# Levetiracetam in the Treatment of Acute Mania: An Open Add-On Study With an On-Off-On Design

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***Background:*** Levetiracetam is a novel antiepileptic drug with a broad spectrum of efficacy in epilepsy. We have tested the antimanic properties of the drug as an add-on to haloperidol in an open trial.

***Method:*** After giving informed written consent, 10 bipolar I acutely manic (DSM-IV) inpatients were investigated in an on-off-on study design. All patients were treated with 5 to 10 mg/day of haloperidol, depending on tolerability, throughout the investigation. Levetiracetam (up to 4000 mg/day) was added until day 14, then discontinued and reintroduced at day 21. The psychopathologic changes were assessed with the Young Mania Rating Scale (YMRS).

***Results:*** After a mean decrease of the YMRS scores from 29.6 to 17.2 during the first "on" phase, manic symptoms worsened during the "off" period (YMRS score 20.9) and ameliorated again during the second "on" phase, with a decrease of the mean YMRS score to 14.7 at the end of the study. The mean dose of levetiracetam was 3125 mg/day. At day 14, only 2 (20%) of 10 patients were responders (defined as a decrease in YMRS scores of 50%) compared with 7 (70%) of 10 responders at the end of the study at day 28.

***Conclusion:*** The results from this open on-off-on add-on study suggest that levetiracetam exhibited additional antimanic effects. Controlled studies are clearly required.

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Several old and new antiepileptic drugs have shown efficacy as mood stabilizers in the treatment of bipolar disorder. Carbamazepine and valproate have their place in treatment algorithms of bipolar disorder[1,2]; lamotrigine has proved to be efficacious in bipolar depression,[3] rapid cycling,[4] and maintenance treatment[5]; and recent data suggest an antimanic efficacy of topiramate.[6] On the other hand, the new antiepileptic drugs tiagabine and gabapentin appear thus far not to be efficacious in the treatment of acute mania.[7,8]

Levetiracetam, an *S*-enantiomer derivative of pyrrolidine acetamide, is a novel agent with a broad spectrum of efficacy in epilepsy. Although the mechanism of action of levetiracetam has not been fully elucidated, the drug does not appear to act at any recognized site of antiepileptic drug activity. Instead, in vitro studies[9] suggest a brain-specific binding site. The efficacy is dependent on stereoselectivity since the *R*-enantiomer lacks activity.[9] Compared with other antiepileptic drugs, levetiracetam has a wider safety margin and a favorable pharmacokinetic profile in humans. Following oral administration, levetiracetam undergoes rapid absorption. The drug has a linear kinetic, is minimally protein bound, and has no effect on the cytochrome P450 system. It is partly metabolized in blood and fully excreted in urine mostly as an unchanged drug.[10–12] Combination treatment with other antiepileptic drugs is not complicated by significant drug-drug interaction.[13]

The antiepileptic effects were investigated in several placebo-controlled studies in which levetiracetam was administered in a dose range between 2000 and 4000 mg daily.[14,15] A recently published single-case report also indicated an antimanic effect of 2500 mg/day levetiracetam.[16] The aim of the present investigation was to test the antimanic efficacy of levetiracetam as an add-on to haloperidol in an open trial applying an on-off-on design. The antimanic efficacy of topiramate[6] and oxcarbazepine[17] has been demonstrated in 2 recent studies with similar designs.

## METHOD

Subjects were recruited from the inpatients of the Departments of Psychiatry at the Universities of Munich

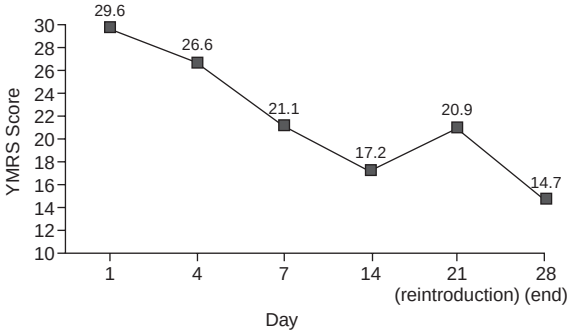
and Freiburg and the Municipal Hospital of Zwickau, Germany.

