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Lamotrigine - A New Generation Mood Stabilizer?

Introduction

Bipolar disorder (BPD) impacts about 1-3% of the population and its course can be variable. BPD in the depressive phase is associated with a suicide risk of about 3.2 per 100 patient-year. The current treatment of BPD focuses on decreasing the frequency and severity of episodes of depression or mania by the use of medication and psychotherapy. Lithium is one of the standard treatments for BPD (others include carbamazepine and valproate). Patients with mixed states and rapid cycling are more treatment resistant. The use of antidepressants to treat the depressed phase has been associated with increases in the frequency of cycling, mood instability and induction of mania.

Lamotrigine (LTG), an approved third-generation anticonvulsant for the adjunctive treatment of complex-partial seizures in adults with epilepsy, has been used as a mood stabilizer in patients with BPD. Initial data indicate efficacy in the treatment of mania, depression, refractory BPD and rapid cycling BPD.

Adverse Effects and Drug Interactions

The most common adverse effects include dizziness, headache, double vision, unsteadiness, nausea, blurred vision, somnolence, drowsiness, ataxia, asthenia, tremor, in-coordination, vomiting and rash. The most concerning potential adverse effect is Steven-Johnson syndrome which occurs in about 0.1% of adults. The risk of rash increases with the combined use of LTG with valproate, as well as rapid titration of LTG and most rashes appear within two weeks of initiation of LTG and resolve with discontinuation. LTG is metabolized hepatically and is >50% protein bound. Valproate competes with LTG for glucuronization in the liver, inhibiting LTG's metabolism and increasing its half-life to 60

hours. Carbamazepine, phenytoin and primidone enhance LTG metabolism so that its half-life is decreased to 15 hours.

Dosing

Dosing must be individualized and should be based on clinical response. The maximum dose in clinical trials has been up to 700 mg/day. The usual target dose is 100-200 mg/day. No correlation has been established between plasma concentration and clinical efficacy. One disadvantage of LTG use is the need to titrate the dose slowly. It can take up to one month to reach target dose, which limits its use in acute treatment.

Clinical Studies

There has been several case reports and open label studies (see Table 1 & 2) suggesting moderate to marked responses to LTG in treatment of BPD in the depressive phase, hypomania and mixed states as add-on and monotherapy. One study has shown that LTG may not be as effective in severe mania as in depression and mild to moderate mania. Three double-blind randomized trials and four open label studies are included in this newsletter to verify the efficacy of LTG in bipolar disorder.

Calabrese et al. conducted a double-blind, parallel group study in outpatients with non-rapid-cycling bipolar I depression. Significantly greater improvement was observed for the 200mg/day of LTG than placebo using the HAM-D and MADRS scores. There was no difference between LTG and placebo groups in the development of adverse mood episodes.

Berk designed a similar study, but compared LTG to lithium and olanzapine in 45 hospitalized patients with mania. Significant improvement was noted for all treatment groups based on MRS scores. The study was limited by the small sample size and lack of placebo control.

Frye et al. conducted a randomized double-blind, crossover series of three 6-week monotherapy evaluating LTG, gabapentin vs. placebo. LTG was increased gradually from an initial dose of 25 mg/day (week 1) to 300-500 mg / day (weeks 5 and 6). The initial dose of gabapentin was 900 mg/ day (week 1) and increased to 4800 mg/ day (by week 5). 52% of patients on LTG, 26% of patients on gabapentin and 23% of those on placebo were rated much or very much improvement on the CGI (overall).

Open Label Studies

Fatomi et al. in 1997 conducted a 32-week study of 5 rapid-cycling bipolar patients who received a minimum of 150 mg/day of LTG (mean dose of 185 mg/ day) as mono-therapy or in combination with other psychotropic agents. Most patients were already non-responders or poor partial responders to other conventional mood stabilizers. It was concluded that LTG augmentation therapy and monotherapy appeared to have mood stabilizing and antidepressant efficacy in the treatment of rapid cycling patients. The effect persisted for an average of 7.5 months.

