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Lamotrigine in bipolar disorder: an overview

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*Chapter 4 Pharmacological profile and clinical utility of lamotrigine in mood disorders*  
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Introduction

There remains a pressing need for additional treatment options for mood disorders, particularly those refractory or difficult to treat disorders such as bipolar disorder. Estimates of the prevalence of bipolar I disorder across diverse cultures and ethnic groups are consistent, ranging between 0.4% and 1.6% in adults (Weissman 1996 and Regeer 2004). Recent estimates of the overall prevalence of bipolar disorder (types I and II as well as NOS) suggest that 4-5% suffers from this debilitating mental disorder (Hirschfeld.2003; Regeer 2004). Bipolar disorders carries a high burden, negatively affecting lives in many areas, most notably the performance of work-related, leisure, and interpersonal activities (Calabrese 2003). The greatest need exists in the treatment of depressive episodes associated with bipolar disorders as symptoms of depression are much more commonly experienced and more difficult to treat than manic symptoms (Post 2002; Judd 2002 and Kupka 2005).

Reports of lamotrigine’s beneficial effects on mood in epilepsy patients led to its use and study in affective disorders. Studies involving bipolar patients suggested that lamotrigine possessed a broad spectrum of therapeutic activity in bipolar disorder, with later descriptions of greater efficacy for depressive than for manic symptoms. Given the significant burden, prevalence, and recurrent nature of bipolar disorder - especially bipolar depression – lamotrigine appears to begin to address an area of serious unmet public health need (Calabrese 2003).

Clinical Pharmacology of Lamotrigine

Pharmacodynamics

Lamotrigine is an antiepileptic drug of the phenyltriazine class that has demonstrated efficacy as add-on treatment of partial seizures (Mikati 1989; Matsuo 1993) and as maintenance treatment of bipolar I disorder to delay the time of occurrence of mood episodes (Bowden 2003; Calabrese 2003). Although its mechanism of therapeutic action in humans is not definitively understood, lamotrigine is thought to possess modulatory and protective effects
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Structurally distinct from other antiepileptic drugs, lamotrigine interacts preferentially on the slow inactivated state of presynaptic neuronal sodium and calcium channels to prolong inactivation of the neuron and promote stabilization of the neuronal membrane (Xie 1998). This effect is augmented by a use-dependent action in which further inhibition by the drug develops during rapid, repetitive stimulation (i.e., epileptiform bursts). Consequently, the release of the excitatory amino acid glutamate is antagonized (Fitton 1995, Li and Ketter 2002). Lamotrigine has also been observed to inhibit cortical and amygdaloid kindling (Gilman 1995, Leach 1986 and Xie 1995).

Lamotrigine has no substantial in vitro affinity for adenosine, adrenergic, dopaminergic, muscarinic and opioid receptors at clinically applicable concentrations and binds only weakly to inhibit serotonin 5HT3 receptors (Leach 1991). Lamotrigine lacks clinically meaningful activity at the 5HT1A receptor, where changes in 5HT1A receptor-mediated cyclic adenosine monophosphate pathway have been implicated in affective disorders (Shiah 1998 and Vinod 2002).

In early epilepsy studies with lamotrigine it was noted that many patients reported improvement in mood and psychological well-being independent from reduction in seizure frequency, which led to its investigation for use in affective disorders (Smith 1993a; Smith 1993b). Significantly, lamotrigine has minimal negative effects on cognitive, memory, or psychomotor function and is not associated with sedative effects or weight gain (Goa 1993, Cohen 1985 and Ginsberg 2003).

Pharmacokinetics

Lamotrigine is extensively absorbed demonstrating linear kinetics, resulting in 98% bioavailability (Garnett 1997). Peak plasma concentrations are attained after 1-3 hours with mean plasma protein binding of 55-68% (Cohen 1987, Ramsay, 1991 and Rambeck 1993). Lamotrigine readily crosses the placental barrier causing fetal blood concentrations similar to maternal levels and passes into breast milk reaching 40-80% of the maternal lamotrigine.
concentration (Ohman, 2000 and Pennell 2003).

The rate-limiting step in the elimination of lamotrigine is N-glucuronidation by the liver with a plasma elimination half-life of 25 + 10 hours (Cohen 1987). Autoinduction of its own metabolism does not occur and there are no active metabolites. Pregnancy increases lamotrigine clearance by more than 50% early during pregnancy and reverts quickly after delivery (Tran 2002). Clearance may be reduced in the elderly and in patients with moderate to severe hepatic dysfunction.

