

# Lamotrigine Use in Geriatric Patients With Bipolar Depression

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**Objective:** To study the effectiveness of adding lamotrigine to the treatment of inpatient geriatric patients with bipolar disorder (BD) who were in the depressed phase and had been on lithium and valproate for at least 3 months.

**Method:** Lamotrigine was started at 25 mg given at bedtime, with weekly incremental increases of 12.5 mg daily until a total dosage of either 75 mg or 100 mg was obtained. Improvement was measured by clinical interview and Hamilton Depression Rating Scale (HDRS) scores. Patients were reassessed at 6 weeks, and if their HDRS score had decreased by at least 50%, they were considered to have improved.

**Results:** The study group comprised 5 women with an average age of 71.5 years (range 65 to 85). Four had rapid-cycling BD, and 1 had mixed BD. All patients had early age of onset, as judged by their first contact with a psychiatrist or their first hospitalization. The average initial HDRS score was 27 (range 20 to 35). Of the patients, 3 out of the 5 had remission of symptoms, as judged by clinical interview and reduction of their HDRS score by 50%. At 3 month follow-up, these 3 patients had not required rehospitalization and were doing well. Lamotrigine was well tolerated, and none of the patients developed a rash. One patient did develop coarse hand tremor that improved when the lamotrigine dosage was decreased.

**Conclusions:** Lamotrigine in conjunction with lithium and valproate may be effective in treating geriatric patients with BD and depression.

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## Clinical Implications

- Lamotrigine has a role as a first-line treatment of elderly patients with bipolar disorder (BD) and depression.
- We recommend that it be combined with lithium or valproate in such patients, because efficacy in preventing manic episodes has not been proven.

## Limitations

- Skepticism and caution are warranted when interpreting the results of an open, small, uncontrolled case series.
- More randomized controlled studies are needed.

**Key Words:** *anticonvulsants, bipolar disorder*

Lamotrigine is an anticonvulsant that appears to have some mood-stabilizing properties and may even have some modest antidepressant effect. Lamotrigine's mechanism of

action is unknown. Animal models of self-injurious behaviour suggest glutamatergic interactions, and lamotrigine may inhibit neuronal glutamate release.

The initial dosage of lamotrigine is generally 25 mg once or twice daily, and this can be increased by 25 or 50 mg every week or 2 weeks. If a patient is taking valproate, start lamotrigine at 12.5 mg daily and increase the dosage by 12.5 or 25 mg every 2 weeks because of the drug–drug interaction: valproate doubles the plasma level of lamotrigine, and lamotrigine decreases the level of valproate by 25%. If a patient is taking carbamazepine, somewhat larger dosages and more rapid dosage increases are possible: carbamazepine lowers the concentration of lamotrigine in the blood, and lamotrigine increases the level of carbamazepine and its metabolites. Some patients may require a total dosage of up to 400 mg daily to benefit from this medication. Salzman has suggested that a dosage of 25 to 75 mg daily will probably be effective (1).

Open-label studies, case series, and individual reports indicate that lamotrigine may be efficacious in treating various psychiatric conditions, including posttraumatic stress disorder (PTSD) and bipolar disorder (BD). The manufacturer of lamotrigine is conducting several large multicentre studies of mania, bipolar depression, and maintenance treatment.

A double-blind placebo-controlled study has shown lamotrigine to be effective in treating acute bipolar depression: 195 patients were randomized into 3 groups (placebo, lamotrigine monotherapy 50 mg daily, or lamotrigine monotherapy 200 mg daily). Results indicated that patients randomized to lamotrigine 200 mg daily showed significantly greater improvement, compared with those randomized to placebo (2).

There are 3 case reports of lamotrigine use in patients with BD. In an open trial, Fogelson and Sternbach used lamotrigine to treat 5 women and 2 men, aged 28 to 54 years, for treatment-refractory BD (3). After 8 weeks of lamotrigine 200 to 400 mg daily, 3 patients (all with rapid-cycling BD) showed marked improvement, 2 showed moderate improvement, and 2 were unchanged. Two patients had monotherapy with lamotrigine, and the other 5 had concomitant psychotropic medications. One patient discontinued lamotrigine after 8 weeks, owing to nausea.

Calabrese and colleagues describe another patient with rapid-cycling BD who responded to lamotrigine (4). This 49-year-old man had failed to respond satisfactorily to individual trials of lithium, fluoxetine, and carbamazepine. After 8 weeks of lamotrigine monotherapy up to 200 mg daily, his depression symptoms decreased by about 80%. He continued taking lamotrigine and remained euthymic for 11 months.