In a 1999 study, Bowden et al. used LTG as add-on therapy (60 patients) or monotherapy (15 patients) in an effort to assess the drug's efficacy in rapid-cycling and non-rapid-cycling patients with bipolar disorder. The patients had diagnoses of refractory BPD and were experiencing mixed, depressive, or hypomanic episodes. A subset of rapid-cycling patients with severe initial manic symptomatology had little improvement in mania on LTG. Investigators concluded that LTG was generally effective and well tolerated in previously non-responsive, rapid-cycling bipolar patients.

A 2000 study conducted by Walden et al. evaluated 14 patients with rapid-cycling BPD who were treated with either LTG or lithium for 1 year. Out of the 7 patients treated with lithium, 3 had less than 4 episodes, whereas the remaining 4 patients had 4 or

more episodes. Six out of 7 patients treated with LTG had less than 4 episodes, while the remaining 1 patient had more than 4 affective episodes (depressive, manic, hypo-manic or mixed). Additionally, 3 patients in the LTG group were without any further affective episodes. Although the study was limited by the small number of patients, investigators suggest efficacy for LTG and a suboptimal response for lithium in rapid-cycling bipolar disorder.

In a small 1998 study, Erfurth et al. evaluated 3 females diagnosed with schizoaffective disorder. With dosages up to 200 mg/ day (serum concentrations < 5 mg/L), the patients experienced partial response. Dosages up to 400 mg /day (serum concentrations > 10 mg/day) lead to considerable mood stability and complete remission from paranoid symptoms. The authors suggested that LTG might be helpful in the treatment of schizoaffective disorder, probably with serum concentrations 5mg/L or more.

Summary

Lamotrigine, a new generation of anticonvulsant, appears to be an effective mood stabilizer in the treatment of bipolar-depressed type of patients. The open and controlled studies have shown response rate of 51% to 72%. There appears, however, to be a subset of rapid-cycling patients with severe initial mania that do not respond well to lamotrigine. Lamotrigine has shown efficacy in treatment of refractory, rapid-cycling bipolar disorder and is found to be as effective as lithium or olanzapine in the treatment of acute mania. One limitation might be the need for slow titration of dosages of LTG to avoid the risk of rash. A lower incidence of switching to mania observed with lamotrigine may have application in the management of patients prone to drug-induced switching (e.g. antidepressants). Further investigations are needed to validate the efficacy of lamotrigine in the treatment of schizoaffective disorder. To date, lamotrigine has demonstrated its efficacy in the treatment of bipolar disorder and has provided an alternative for treatment of refractory bipolar disorder.

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Table 1. Double-Blind Clinical Studies of Lamotrigine Treatment of Bipolar Disorder

Reference	Study Design	N	Dosage	Diagnosis	Duration	Outcome
14 (1999) Berk, M. et al.	DB, PG – monotherapy LTG vs Lithium vs Olanzapine	45	LTG 100mg/day Li 800mg/day Olanzapine ?	Acute mania	4 wk	Significant improvement in MRS in all groups
10 (1999) Calabrese, J.R. et al.	DB, PC – monotherapy or Placebo	195	LTG 200mg or 50mg/day	Bipolar-depressed	7 wk	51%(32) responded to 200mg LTG/day 41%(27) to 50mg/day 26%(17) to placebo
5 (2000) Frye, M.A. et al.	DB, CO - monotherapy LTG, GBP, PB	31	Mean dose - LTG 274mg/day GBP 3879mg/day	Bipolar I & II Unipolar- depressed (23 rapid-cyclers 2 non " " " 6 unipolar depressed)	6 wk	52%(16) responded to LTG 26%(8) to GBP 23%(7) to placebo
15 (2000) Ichim, L et al.	DB, randomized monotherapy - LTG, Li	30	LTG 25mg/d wk 1 50mg/d wk 2 100mg/d wk 3,4	Bipolar I -manic	4 wk	MRS scores improved in both LTG & Li groups
11 (1999) Bowden, C.L. et al.	Randomized PC monotherapy	195	LTG 200mg or 50mg, PB	Bipolar -moderate to severe depressed	7 wk	Improvement in the MADRS scores 56% of LTG 200mg/d 48% of LTG 50mg/d 29% of placebo group no evidence of LTG destabilized mood or precipitated mania
20 (2000) Calabrese, J.R. et al.	DB, PC prophylaxis - Open-label LTG monotherapy (n=324) Randomly DB maintenance phase (n=182)	506	Range: 100-300mg/d LTG Target dose of 200mg/d up to 300mg/d	Bipolar - rapid cycling	6 months	41% of LTG stable without relapse x 6/12 26% placebo stable without relapse x 6/12

