Preliminary Observations on the Effectiveness of Levetiracetam in the Open Adjunctive Treatment of Refractory Bipolar Disorder

Robert M. Post, M.D.; Lori L. Altshuler, M.D.; Mark A. Frye, M.D.; Trisha Suppes, M.D., Ph.D.; Susan L. McElroy, M.D.; Paul E. Keck, Jr., M.D.; Gabriele S. Leverich, M.S.W.; Ralph Kupka, M.D., Ph.D.; Willem A. Nolen, M.D.; David A. Luckenbaugh, M.A.; Jorg Walden, M.D.; and Heinz Grunze, M.D.

Objective: Levetiracetam is a recently approved, well-tolerated anticonvulsant with a unique mechanism of action yielding efficacy in treatment-refractory seizure disorders and positive effects in an animal model of mania. Given the effectiveness of a range of other anticonvulsants in bipolar disorder, we sought to evaluate levetiracetam in patients with treatment-resistant illness.

Method: Thirty-four patients received 500 to 1000 mg of levetiracetam titrated to a target dose of 2000 mg/day (maximum dose = 3000 mg/day) as open, adjunctive treatment for clinically significant symptoms of depression (N = 13), mania (N = 7), or cycling (N = 14) despite ongoing treatment with mood stabilizers. Inventory for Depressive Symptomatology-Clinician version (IDS-C), Young Mania Rating Scale (YMRS), and Clinical Global Impressions scale for use in Bipolar Illness ratings were completed at each visit for 8 weeks, and partial responders were offered continuation treatment. Data were collected from July 2001 to December 2002.

Results: Five of 16 (31%; 13 depressed, 3 cycling) patients with initial depressive symptoms met the criterion for remission (IDS-C score of ≤ 13) at last observation. All of these patients were less severely ill at baseline, whereas none of those more severely depressed at baseline responded. The majority of the 16 patients (7 manic, 9 cycling) with manic symptoms at baseline showed improvement in the YMRS in the first 2 weeks. While 7 of the 16 (44%) patients met the criterion for manic response and remission at last observation, 4 showed intervening periods of moderate to marked exacerbation. Levetiracetam was weight neutral.

Conclusion: Other pilot trials should explore possible areas of psychotropic action of levetiracetam prior to the conduct of more controlled clinical trials.

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Received April 15, 2004; accepted Aug. 17, 2004. *From the Biological Psychiatry Branch (Dr. Post and Ms. Leverich) and the Mood and Anxiety Disorders Program (Mr. Luckenbaugh), National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, Md.; UCLA Ambulatory Clinical Research Center and VA Medical Center, Los Angeles, Calif. (Drs. Altshuler and Frye); University of Texas-Southwestern Medical Center, Dallas (Dr. Suppes); the Psychopharmacology Research Program, Department of Psychiatry, University of Cincinnati College of Medicine (Drs. McElroy and Keck) and the Mental Health Care Line and General Clinical Research Center, Cincinnati Veterans Affairs Medical Center (Dr. Keck), Cincinnati, Ohio; the University of Utrecht, Utrecht (Dr. Kupka), and the Department of Psychiatry, University Hospital, Groningen (Dr. Nolen), the Netherlands; Zentrum für innovative Therapie bipolarer Störungen am Universitätsklinikum (Center for Innovative Therapy of Bipolar Disturbances at the University Clinic), Freiburg (Dr. Walden), and Psychiatrische Klinik der Ludwig-Maximilians-Universität (Psychiatric Hospital of the Ludwig-Maximilians University), Munich (Dr. Grunze), Germany.*

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Corresponding author and reprints: Robert M. Post, M.D., Bldg. 10, Room 3S239, 10 Center Dr. MSC 1272, Bethesda, MD 20892-1272 (e-mail: Robert.Post@nih.gov).

There is a rationale for the preliminary evaluation of the possible effectiveness of levetiracetam in bipolar illness. First, the drug is a recently approved, well-tolerated anticonvulsant,[1–5] and 3 other anticonvulsants (carbamazepine, valproate, and lamotrigine) have gained wide acceptance in the treatment of bipolar illness.[6,7] Second, levetiracetam has a unique mechanism of action that differs from most other compounds in both (1) not interacting with traditional neurotransmitter and receptor mechanisms directly and (2) not being active in the 2 primary animal models of epilepsy, maximal electroshock seizures and pentylenetetrazol seizures, which are widely used for screening for efficacy in complex partial and major motor seizures versus absence epilepsy, respectively.[8] Third, levetiracetam has an unusual profile of not only inhibiting completed amygdala-kindled seizures (as do carbamazepine and lamotrigine), but also blocking the

initial phase of development of amygdala kindling (as do valproate and the barbiturates).[9,10] The physiologic and mechanistic differences of levetiracetam from the 3 current widely used anticonvulsants carbamazepine, valproate, and lamotrigine at least raised the possibility that the unique actions of levetiracetam might contribute additional benefit to those with illness inadequately responsive to more traditional approaches. Fourth, levetiracetam has its own unique binding site in the brain that has not yet been linked to any specific endogenous ligand.[11] Furthermore, recent evidence suggests that it may enhance γ-aminobutyric acid (GABA)-benzodiazepine chloride ionophore function via inhibition of negative modulation of this site by zinc and beta carbolines.[12]