Ten consecutively admitted acutely manic patients participated after being extensively informed about the trial and giving written informed consent. Their ability to give informed consent was confirmed by a certified psychiatrist not participating in the study. The study protocol was reviewed and accepted by the institutional review board of the Ludwig-Maximilians University Munich, and the study was performed in accordance with the Declaration of Helsinki. The patient group consisted of 6 men and 4 women, all of Caucasian origin, with a mean age of 38.4 years (range, 28–48 years). Patients remained hospitalized throughout the trial. The inclusion criterion was a bipolar I diagnosis with an acute manic episode (Young Mania Rating Scale [YMRS][18] score ≥ 20) according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV). Exclusion criteria were another DSM-IV Axis I disorder, inability to give informed consent, and suicidality. Seven patients were diagnosed with euphoric mania, and 3 with dysphoric mania. At the time of inclusion, all patients were drug-naive to a mood stabilizer or antipsychotic or treated only with an insufficient dose. All patients were routinely treated with a standard dose of 5 to 10 mg/day of haloperidol throughout the investigation, depending on tolerability. The only other additional treatment allowed during the study period was lorazepam, at a maximum dose of 8 mg/day.

The psychometric scales administered at baseline (day 1) and days 4, 7, 14 (off), 21 (reintroduction), and 28 included the YMRS, the 21-item Hamilton Rating Scale for Depression (HAM-D-21),[19] and the Clinical Global Impressions scale, version for bipolar patients (CGI-BP).[20] Raters were not informed about the "off period." Significance of the primary outcome criterion, YMRS score, was tested for all evaluation points against baseline and prior measurement using the Wilcoxon signed rank test.

Levetiracetam was administered according to an on-off-on design. The patients initially received 1000 mg of levetiracetam on day 1. Within 4 days, levetiracetam was titrated on an individual basis, depending on clinical impression and tolerability. Starting from a 1000-mg daily dose, levetiracetam was administered twice daily in a range of 2000 to 4000 mg/day. The mean ± SD maximal dose was 3125 ± 784 mg/day. On day 14, levetiracetam was discontinued without a tapering phase, and reintroduced on day 21 after the final rating of the "off" period, starting with 1000 mg and individual dosage increase for another 7 days until day 28 (end of the trial). During this second "on" period, levetiracetam was titrated more rapidly in those patients who showed good tolerability during the first "on" period and who were still severely manic.

**Figure 1. Mean YMRS Ratings in 10 Bipolar I Patients Receiving Levetiracetam**




Abbreviation: YMRS = Young Mania Rating Scale.

## RESULTS

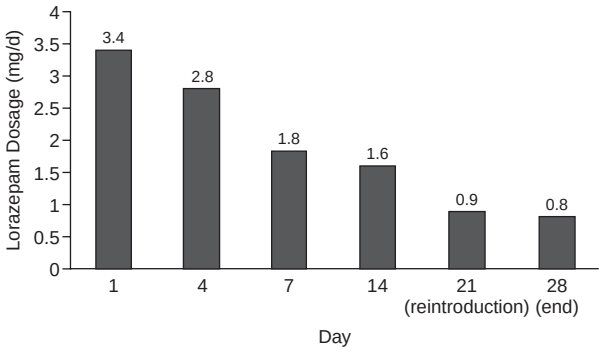
At baseline, the mean ± SD YMRS score for all patients was 29.6 ± 4.1 (range, 24–35). Five patients had a score ≥ 30. On day 14, before discontinuation of levetiracetam, the YMRS score had declined to 17.2 ± 4.2 (range, 13–23, $p < .05$). At day 14, only 2 of the 10 patients showed a predefined antimanic response with ≥ 50% reduction in YMRS scores. During and shortly after the "off" period, the YMRS scores increased again, reaching a mean value of 20.9 ± 3.9 (range, 17–27, $p < .05$ compared with day 14) shortly before reintroduction of levetiracetam. Finally, at the end of the observation at day 28, the YMRS scores had declined again to 14.7 ± 3.2 (range, 9–20, $p < .05$ compared with baseline and prior measurement). At this stage, 7 of the 10 patients fulfilled the responder criterion of ≥ 50% YMRS reduction compared with their baseline scores. The change in YMRS scores during "on-off-on" treatment with levetiracetam is presented in Figure 1.