Maltese reports 2 cases of middle-aged women with treatment-refractory depression who responded when lamotrigine was used as adjunctive therapy (5). The dosage range was 25 to 75 mg daily.

There are 5 open trials of lamotrigine use in patients with BD. In a study of valproate and lamotrigine in 18 normal

volunteers, Anderson and colleagues found that valproate markedly increased the half-life of lamotrigine and decreased its clearance, while lamotrigine decreased plasma concentrations of valproate to a lesser degree (6). The authors recommend reducing lamotrigine dosages in patients taking this combination of antiepileptic drugs.

Walden and others report the case of a 39-year-old man with BD who failed to improve on several different combinations of medications following hospitalization for a manic episode (7). When lamotrigine was added to a regimen of valproic acid and trimipramine, the patient's condition gradually improved over several weeks. His lamotrigine dosage of 150 mg daily had to be lowered to 100 mg daily when his lamotrigine blood levels increased threefold, presumably as a result of an interaction with valproate.

Sporn reports on lamotrigine's apparent antidepressant and mood stabilizing effect in 8 of 16 patients (8). In this study, patients were taking other psychotropic medications in conjunction with lamotrigine. In a few cases, patients remained well for a long period of time, which suggests that lamotrigine might have helped the episode of mood disturbance and also might have mood-stabilizing effects.

Fatemi reports that both lamotrigine augmentation therapy and monotherapy appeared to have mood-stabilizing and antidepressant efficacy in the treatment of 5 patients with rapid-cycling BD (9). The effect persisted for an average of 7.5 months. Kusumakar reports on 7 patients with refractory rapid-cycling BD (10). Of this group, 4 patients responded to lamotrigine after 1 to 3 weeks of treatment. One elderly woman in this series was concurrently taking valproate. She developed a rash after 4 weeks, and lamotrigine was subsequently discontinued.

Calabrese and others report on an open trial of 75 patients with BD who were involved in a 48-week open-label prospective study (11). Of the 40 depression patients included in the efficacy analysis, 48% exhibited a marked response and 20% a moderate response with regard to reduced Hamilton Depression Rating Scale (HDRS) scores. Of the 31 patients with a hypomanic, manic, or mixed state, 81% displayed a marked response and 3% a moderate response on Mania Rating Scale scores. The most common drug-related adverse events were dizziness, tremor, somnolence, headache, and nausea. As well, 9% developed a rash, which resulted in drug discontinuation. The mean age of patients in this study was 44 years (range 23 to 70 years).

In 2 unpublished double-blind studies, lamotrigine has been shown to prevent relapse or recurrence of depressive episodes, as well as preventing manic or hypomanic relapses and recurrences (12,13).

There is little in the literature about the use of new anticonvulsants such as gabapentin and lamotrigine in treating elderly patients with BD. We studied the effectiveness of adding lamotrigine to the treatment of inpatient geriatric patients with BD who were in the depressed phase and had been on both lithium and valproate for at least 3 months.

## Method

Patients for this study were over age 65 years and diagnosed with BD, based on DSM-IV criteria. They were admitted to a geriatric psychiatry inpatient unit for assessment and management of a depressive episode. There were no exclusion criteria. This trial of lamotrigine was given to the first 5 consecutively admitted patients. The patients had been taking both lithium and valproate for at least 4 months prior to the study. Lamotrigine was added because the depressive episode had not responded to a serotonin reuptake inhibitor (sertraline) or a tricyclic antidepressant (nortriptyline) after 2 months. We obtained informed consent from both patient and family. Lamotrigine was started at a dosage of 25 mg at bedtime, with weekly incremental increases of 12.5 mg daily until a total dosage of either 75 mg or 100 mg daily was obtained. Improvement was measured by clinical interview as well as by HDRS scores, both done by the same psychiatrist. Patients were reassessed at 6 weeks; if the HDRS scores had decreased by at least 50%, they were considered to have improved.

## Results

The study group contained 5 women. Their average age was 71.5 years (range 65 to 85). The average score on the HDRS at the beginning of the study was 27 (range 20 to 35). Four patients had rapid-cycling BD. One patient had mixed BD. All patients had an early age of onset, as judged by their first contact with a psychiatrist or their first hospitalization. Table 1 displays their HDRS scores before and after lamotrigine treatment.

Of the 5 who were given lamotrigine, 3 had remission of symptoms, as judged by clinical interview and reduction of HDRS scores by 50%. These 3 patients had rapid-cycling BD.

