dyskinesias in Parkinson's disease. Mov Disord 2005;20:1205–1209
18. Lyons KE, Pahwa R. Efficacy and tolerability of levetiracetam in Parkinson disease patients with levodopa-induced dyskinesia. Clin Neuropharmacol 2006;29:148–153
19. Meco G, Fabrizio E, Epifanio A, et al. Levetiracetam in L-dopa-induced dyskinesia. Clin Neuropharmacol 2005;28:102–103
20. Hill MP, Bezard E, McGuire SG, et al. Novel antiepileptic drug levetiracetam decreases dyskinesia elicited by L-dopa and ropinirole in the MPTP-lesioned marmoset. Mov Disord 2003;18:1301–1305
21. Hill MP, Brotchie JM, Crossman AR, et al. Levetiracetam interferes with the L-dopa priming process in MPTP-lesioned drug-naive marmosets. Clin Neuropharmacol 2004;27:171–177
22. Hill MP, Ravenscroft P, Bezard E, et al. Levetiracetam potentiates the antidyskinetic action of amantadine in the 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MPTP)-lesioned primate model of Parkinson's disease. J Pharmacol Exp Ther 2004;310:386–394
23. Bezard E, Hill MP, Crossman AR, et al. Levetiracetam improves choreic levodopa-induced dyskinesia in the MPTP-treated macaque. Eur J Pharmacol 2004;485:159–164
24. Chatterjee A, Louis ED, Frucht S. Levetiracetam in the treatment of paroxysmal kinesiogenic choreoathetosis. Mov Disord 2002;17:614–615
25. Della Marca G, Vollono C, Mariotti P, et al. Levetiracetam can be effective in the treatment of restless legs syndrome with periodic limb movements in sleep: report of two cases. J Neurol Neurosurg Psychiatry 2006;77:566–567
26. Striano P, Manganelli F, Boccella P, et al. Levetiracetam in patients with cortical myoclonus: a clinical and electrophysiological study. Mov Disord 2005;20:1610–1614
27. Sullivan KL, Hauser RA, Louis ED, et al. Levetiracetam for the treatment of generalized dystonia. Parkinsonism Relat Disord 2005;11: 469–471
28. D'Amelio M, Callari G, Gammino M, et al. Levetiracetam in the treatment of vascular chorea: a case report. Eur J Clin Pharmacol 2005;60: 835–836
29. Zesiewicz TA, Pathak A, Sullivan KL, et al. Treatment of chorea with levetiracetam [letter]. Eur J Clin Pharmacol 2006;62:87
30. Tarsy D, Ryan RK, Ro SI. An open-label trial of levetiracetam for treatment of cervical dystonia. Mov Disord 2006;21:734–735
31. Magaudda A, Gelisse P, Genton P. Antimyoclonic effect of levetiracetam in 13 patients with unverricht-lundborg disease: clinical observations. Epilepsia 2004;45:678–681
32. Genton P, Gelisse P. Antimyoclonic effect of levetiracetam. Epileptic Disord 2000;2:209–212
33. Frucht SJ, Louis ED, Chuang C, et al. A pilot tolerability and efficacy study of levetiracetam in patients with chronic myoclonus. Neurology 2001;57:1112–1114
34. Imperiale D, Bortolotto S, Cucatto A, et al. Levetiracetam control of myoclonus in a patient with Creutzfeldt-Jakob disease. Eur Neurol 2003; 49:189–190
35. Gelisse P, Crespel A, Genton P, et al. Dramatic effect of levetiracetam on epileptic negative myoclonus. Acta Neurol Scand 2003;107:302–303
36. Keswani SC, Kossoff EH, Krauss GL, et al. Amelioration of spinal myoclonus with levetiracetam. J Neurol Neurosurg Psychiatry 2002;73: 457–458
37. Schauer R, Singer M, Saltuari L, et al. Suppression of cortical myoclonus by levetiracetam. Mov Disord 2002;17:411–415
38. Krauss GL, Bergin A, Kramer RE, et al. Suppression of posthypoxic and postencephalitic myoclonus with levetiracetam. Neurology 2001;56: 411–412
39. Fehr C, Dahmen N, Klawe C, et al. Piracetam in the treatment of tardive dyskinesia and akathisia: a case report. J Clin Psychopharmacol 2001; 21:248–249
40. Chaturvedi SK. Piracetam for drug-induced dyskinesia. J Clin Psychiatry 1987;48:255
41. Glazer WM, Morgenstern H, Doucette JT. Predicting the long-term risk of tardive dyskinesia in outpatients maintained on neuroleptic medications. J Clin Psychiatry 1993;54:133–139
42. Branch PR. Abnormal Involuntary Movement Scale (AIMS). Early Clinical Drug Evaluation Unit Intercom 1975;4:3–6
43. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P version 2.0). New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 1995
44. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
45. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity, and sensitivity. Br J Psychiatry 1978;133:429–435
46. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
47. Hamilton MA. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
48. Shear MK, Vander Bilt J, Rucci P, et al. Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). Depress Anxiety 2001;13:166–178