Haloperidol doses were between 5 and 10 mg/day, with a fixed starting dose of 5 mg and daily adjustment up to 10 mg according to tolerability. The mean haloperidol dose was 8.7 ± 5.2 mg/day at day 7, 8.3 ± 3.1 at day 14, 8.3 ± 3.1 at day 21, and 7.4 ± 2.8 at day 28. The mean haloperidol dose at day 28 did not differ between responders and nonresponders (7.2 ± 3.1 mg/day for responders, 7.7 ± 3.9 for nonresponders).

The total amount of coadministered lorazepam is shown in Figure 2. The total mean use of lorazepam in all 10 patients declined from 3.4 ± 1.7 mg/day at the beginning of the observation to 1.6 ± 1.6 at the end of the "on" phase. Even in the "off" phase, the usage of lorazepam decreased further to 0.9 ± 1.2 mg/day and later to 0.8 ± 1.2 at the end of the study.

Levetiracetam was introduced at a starting dose of 1000 mg/day and titrated within 4 days to a final dose in the range of 2000 to 4000 mg/day, depending on clinical

Figure 2. Mean Dose of Lorazepam in 10 Bipolar I Patients Receiving Levetiracetam




efficacy and tolerability. The mean dose of levetiracetam at day 14 was 3125 ± 784 mg/day. The 2 responders at day 14 received the maximal dose of 4000 mg/day. Levetiracetam was abruptly discontinued after 14 days while concomitant medication remained unchanged. After day 21, levetiracetam was reintroduced at 1000 mg/day and then increased to the initial dose at the end of the first "on" phase by the third day of reintroduction.

Levetiracetam was generally well tolerated despite the more aggressive dose escalation scheme compared with epilepsy treatment. As also appears to be the case in other studies with manic patients, this patient population appears to tolerate higher dosages and more rapid titration of antiepileptic drugs than other patient populations studied. Except for worsening of manic symptoms, the abrupt discontinuation of levetiracetam caused no withdrawal effects. The following adverse events were reported by the patients upon questioning: sedation (3 patients), dizziness (1 patient), and asthenia (1 patient).

## CONCLUSION

In this trial, levetiracetam showed additional antimanic efficacy to standard haloperidol treatment. This conclusion is, however, clearly limited by the open nature of the study. As the patients were aware of the "off" period, since a substitution by matching placebos could not be done, it cannot be excluded that the raters also became aware of the drug discontinuation by spontaneous patient reports. Thus, single-blind conditions cannot be assumed for certain.

Concerning the onset of action, it appears that levetiracetam is not a very fast-acting antimanic substance, despite rapid titration at the beginning of the trial. Only 2 of 10 patients showed a sufficient response after 2 weeks of treatment. A comparable treatment approach with valproate loading, either oral or intravenously,[21,22] demonstrated a much more rapid onset of action. This delayed onset may be related to the proposed mechanisms of action of levetiracetam, having only weak or no influence on acute excitability of cells and some animal models of acute seizures,[23] but showing efficacy in long-term models of epileptogenesis.[24] At the end of the 28-day study, 7 of 10 patients could be classified as responders.

Levetiracetam was generally very well tolerated despite a more rapid dosage increase compared with epilepsy treatment. As no additional anticholinergic drugs were needed despite treatment with haloperidol, it can be speculated that levetiracetam may have an ameliorating effect on extrapyramidal motor symptoms. It may be interesting to study this possible effect more systematically in placebo-controlled, add-on trials with fixed dosages of neuroleptics.

In summary, it appears that levetiracetam exhibits distinct antimanic effects combined with good tolerability of the drug. As the onset of action appears not very fast, levetiracetam may not be a first-choice drug for the treatment of acute mania. However, it may be a suitable alternative for patients with mild manic syndromes and possibly for the prophylaxis of mania. These uses may coincide with its mechanism of action, as far as levetiracetam is not effective in acute models of convulsion, but very sufficient in preventing long-term changes induced by kindling.[23] It will be the task of future controlled trials to consolidate the clinical profile of levetiracetam in bipolar disorder.

*Drug names:* carbamazepine (Tegretol and others), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), levetiracetam (Keppra), lorazepam (Ativan and others), oxcarbazepine (Trileptal), tiagabine (Gabitril), topiramate (Topamax).

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