**Drug Interactions**

Lamotrigine administration affects hardly the serum concentrations of other drugs. However, enzyme-inhibiting drugs such as divalproex sodium increase lamotrigine concentrations by significantly competing for metabolism through glucuronidation effectively increasing the mean half-life of lamotrigine to about 70 hours (Yuen 1992 and Anderson 1996). Enzyme-inducing drugs, such as phenytoin, carbamazepine, and phenobarbital, reduce the lamotrigine’s mean elimination half-life to about 12 hours and decrease lamotrigine concentrations (Hachad 2002). There are pharmacokinetic interactions between lamotrigine and anti-conceptive medication (Sidhu 2005). The clearance of levonogestrel is increased with a possible decrease of the anti-conceptive reliability. On the other hand is the clearance of lamotrigine enhanced by anti-conceptive medication, with a lowering of lamotrigine plasma levels.

Lamotrigine does not significantly affect the pharmacokinetics of lithium (Chen 2000).

**Lamotrigine and Mood Disorders**

**Acute treatment of bipolar depression**

The observations of Smith and colleagues (Smith 1993a, 1993b) that patients treated with add-on lamotrigine for partial seizures experienced improved mood apart from effects on epilepsy stimulated investigations of lamotrigine’s efficacy to treat mood disorders. Early case reports involving
bipolar patients suggested that lamotrigine possessed a broad spectrum of therapeutic activity in bipolar disorder, including rapid cycling and mixed states (Weisler 1994, Calabrese 1996 and Walden 1996). A subsequent open-label study provided preliminary data that lamotrigine was effective for patients with refractory bipolar disorder, with 68% of depressed patients and 84% of manic / hypomanic / mixed patients showing moderate to marked response (Calabrese 1999a).

An open naturalistic study of twenty-two depressed bipolar patients who were refractory to treatment with a combination of divalproex sodium and another mood stabilizer or divalproex sodium and an antidepressant for 6 weeks were treated with add-on lamotrigine. Sixteen out of 22 (72%) responded by the end of week 4, suggesting that lamotrigine may be useful in bipolar depression (Kusumakar 1997). In a double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with non rapid-cycling bipolar I depression, treatment with lamotrigine over 7 weeks (50 or 200 mg/day) did not result in a significant difference versus placebo on the primary outcome measure (HAM-D), but did so on several secondary outcome measures including the MADRS, particularly in the 200 mg group, compared with placebo (Calabrese 1999b). Improvements were observed as early as week 3.

After this first positive result for lamotrigine in a RCT, lamotrigine was tested against placebo in four other RCT’s (Calabrese 2007 and Goldsmith 2003). None of these RCT’s discriminated significantly between lamotrigine and placebo on the primary outcome criteria. Part of this negative result was because of a high placebo response in all four studies. Nevertheless, a meta-analysis of all five studies showed a significant although modest benefit for lamotrigine. (Geddes 2009)

Thirty-one patients with refractory bipolar and unipolar mood disorders participated in a double-blind, randomized, crossover study of three 6-week monotherapy evaluations including lamotrigine, gabapentin, and placebo. Using the Clinical Global Impressions Scale for Bipolar Illness (CGI-BP) as the primary outcome variable, this study reported a 52% response rate (CGI-BP as much or very much improved) for lamotrigine, compared to 26% for gabapentin and 23%
for placebo-treated patients (Frye 2000).

The final study (n=410) compared lamotrigine (dose uptitrated to 200 mg/day) with olanzapine/fluoxetine (dose 6/25, 6/50, 12/25 or 12/50 mg/day) (Brown.2006) and showed a small but significant advantage (improvement on the MADRS after 7 weeks of 14.91 vs 12.92 respectively p=0.002) for the olanzapine/fluoxetine combination.

**Acute treatment of mania / mixed states**

The 1999 open-label study by Calabrese and colleagues observed a robust response to lamotrigine (primarily as add-on therapy) in 84% of manic / hypomanic / mixed patients (Calabrese 1999a). In the first double-blind, randomized, controlled study of lamotrigine in acute mania lamotrigine titrated to 100 mg/day over three weeks was as effective as lithium 800 mg/day (mean blood level 0.77 mmol/L) in reducing manic symptoms (Ichim 2000). However, lamotrigine has not shown anti-manic activity in placebo-controlled studies (Bowden 2003). Unpublished studies (data on file, GlaxoSmithKline 2003) in patients with acute manic or mixed exacerbations of bipolar I disorder have found no significant difference from baseline in the 11-item Mania Rating Scale (MRS) between lamotrigine and placebo (Goldsmith 2003).