49. Levine J, Schooler NR. SAFTEE: a technique for the systematic assessment of side effects in clinical trials.

Psychopharmacol Bull 1986;22:343–381
50. Heinrichs DW, Hanlon TE, Carpenter WT Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. Schizophr Bull 1984;10:388–398
51. American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. Am J Psychiatry 1997;154(suppl 4):1–63
52. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 2003;64:663–667
53. Nayak RK, Doose DR, Nair NP. The bioavailability and pharmacokinetics of oral and depot intramuscular haloperidol in schizophrenic patients. J Clin Pharmacol 1987;27:144–150
54. Schooler NR, Levine J. The initiation of long-term pharmacotherapy in schizophrenia: dosage and side-effect comparisons between oral and depot fluphenazine. Pharmakopsychiatr Neuropsychopharmakol 1976; 9:159–169
55. Chue P, Eerdekens M, Augustyns I, et al. Comparative efficacy and safety of long-acting risperidone and risperidone oral tablets. Eur Neuropsychopharmacol 2005;15:111–117
56. Gibbons RD, Hedeker D, Elkin I, et al. Some conceptual and statistical issues in analysis of longitudinal psychiatric data: application to the NIMH treatment of Depression Collaborative Research Program dataset. Arch Gen Psychiatry 1993;50:739–750
57. Mallinckrodt CH, Clark WS, David SR. Type I error rates from mixed effects model repeated measures versus fixed effects ANOVA with missing values imputed via last observation carried forward. Drug Inf J 2001;35:1215–1225
58. Mallinckrodt CH, Clark WS, David SR. Accounting for dropout bias using mixed-effects models. J Biopharm Stat 2001;11:9–21
59. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ: Lawrence Erlbaum Assoc, Publishers; 1988
60. Matsunaga T, Ohyama S, Takehara S, et al. The effect of ceruletide on tardive dyskinesia: a double-blind placebo-controlled study. Prog Neuropsychopharmacol Biol Psychiatry 1988;12:533–539
61. Egan MF, Hyde TM, Albers GW, et al. Treatment of tardive dyskinesia with vitamin E. Am J Psychiatry 1992;149:773–777; comment in Am J Psychiatry 1993;150:992–993
62. Adler LA, Rotrosen J, Edson R, et al. Vitamin E treatment for tardive dyskinesia. Veterans Affairs Cooperative Study #394 Study Group. Arch Gen Psychiatry 1999;56:836–841
63. Kojima T, Yamauchi T, Miyasaka M, et al. Treatment of tardive dyskinesia with ceruletide: a double-blind, placebo-controlled study. Psychiatry Res 1992;43:129–136
64. Richardson MA, Bevans ML, Read LL, et al. Efficacy of the branched-chain amino acids in the treatment of tardive dyskinesia in men. Am J Psychiatry 2003;160:1117–1124
65. Emsley R, Niehaus DJH, Koen L, et al. The effects of eicosapentaenoic acid in tardive dyskinesia: a randomized, placebo-controlled trial. Schizophr Res 2006;84:112–120
66. Gelenberg AJ, Dorer DJ, Wojcik JD, et al. A crossover study of lecithin treatment of tardive dyskinesia. J Clin Psychiatry 1990;51:149–153
67. Goff DC, Renshaw PF, Sarid-Segal O, et al. A placebo-controlled trial of selegiline (L-deprenyl) in the treatment of tardive dyskinesia. Biol Psychiatry 1993;33:700–706
68. Huang CC, Wang RI, Hasegawa A, et al. Reserpine and alpha-methyldopa in the treatment of tardive dyskinesia. Psychopharmacology (Berl) 1981;73:359–362
69. Lohr JB, Cadet JL, Lohr MA, et al. Vitamin E in the treatment of tardive dyskinesia: the possible involvement of free radical mechanisms. Schizophr Bull 1988;14:291–296
70. Shriqui CL, Bradwejn J, Annable L, et al. Vitamin E in the treatment of tardive dyskinesia: a double-blind placebo-controlled study. Am J Psychiatry 1992;149:391–393
71. Simpson GM, Voitashevsky A, Young MA, et al. Deanol in the treatment of tardive dyskinesia. Psychopharmacology 1977;52:257–261
72. Stewart RM, Rollins J, Beckham B, et al. Baclofen in tardive dyskinesia patients maintained on neuroleptics. Clin Neuropharmacol 1982;5: 365–373
73. Keppra [package insert]. Smyrna, Ga: UCB Pharmaceuticals, Inc; 2000
74. Cramer JA, De Rue K, Devinsky O, et al. A systematic review of the behavioral effects of levetiracetam in adults with epilepsy, cognitive disorders, or an anxiety disorder during clinical trials. Epilepsy Behav 2003;4:124–132