Following the initiation of this pilot study, a preliminary case report by Goldberg and Burdick[13] suggested antimanic and prophylactic effectiveness in a single patient treated with levetiracetam. In an abstract, Soria and Remedi[14] reported mood stabilization responses in 13 of 15 elderly bipolar II patients (aged 59–71 years) treated with open levetiracetam monotherapy. Rugino and Samsock[15] noted potential positive effects of levetiracetam in children with autism. Moreover, a recent open study of adjunctive levetiracetam (to haloperidol) in 10 bipolar I acutely manic patients, using an on-off-on study design, showed a decrease in manic symptoms in both "on" phases with levetiracetam (up to 4000 mg/day); 70% of the patients were classified as responders at the end of the 28-day study.[16]

The drug is generally well tolerated and has no apparent serious side effects[1–5] and few drug-drug interactions.[17] Levetiracetam, as well as lithium, carbamazepine, and valproate, shows a normalization of hyperactivity in the animal model of mania using dextroamphetamine and chlordiazepoxide.[18] Finally, levetiracetam is closely related to the nootropic drug piracetam, which has shown memory-enhancing properties in animal studies.[19] Given this series of unique characteristics, we examined the areas of potential efficacy of levetiracetam in the treatment of manic and depressive phases of bipolar disorder, so that more systematic controlled studies could be designed based on these initial observations.

METHOD

Thirty-four patients with *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)–diagnosed bipolar disorder according to Structured Clinical Interview for DSM-IV (SCID-I)[20] interviews were included in this study. Patients gave oral and written informed consent for the protocol approved by the Institutional Review Board at each institution. Data were collected from July 2001 to December 2002.

The general characteristics of the patients enrolled in the Stanley Network have been described previously[21–24] and included all of those willing to participate in intensive evaluation of their illness; the only exclusion was for medical comorbidities precluding their enrollment in open and randomized clinical trials and active current substance abuse requiring acute treatment in another setting.

Thirty-four patients with acute depression (N = 13), mania (N = 7), or cycling (N = 14) who had not responded adequately to several trials with conventional mood-stabilizing, antimanic, and antidepressant modalities were included. Other medications were to remain unchanged during the adjunctive use of levetiracetam.

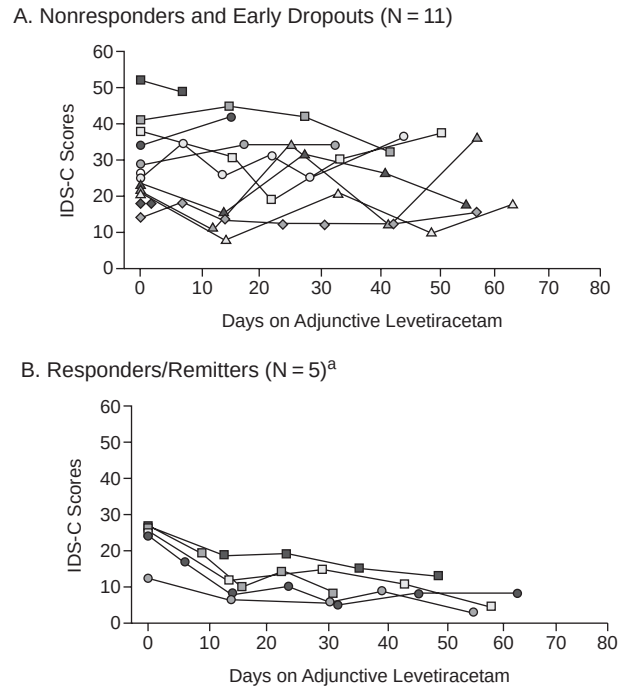
The drug was started at 500 mg at night, except in 1 instance of acute mania in which it was initiated at 1000 mg at night. Upward dose titration proceeded as tolerated to 2000 mg/day as the target dose, based on studies in epilepsy showing efficacy, with additional increases as needed to a maximum of 3000 mg/day. The acute phase of observation lasted 8 weeks.