DB, double-blind; PC, placebo-controlled; PG, parallel group; CO, cross over; LTG, lamotrigine; Li, lithium; GBP, gabapentin; PB, placebo; MRS score, Mania Rating Scale score; MADRS, Montgomery-Asberg Depression Rating Scale.

Table 2. Open label Clinical Studies of Lamotrigine Treatment of Bipolar Disorder

Reference	Study Design	N	Dosage	Diagnosis	Duration	Outcome
7 (1999) Suppes, T. et al.	Open-label - add on	17	Range 50-600mg/d Mean dose 187 ± 157mg/d	Bipolar I (n=9) Bipolar II (n=8)	Range: 14-455 days Mean: 159 ± 109 days	65%(11) were rated as very much to much improved in the CGI modified for Bipolar disorder scores
8 (1997) Sporn, J. et al.	Case series - add on	16	Range 50-250mg/d Mean 141 mg/d	Treatment resistant Bipolar I or II depressed, mixed or manic	Average 5 wk	50%(8) rated as responders
9,19 (1999) Calabrese, J.R. et al. Bowden, C.L. et al.	Open-label - Adjunctive(n=60) Monotherapy(n=15)	75	Monotherapy -up to 500mg /d with VPA up to 200mg /d with CBZ up to 700mg /d escalating dose over 4 weeks	Bipolar I or II depressed, hypomanic, manic or mixed	48 wk	Overall: Depressed - 42% ↓ in HAM-D Manic 74% ↓ in MRS Depressed(n=40): 48% marked response 20% moderate response Hypomanic,manic/mixed (n=31): 81% marked response 3% moderate response
12 (1997) Kusumakar, V. et al.	Open naturalistic - Add on to DVP	22	LTG 50-100mg/d DVP 1000-2250 mg/d	Bipolar-depressed Refractory to Tx	6 wk	72%(16) responded at the end of wk 4 63% entered remission by wk 6 none switched to mania
16 (1998) Erfurth, A. et al.	Single case report - Monotherapy	1	LTG up to 300mg/d	Bipolar I-acute mania-severe dysphoria	15 days severe skin rash	Slow, continuous decrease in manic symptoms
18 (1997) Fatemi, S.H. et al.	Open naturalistic prospective study- Monotherapy or add on	5	Range150-225mg/d Mean 185±33.5mg/d	Bipolar rapid cycling Refractory or partial responders	225.8± 28 days	80%(4) responders
23 (1996) Calabrese, J.R. et al.	Case series - monotherapy	1	200mg/d over 8 weeks	Bipolar I - depressed - rapid cycling to mania	11 months	HAM-D dropped from 46 to 9 over 20 wks. Remained euthymic without rapid cycling for 11 months
24 (1997) Kusumakar, V. et al.	Case series - monotherapy	7	LTG up to 150mg/d	Bipolar - rapid cycling	>5 wk	67% responded 17% euthymic by wk 2 50% euthymic by wk 3 1/6 -rash 4 wk later

VPA, DVP, valproate; CBZ, carbamazepine; LTG, lamotrigine; CGI, Clinical Global Impression scale; HAM-D, Hamilton Rating Scale for Depression; MRS, Mania Rating Scale.