75. French J, Edrich P, Cramer JA. A systematic review of the safety profile of levetiracetam: a new antiepileptic drug. Epilepsy Res 2001;47:77–90
76. Boraud T, Bezard E, Bioulac B, et al. From single extracellular unit recording in experimental and human Parkinsonism to the development of a functional concept of the role played by the basal ganglia in motor control. Prog Neurobiol 2002;66:265–283
77. Heimer G, Bar-Gad I, Goldberg JA, et al. Dopamine replacement therapy reverses abnormal synchronization of pallidal neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine primate model of parkinsonism. J Neurosci 2002;22:7850–7855
78. Meissner W, Ravenscroft P, Reese R, et al. Increased slow oscillatory activity in substantia nigra pars reticulata triggers abnormal involuntary movements in the 6-ohda-lesioned rat in the presence of excessive extracelullar striatal dopamine. Neurobiol Dis 2006;22:586–598
79. Alonso-Frech F, Zamarbide I, Alegre M, et al. Slow oscillatory activity and levodopa-induced dyskinesias in Parkinson's disease. Brain 2006; 129:1748–1757
80. Margineanu DG, Klitgaard H. Inhibition of neuronal hypersynchrony in vitro differentiates levetiracetam from classical antiepileptic drugs. Pharmacol Res 2000;42:281–285
81. Klitgaard H, Matagne A, Grimee R, et al. Electrophysiological, neurochemical, and regional effects of levetiracetam in the rat pilocarpine model of temporal lobe epilepsy. Seizure 2003;12:92–100
82. Niespodziany I, Klitgaard H, Margineanu DG. Desynchronizing effect of levetiracetam on epileptiform responses in rat hippocampal slices. Neuroreport 2003;14:1273–1276
83. Fibiger HC, Lloyd KG. Neurobiological substrates of tardive dyskinesia: the GABA hypothesis. Trends Neurosci 1984;7:462–464
84. Tsai GC, Goff DC, Chang RW, et al. Markers of glutamatergic neurotransmission and oxidative stress associated with tardive dyskinesia. Am J Psychiatry 1998;155:1207–1213
85. Cadet JL, Kahler LA. Free radical mechanisms in schizophrenia and tardive dyskinesia. Neurosci Biobehav Rev 1994;18:457–467
86. Gunne LM, Haggstrom JE, Sjoquist B. Association with persistent neuroleptic-induced dyskinesia of regional changes in brain GABA synthesis. Nature 1984;309:347–349
87. Gunne LM, Haggstrom JE. Experimental tardive dyskinesia. J Clin Psychiatry 1985;46(4, sec. 2):48–50
88. Andersson U, Haggstrom JE, Levin ED, et al. Reduced glutamate-decarboxylase activity in the subthalamic nucleus in patients with tardive dyskinesia. Mov Disord 1989;4:37–46
89. Johansson PE, Terenius L, Haggstrom JE, et al. Neuropeptide changes in a primate model (cebus-apella) for tardive dyskinesia. Neuroscience 1990;37:563–567
90. Gunne LM, Andren PE. An animal model for coexisting tardive dyskinesia and tardive parkinsonism: a glutamate hypothesis for tardive dyskinesia. Clin Neuropharmacol 1993;16:90–95
91. Mitchell IJ, Crossman AR, Liminga U, et al. Regional changes in 2-deoxyglucose uptake associated with neuroleptic-induced tardive dyskinesia in the cebus monkey. Mov Disord 1992;7:32–37
92. Delfs JM, Ellison GD, Mercugliano M, et al. Expression of glutamic acid decarboxylase mRNA in striatum and pallidum in an animal model of tardive dyskinesia. Exp Neurol 1995;133:175–188
93. Andreassen OA, Jorgensen HA. Neurotoxicity associated with neuroleptic-induced oral dyskinesias in rats: implications for tardive dyskinesia? Prog Neurobiol 2000;61:525–541
94. Loscher W, Honack D, Blomsfunke P. The novel antiepileptic drug levetiracetam (ucb L059) induces alterations in GABA metabolism and turnover in discrete areas of rat brain and reduces neuronal activity in substantia nigra pars reticulata. Brain Res 1996;735:208–216
95. Dagonnier M, Laute MA, Pandolfo M, et al. Effects of levetiracetam on the production of nitric oxide: an in vivo study. J Neurol 2005;252: 727–730
96. Ringo DL, Half LM, Faustman WO. Validating the St. Hans rating scale with the Abnormal Involuntary Movement Scale (AIMS) in the assessment of tardive dyskinesia. J Clin Psychopharmacol 1996;16:94–95