In the overall group, 3 of the 4 women with rapid-cycling BD responded, and the patient with mixed-state BD did not respond. At 3-month follow up, these 3 patients had not required rehospitalization and were doing well. Lamotrigine was well tolerated, and none of the patients developed a rash. One patient did develop coarse hand tremor that improved when the dosage of lamotrigine was decreased.

## Discussion

From this small case series, it is clear that the management of refractory rapid-cycling or mixed BD in elderly patients remains a challenge. Lamotrigine appeared to help and be well tolerated by the patients and was used in combination with both lithium and valproate. None of these patients had any difficulty with rashes. The nature of rapid-cycling BD (with spontaneous switches to depression, hypomania, mania, or euthymia) makes it difficult to ascertain whether any new agent actually helped in the acute phase of the episode of mood disturbance or even helped in the long-term maintenance of these patients. Prolongation of the wellness period in these patients is probably what clinicians should strive for, rather than the therapeutic goal of keeping patients euthymic for the rest of their lives. It is also important to note that in this study psychosocial issues in addition to medication were considered to be an integral contributing factor in the improvement of depressive symptoms. Three of the 5 patients had experienced difficulty coping in the community and were to be transferred to a nursing home facility after discharge from the inpatient psychiatric unit. At the nursing home, they would receive a much higher level of care than they had received in the community prior to their admission. For example, their medication would be supervised and they would be helped with activities of daily living, such as meal preparation. This was a source of comfort that would reduce worry and stress for both the patients and their families and promote compliance with medication.

In summary, lamotrigine may have a role in the treatment of geriatric patients with BD 1 depression. We recommend that lamotrigine be combined with lithium or valproate in these

**Table 1** Hamilton Depression Rating Scale scores before and after lamotrigine

Patient	BD subtype	HDRS scale before LAM	HDRS score after LAM
1	Rapid-cycling	26	6
2	Mixed-state	28	27
3	Rapid-cycling	29	7
4	Rapid-cycling	34	30
5	Rapid-cycling	35	17

BD = bipolar disorder; HDRS = Hamilton Depression Rating Scale; LAM = lamotrigine

patients, because its efficacy in preventing manic episodes has not been proven. Lamotrigine may also be used as monotherapy in patients with BD II depression or rapid-cycling BD II (14).

Skepticism and caution are warranted when interpreting the results of an open, small, uncontrolled case series, because potential unintentional bias, placebo response, and random variability can lead to false-positive results. Thus, the methodological limitations of this study highlight the need for randomized controlled trials. In clinical work, lamotrigine is a part of our armamentarium, and it seems to have a role as an adjuvant medication with lithium and valproate, or with both together.

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### Résumé : Utilisation de la lamotrigine chez les patients gériatriques souffrant de dépression bipolaire

**Objectif :** Étudier l'efficacité de l'ajout de lamotrigine au traitement de patients gériatriques hospitalisés souffrant de trouble bipolaire (TB) qui étaient en phase déprimée, et qui prenaient du lithium et du valproate depuis au moins 3 mois.

**Méthode :** On a commencé la lamotrigine à raison de 25 mg au coucher, avec des augmentations graduelles de 12,5 mg par jour, jusqu'à l'obtention d'un dosage total de 75 mg ou de 100 mg. On a mesuré l'amélioration par une entrevue clinique et par les scores obtenus à l'échelle de dépression de Hamilton (HDRS). Les patients ont été réévalués à 6 semaines, et si leurs scores à l'HDRS avaient diminué d'au moins 50 %, ils étaient estimés s'être améliorés.

**Résultats :** Le groupe de l'étude comprenait 5 femmes dont la moyenne d'âge était de 71,5 ans (de 65 à 85). Quatre avaient le TB à cycle rapide, et 1 avait le TB mixte. Toutes les patientes avaient eu une apparition précoce de la maladie, à en juger par leur premier contact avec un psychiatre ou par leur première hospitalisation. Le premier score moyen à l'HDRS était 27 (de 20 à 35). Trois des 5 patientes ont eu une rémission des symptômes, constatée par l'entrevue clinique et la réduction de 50 % de leurs scores à l'HDRS. Au suivi de 3 mois, ces 3 patientes n'avaient pas nécessité de réhospitalisation et allaient bien. La lamotrigine était bien tolérée, et aucune des patientes n'avait développé d'éruption cutanée. Une patiente avait développé un important tremblement des mains, qui s'est amélioré quand on a diminué la dose de lamotrigine.

**Conclusions :** La lamotrigine, conjointement avec le lithium et le valproate, peut être efficace pour traiter les patients gériatriques souffrant de TB et de dépression.