



PHARMAC and treatment of bipolar depression—the limits of utilitarianism

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Abstract

Bipolar disorder affects 1.6% of the population. The majority of the burden of illness for people with bipolar disorder is due to depression. Suicide rates for people with bipolar disorder are 15 times higher than in the general population, and the majority of these deaths occur during depressive episodes. More effective prevention of such depressive episodes is important.

Lamotrigine is an anticonvulsant and a mood stabiliser that is more effective at preventing depressive relapses than most other mood stabilising drugs. Its use for this purpose has been recommended by English language treatment guidelines since 2002. Lamotrigine is approved for use in the prophylaxis of depression in bipolar disorder and for epilepsy.

PHARMAC subsidises its use in treatment-resistant epilepsy (subject to a 'special authority' application) but not in bipolar disorder. The New Zealand Mental Health Strategy and the imminent New Zealand Suicide Strategy identify reducing suicide as a key goal. Among other initiatives, this requires effective treatment of bipolar depression, yet a treatment likely to support this is not currently subsidised.

<i>Drug</i>	Lamotrigine
<i>Indications</i>	Well supported: prophylaxis of bipolar disorder when depression is prominent Supported: acute treatment of bipolar depression of mild to moderate severity.
<i>Recommended dose</i>	200 mg (range 50–300 mg) (RANZCP guidelines ¹)
<i>Clinical efficacy</i>	Lamotrigine is recommended for the prophylaxis of bipolar depression in bipolar depression of mild or moderate severity by evidence-based guidelines produced by: <ul style="list-style-type: none">• The Royal Australian and New Zealand College of Psychiatrists,¹• The American Psychiatric Association,²• The British Association for Psychopharmacology,³• The Canadian Network for Mood and Anxiety Treatments,⁴

- The World Federation of Societies for Biological Psychiatry;^{5,6} and
- The influential Texas Medication Algorithm group.⁷

It also receives support in the current consultation draft of 'The treatment of bipolar disorder' prepared by NICE in the UK.⁸

There are five RCTs comparing lamotrigine to placebo and other compounds. They suggest small but significant benefit from treatment with lamotrigine in bipolar depression acutely and prophylactically in reducing the frequency of episodes of bipolar depression.⁹⁻¹³ In addition there are two well-conducted open trials that report significant but modest effects of lamotrigine in treatment resistant bipolar depression and in preventing recurrence of bipolar depression.^{14,15}

The major adverse event is a rash, which can develop into the potentially fatal Stevens-Johnson syndrome.

Background

The lifetime risk of bipolar disorder is 1.6%. The suicide rate is about 15 times that of the general population, with many of these deaths during episodes of depression.¹⁶

While manic episodes can quickly destroy relationships and employment, the overall burden of the condition is more often due to recurrent and more enduring episodes of depression. While lithium and other currently available mood stabilisers are valuable in reducing the recurrence of mania, they are of limited efficacy in preventing depressive episodes.¹

The place of antidepressants in treating bipolar depression has been controversial because of their relatively limited efficacy; their potential to induce manic episodes and more rapid cycling of the illness; and limited prophylactic benefit.¹⁷⁻¹⁹

Clearly, there would be significant benefits to be gained from more effective treatment of bipolar disorder. Adherence to guidelines for the treatment of bipolar disorder leads to better outcomes.²⁰ Some, but not all, consider that more frequent relapses can worsen the overall outcome, making the prevention of episodes even more important.^{21,22}

In fact, lamotrigine is now recommended as the treatment of choice for prophylaxis of bipolar disorder in which depression is prominent by national guidelines for the treatment of bipolar disorder in Australasia, Canada, the UK, the US, and by international groups.

<i>Government policy</i>	The current mental health plan, <i>Tetahuhu – improving mental health</i> , mandates action on 10 key areas. One of these is promotion and prevention, including the sub-goal of: “implementing the Government’s strategy to reduce suicide and suicide attempts, and the negative impacts of depression”. ²³ The draft NZ Suicide Strategy, goal 2, is “to improve the care of people with mental disorders associated with suicide”. ²⁴
<i>Current situation</i>	Lamotrigine is fully subsidised by PHARMAC for treatment of epilepsy when older antiepileptic agents have been unsuccessful, on a Special Authority basis, supported by a neurologist. Application for a subsidy for its use in bipolar disorder was referred to the relevant PTAC subcommittee in May 2003 and recommended for listing with a medium priority in January 2004.
<i>Access/supply</i>	Lamotrigine 200 mg/day costs \$5.35/day (PHARMAC full subsidy, on relevant special authority). Existing commonly used mood stabilisers are: sodium valproate (1200 mg/day at \$1.32/day) and lithium carbonate capsules (1000 mg/day at \$1.05/day). Olanzapine is not approved for prophylaxis of bipolar disorder in New Zealand. Such use (10 mg/day) would cost \$7.30/day. Current treatment of bipolar depression in New Zealand commonly involves co-prescription of a mood stabiliser and an antidepressant, generally an SSRI.
<i>Economic analysis</i>	We are not aware of a detailed economic analysis of the benefits of lamotrigine. However, the availability of lamotrigine for those with treatment-resistant epilepsy, but not bipolar disorder, raises issues of equity.
<i>Comment</i>	Evaluation of the eventual place of new therapies is challenging. The current evidence base for lamotrigine rests on 5 randomised controlled trials. Bipolar depression causes severe levels of disability and mortality for which current treatments provide only limited relief. Lamotrigine appears to be at least as effective, and is probably more effective, than existing treatment options. It is considered the treatment of choice by all current English language guidelines in the prophylaxis of bipolar depression and may have a place to play in the acute treatment phase.