Patients were rated weekly or once every other week with the Young Mania Rating Scale (YMRS),[25] the Inventory for Depressive Symptomatology-Clinician version (IDS-C),[26,27] and the Clinical Global Impressions scale for use in Bipolar Illness (CGI-BP)[28] for severity of mania, depression, and overall illness as previously described.[29] These and related rating scales were completed with each clinic visit, usually weekly or every other week. A positive response was operationalized as a 50% drop in YMRS or IDS-C rating and considered the primary outcome measure. In addition, manic recovery (remission) was considered a score of < 8 on the YMRS and depression recovery a score of ≤ 13 on the IDS-C. Those who showed evidence of partial improvement in the first 8 weeks were offered open continuation for 6 months.

Sixteen patients (7 manic, 9 cycling) had manic symptoms at baseline (YMRS ratings > 10), and 16 had depressive symptoms (13 depressed and 3 cycling) at baseline. Two of the cyclers were not initially symptomatic. Four patients dropped out within the first week of treatment for administrative reasons, drug intolerance, or mood worsening, and another 8 prior to week 3, mostly for lack of efficacy. Only 1 patient experienced psychosis.

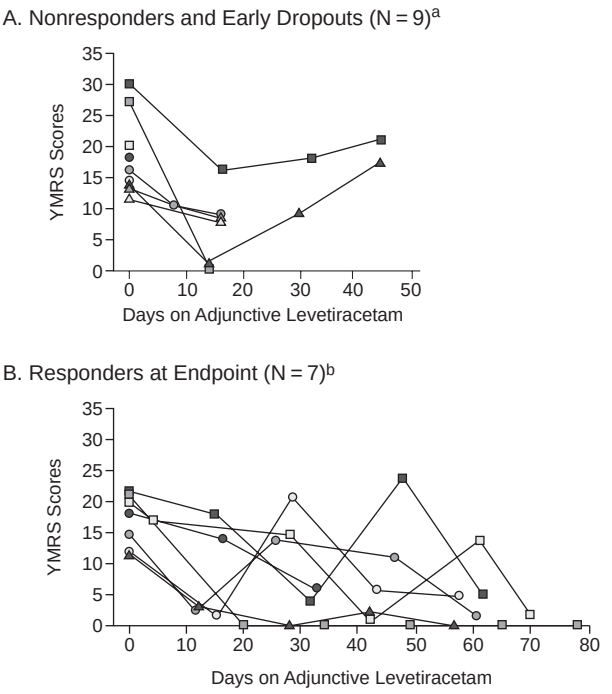
Patients were a mean age of 41.9 years, and 63% (N = 21) were female. Most were bipolar I, except 5 who were bipolar II or bipolar not otherwise specified. Mean age at onset was 17.9 ± 14.3 years, indicating that most patients had a duration of illness of 20 years or more. Depressed patients had a mean of 3.1 hospitalizations for depression and 0.6 for mania, whereas the manic and cycling patients had 4.3 and 2.2 hospitalizations for depression and 5.9 and 1.3 for mania, respectively. Eighty-nine percent (N = 8) of the 9 cycling patients with cycling data had a prior history of rapid cycling, whereas only 38% (N = 3) of the 8 depressed patients with cycling data had this history.

Figure 1. Time Course of Individual Acute Antidepressant Response to Adjunctive Levetiracetam by IDS-C Ratings



[a]Responders (1B) were less depressed at baseline than nonresponders (1A).
Abbreviation: IDS-C = Inventory for Depressive Symptomatology-Clinician version.

Figure 2. Time Course of Individual YMRS Scores of Patients Receiving Adjunctive Levetiracetam



[a]Seven patients dropped out prior to week 3, and 2 apparent responders relapsed.
[b]Note the unstable course in 4 of the "responders" at endpoint.
Abbreviation: YMRS = Young Mania Rating Scale.

RESULTS

The mean peak dose of levetiracetam was 2175 mg/day, with 12 patients requiring dose reduction (of a mean of 760 mg/day) for side effects, largely sedation. The drug was added to a mean of 3.5 other agents, which were held stable during the open levetiracetam treatment. The major mood stabilizers in the regimen were lithium (N = 10), valproate (N = 7), and lamotrigine (N = 4), and 1 patient each taking carbamazepine, quetiapine, and olanzapine; 20 patients were additionally receiving antidepressants; 13, atypical antipsychotics; 10, benzodiazepines; and 8, thyroid augmentation. Other drugs included topiramate (N = 3), gabapentin (N = 1), zonisamide (N = 1), and trazodone for sleep (N = 4).

As illustrated in Figure 1, most of the more severely depressed patients at baseline were nonresponders (Figure 1A). Five of those with initially mild-to-moderate depressive severity at baseline met the criterion for response and remission (IDS-C score ≤ 13), representing 31% of the originally symptomatically depressed group (Figure 1B).