References

1. Tondo, L. et al Effect of lithium maintenance in suicidal behaviour in major mood disorders. *Ann. NY Acad. Sci.* 1997; 836: 339-351.
2. Dunner, D.L. et al Clinical factors in lithium carbonate prophylaxis failure. *Arch. Gen. Psychiatry* 1974; 30: 229-233.
3. Calabrese, J.R. Introduction *European Neuropsychopharmacology* 9 Suppl. 4(1999): S107-108
4. Zerjav-Lacombe, S. Tabarsi, E. Lamotrigine: A Review of Clinical Studies in Bipolar Disorder. *Can J Psychiatry* may 2001, Vol 46, p51-56
5. Frye, M.A. et al A Placebo-Controlled Study of Lamotrigine and Gabapentin Monotherapy in Refractory Mood Disorder. *Journal of Clinical Psychopharmacology* 2000, 20:607-614.
6. Ghaemi, S.N. Novel Anticonvulsants: A new Generation of Mood Stabilizers? *Harvard Review of Psychiatry* 2000, 8:1-7
7. Suppes, T et al Lamotrigine for the treatment of bipolar disorder: a clinical case series. *Journal of Affective Disorders.* 1999 Apr; 53(1): 95-98.
8. Sporn, J. et al The Anticonvulsant lamotrigine in treatment-resistant manic-depressive illness. *J Clin Psychopharmacology* 1997 Jun; 17 (3): 185-189.
9. Calabrese, J.R. et al Spectrum of Activity of Lamotrigine in Treatment-Refractory Bipolar Disorder. *Am J Psychiatry* 1999; 156:1019-1023.
10. Calabrese, J.R. et al A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. *J Clin Psychiatry* 1999 Feb; 60(2): 79-88.
11. Bowden, C.L. et al Lamotrigine in the treatment of bipolar depression. *Eur Neuropsychopharmacology* 1999 Aug; 9 suppl. 4:S113-117.
12. Kusumakar, V. et al An open study of lamotrigine in refractory bipolar depression. *Psychiatry Research* 1997 Sep; 72(2): 145-148.
13. Calabrese, J.R. et al Controlled trials in bipolar I depression: focus on switch rates and efficacy. *Eur Neuropsychopharmacology* 9 suppl. 4(1999): S109-112.
14. Berk, M. Lamotrigine and the treatment of mania in bipolar disorder. *Eur Neuropsychopharmacology* 9 suppl. 4(1999): S119-123.
15. Ichim, L. et al Lamotrigine compared with lithium in mania: a double-blind randomized controlled trial. *Ann Clin Psychiatry* 2000 Mar; 12(1): 5-10.
16. Erfurth, A. et al New perspectives in the treatment of acute mania: a single case report. *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.* 1998, 22:1053-1059.
17. Botts, S.R. et al Gabapentin and lamotrigine in bipolar disorder. *Am J Health Syst Pharm* 1999 Oct; 56(19):1939-1944.
18. Fatemi, S.H. et al Lamotrigine in Rapid-Cycling Bipolar Disorder. *J Clin Psychiatry* 1997; 58:522-527.
19. Bowden, C.L. et al The Efficacy of Lamotrigine in Rapid Cycling and Non-Rapid Cycling Patients With Bipolar Disorder. *Biol Psychiatry* 1999; 45:953-958.
20. Calabrese, J.R. et al A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. *J Clin Psychiatry* 2000 Nov; 61(11): 841-850.
21. Walden, J. et al An open longitudinal study of patients with bipolar rapid cycling treated with lithium or lamotrigine for mood stabilization. *Bipolar Disord* 2000 Dec; 2(4): 336-339.
22. Erfurth, A. et al Lamotrigine in the treatment of schizoaffective disorder. *Neuropsychiatry* 1998 Oct; 38(3): 204-205.
23. Calabrese, J.R. et al Antidepressant Effects of Lamotrigine in Rapid Cycling Bipolar Disorder. *Am J Psychiatry* 1996 Sep; 153(9):1236.
24. Kusumakar, V. et al Lamotrigine Treatment of Rapid Cycling Bipolar Disorder. *Am J Psychiatry* 1997; 154(8):1171-1172.
25. Calabrese, J.R. et al Clinical studies on the use of lamotrigine in Bipolar Disorder. *Neuropsychobiology* 1998; 38:185-191.