While balancing demands from different sectors for new agents presents a significant challenge for PHARMAC, lamotrigine is a relatively cheap medication that could offer hope of significant relief for some people with chronically relapsing bipolar depression.

The principle of utilitarianism is understandable when seeking to address a nation's overall needs for medication. However, it is important that we do not lose sight of the needs of those unfortunate people for whom subsidized medication is of limited benefit. Just over five dollars a day is cheap for the country and may allow someone to resume their life, including returning to work – but it translates into a monthly bill that is beyond the means of someone living on a sickness benefit. People with treatment-resistant epilepsy can already access somewhat more expensive treatments such as lamotrigine. It would seem only equitable that people with bipolar disorder of predominantly depressive type should have access to a potentially effective treatment – which is considered a first-line option in all major current treatment guidelines.

Disclosure: Professor Ellis has a beneficial interest in GlaxoSmithKline shares.

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References:

1. Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Bipolar Disorder. Australian and New Zealand clinical practice guidelines for the treatment of bipolar disorder. *Aust N Z J Psychiatry*. 2004;38:280–305.
2. Hirschfeld RMA, Bowden CL, Gitlin MJ, et al. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry*. 2002;159(Suppl.):1–50.
3. Goodwin GM, Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2003;17:149–73.
4. Yatham LN, Kennedy SH, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. *Bipolar Disord*. 2005;7(Suppl 3):5–69.
5. Grunze H, Kasper S, Goodwin G, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of bipolar disorders, part I: Treatment of bipolar depression. *The World J Biol Psychiatry*. 2002;3:115–24.

6. Grunze H, Kasper S, Goodwin G, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders, part III: Maintenance treatment. *The World J Biol Psychiatry*. 2004;5:120–35.
7. Suppes T, Dennehy EB, Hirschfeld RM, et al. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. *J Clin Psychiatry*. 2005;66:870–86.
8. National Collaborating Centre for Mental Health. The management of bipolar disorder in adults, children and adolescents, in primary and secondary care Draft for second consultation, February 2006. The National Institute for Health and Clinical Excellence.
9. Calabrese JR, Bowden CL, Sachs GS, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *J Clin Psychiatry*. 1999;60:79–88.
10. Calabrese JR, Suppes T, Bowden CL, et al. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. *J Clin Psychiatry*. 2000;61:841–50.
11. Frye MA, Ketter TA, Kimbrell TA, et al. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *J Clin Psychopharmacol*. 2000;20:607–14.
12. Calabrese JR, Bowden CL, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry*. 2003;64:1013–24.
13. Bowden CL, Calabrese JR, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry*. 2003;60:392–400.
14. McElroy SL, Zarate CA, Cookson J, et al. A 52-week, open-label continuation study of lamotrigine in the treatment of bipolar depression. *J Clin Psychiatry*. 2004;65:204–10.
15. Nierenberg A, Ostacher M, Calabrese J, et al. Treatment-resistant bipolar depression: A STEP-BD Equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiatry*. 2006;163:210–16.
16. Chen YW, Dilsaver SC. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. *Biological Psychiatry*. 1996;39:896–9.
17. Grunze H. Reevaluating therapies for bipolar depression. *J Clin Psychiatry*. 2005;66(Suppl 5):17–25.
18. Gijsman HJ, Geddes JR, Rendell JM, et al. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry*. 2004;161:1537–47.
19. Ghaemi SN, Hsu DJ, Soldani F, et al. Antidepressants in bipolar disorder: the case for caution. *Bipolar Disord*. 2003;5:421–33.
20. Dennehy EB, Suppes T, Rush AJ, et al. Does provider adherence to a treatment guideline change clinical outcomes for patients with bipolar disorder? Results from the Texas Medication Algorithm Project. *Psychol Med*. 2005;35:1695–706.
21. Post RM, Weiss SR. Convergences in course of illness and treatments of the epilepsies and recurrent affective disorders. *Clin EEG Neurosci*. 2004;35:14–24.
22. Hlastala SA, Frank E, Kowalski J, et al. Stressful life events, bipolar disorder, and the "kindling model". *J Abnorm Psychol*. 2000;109:777–86.
23. Minister of Health. Te Tāhuhu – Improving Mental Health 2005–2015: The Second New Zealand Mental Health and Addiction Plan. Wellington: Ministry of Health; 2005. Available online. URL:

<http://www.moh.govt.nz/moh.nsf/by+unid/F2907744575A9DA9CC25702C007E8411?Open>
Accessed March 2006.

24. New Zealand Suicide Prevention Strategy: A Life Worth Living. (Annette Beautrais, personal communication; 2006).

Interim response from PHARMAC: PHARMAC advises that it has not had enough time to draft a response this instance, but wishes to do so in coming issues of the Journal. In the interim, PHARMAC agrees that there may be merits to funding lamotrigine for bipolar depression, and is actively working on this at the moment.