Most of the 16 patients with initial symptoms of mania improved in the first 2 weeks of treatment with levetiracetam. However, 7 dropped out prior to the third week, and 2 worsened over the next visits (Figure 2A). Several of the patients remaining in the trial more than 1 month met the criterion for improvement and remission of mania (YMRS score ≤ 8) at last observation (Figure 2B). However, 4 of these patients showed an intervening exacerbation of their manic symptoms, perhaps consistent with a cyclic course, and in only 2 did sustained and stable improvement occur. The drug was weight neutral with a mean change in weight during levetiracetam treatment of less than 1 kg (baseline = 82.7 ± 16.5, last observation = 83.2 ± 17.3).

DISCUSSION

This preliminary open exploration of levetiracetam in treatment-resistant bipolar illness has not revealed a highly consistent pattern of improvement in treating treatment-residual manic or depressive symptoms. However, of those remaining in the trial more than 1 month, 7 patients (44%) eventually met the criterion for remission of manic symptoms, and 5 (31%) did so for depression. The small number of patients studied in each group, the open add-on design, the inclusion of treatment refractory patients, and the high early dropout rate substantially limit the strength of these preliminary observations.

Additional studies in more typical and less refractory patients may be indicated before these results are general-

ized to other patient groups. At the same time, it should be noted that the degree of treatment resistance in bipolar outpatient populations seen in academic settings is considerable and may have been underestimated,[21–23] such that the apparent high degree of treatment resistance seen here is not unusual or unrepresentative of more carefully followed bipolar outpatients in many clinics.

White et al.[30] reported a 6.9% rate of discontinuation of levetiracetam in a series of 553 epilepsy patients because of behavioral side effects (depression in 16, irritability in 14, aggression in 5, and psychosis in 3). They identified risk factors for discontinuation as a faster rate of titration, a history of previous psychiatric disorder, and symptomatic generalized (as opposed to focal) epilepsy. It is possible that lower initial doses and a slower rate of titration would have decreased the number of dropouts in our study and perhaps altered the degree of psychotropic responsiveness as well. It is unlikely that a faster titration or higher maximal doses would have had added benefit in this population, given the high rate of early dropout and observations in those patients with seizure disorders.[31]

Several anticonvulsant drugs with prominent actions on GABAergic mechanisms have recently been shown not to have potent acute antimanic efficacy.[23,32] These include gabapentin, tiagabine, and topiramate, all of which have been reported to increase brain GABA in humans by magnetic resonance spectroscopy. To the extent that levetiracetam acts by indirectly enhancing benzodiazepine GABA receptor function by removing the negative modulation of this site by zinc and beta carbolines[12] or other GABAergic mechanisms,[33,34] the lack of clear, sustained antimanic effects of levetiracetam might be consistent with this general theoretical perspective.

Conversely, to the extent that this indirect GABA-benzodiazepine enhancement is revealed as a major mechanism of action of levetiracetam, it would suggest the possible utility of further exploration of this drug in anxiety syndromes because gabapentin and pregabalin have shown positive effects in the treatment of anxiety disorder.[35,36] This theoretical rationale would converge with the positive data on levetiracetam for preclinical antianxiety effects in standard animal models, such as the elevated plus-maze test.[37]

One preclinical report[18] suggests additive and activity normalizing effects of levetiracetam and valproate in an animal model of mania (i.e., hyperactivity in rodents induced by chlordiazepoxide and a psychomotor stimulant). Interestingly, 2 rapid cyclers responding well to adjunctive levetiracetam both had valproate in the treatment regimen.[38] More systematic exploration of this combination in bipolar illness may be indicated, although patients in the current series who were taking valproate did not appear to show a more robust response than those not taking that drug.

In summary, this preliminary open exploration of levetiracetam as adjunctive treatment in bipolar patients refractory to other medications does not identify areas of clear overall clinical utility in treatment-resistant bipolar patients. However, given the limitations of this study in a treatment-refractory population already receiving many other and varied psychotropic drug treatments, the relatively rapid dose titration, and the consequent moderate dropout rate, further exploration of the spectrum of efficacy of this anticonvulsant in bipolar and other patient populations may be warranted. Moreover, given a small subgroup of apparently responsive patients in this series and in several other case reports in the literature, examination of illness characteristics associated with individual responsivity may also be useful.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), chlordiazepoxide (Librium and others), dextroamphetamine (Dexedrine, Dextrostat, and others), gabapentin (Neurontin and others), haloperidol (Haldol and others), lamotrigine (Lamictal), levetiracetam (Keppra), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), tiagabine (Gabitril), topiramate (Topamax), trazodone (Desyrel and others), zonisamide (Zonegran).

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