**Maintenance therapy**

The initial lamotrigine maintenance study was a double-blind, placebo-controlled study in rapid cycling bipolar disorder (Calabrese 2000). Open label lamotrigine added to the treatment regimens of 324 patients meeting DSM-IV criteria for rapid cycling bipolar disorder resulted in 182 stabilized patients who were then randomly assigned to the double-blind maintenance phase after being stratified for bipolar I or II disorder. Other psychotropic agents were tapered and patients randomly assigned to either lamotrigine monotherapy or placebo in a 1:1 ratio for the six-month maintenance phase. Overall 49 placebo patients (56%) and 45 lamotrigine-treated patients (50%) required treatment of an emerging mood episode with additional pharmacotherapy. Although there was no statistical significance between these two treatment groups on the primary
outcome measure of time to additional pharmacotherapy (median of 12 weeks for placebo versus 18 weeks for lamotrigine), lamotrigine was significantly more effective than placebo in the survival in study analysis (median of 8 weeks for placebo versus 14 weeks for lamotrigine). In the sub-analysis according to disease type, lamotrigine was significantly more effective than placebo in delaying time to additional pharmacotherapy for bipolar II patients than bipolar I patients. Forty-six percent of bipolar II patients on lamotrigine monotherapy were stable without relapse after 6 months compared to only 18% of placebo-treated bipolar II patients. (Calabrese 2000). These results were confirmed in a post hoc analysis of the same patient sample with the Life chart method. Measured with the life chart at least once weekly patients taking lamotrigine were 1.8 times more likely to achieve euthymia than those taking placebo (Goldberg 2008). In an unpublished study (data on file, GlaxoSmithKline 2003), these findings were not replicated. However, significantly fewer lamotrigine treated rapid cyclers required intervention for a depressive episode. Collectively, these results suggest that lamotrigine may be a useful treatment for rapid cycling bipolar patients, especially for type II and for the prevention of depressive relapses.

Two 18-month maintenance studies (Bowden 2003 and Calabrese 2003) comparing lamotrigine, lithium, and placebo provided further support for the use of lamotrigine as a mood stabilizer and led to its approval by the US FDA in June 2003 as a maintenance treatment for bipolar I disorder. These complementary studies enrolled patients in a double-blind phase of maintenance therapy after a recent depressed, hypomanic, or manic episode remitted (CGI-S score of < 3 for 4 consecutive weeks) during open-label stabilization during which lamotrigine was initiated as adjunctive or monotherapy and other psychotropics discontinued. In both studies, 50% of patients achieved stabilization criteria allowing for progression into double-blinded maintenance therapy with lamotrigine (50-400 mg/day), lithium (0.8-1.1 mEq/L), or placebo. The primary efficacy endpoint used was time to intervention for any mood episode.

In both of these studies, lamotrigine and lithium demonstrated effective prophylaxis against any emerging mood episode compared with placebo. There were statistically fewer relapsing mood episodes and longer median survival in
lamotrigine and lithium treated patients compared with placebo. Median survival before intervention for any mood episode for lamotrigine-treated patients ranged from 118-256 days, significantly better than placebo (85-93 days). Lithium also outperformed placebo with a median survival of 170-292 days. However, there were important differences in the spectra of maintenance efficacy.

In both studies, lithium, but not lamotrigine was superior to placebo at delaying the time to intervention for a manic or hypomanic episode. In total for both studies 123 hypomanic/manic events emerged during maintenance, with 25% of placebo treated patients experiencing a hypomanic, manic, or mixed episode (47 of 188); 21% of the lamotrigine group relapsed (58 of 273), but only 11% of patients in the lithium-treatment arm had breakthrough mania or hypomania (18 of 164). Lithium was clearly more effective than placebo and lamotrigine in preventing manic and hypomanic relapse in recently symptomatic bipolar I patients.

In contrast, lamotrigine appears to be more effective than lithium in the prevention of depressive relapse in bipolar I patients. In both studies, lamotrigine but not lithium, was significantly better than placebo at prolonging time to intervention for a depressive mood episode. There were 209 depressive relapses in the patients observed in the two studies, with a higher rate of relapse in the placebo (68 of 188, or 36%) and lithium treatment groups (56 of 164, or 34%); lamotrigine was better at preventing recurrence of depression with a 31% rate of depressive relapse and a longer median survival before treatment of depression was necessary. The difference was particularly evident in the treatment of recently manic or hypomanic patients in whom only 14% of those receiving lamotrigine (8 of 58) needed intervention for emergent depression compared with 23% of patients receiving lithium (10 of 44) and 30% receiving placebo (21 of 69). In a post hoc analysis of the first 6 months of the bipolar I patients (index episode depression) there was no evidence for a greater risk for mood destabilization (emergent (hypo) manic symptoms) in the lamotrigine group versus the placebo group (Goldberg 2009).
Safety

Rash

Rashes requiring hospitalization and discontinuation of treatment have been reported with lamotrigine. The reported rash rate is 10% in adult patients with epilepsy treated with adjunctive lamotrigine and 7% in bipolar I adults treated with monotherapy; the placebo rate is 5% in both populations (lamotrigine package insert). Serious rash rates are considerably lower at 0.8% in pediatric epilepsy patients, 0.3% in epileptic adults as monotherapy and 0.13% as adjunctive therapy. A retrospective analysis conducted of rates of lamotrigine-related rash in 12 multicenter studies of lamotrigine for mood disorders (n=1955), including 1 open study, 7 randomized controlled acute trials, and 4 randomized controlled maintenance trials from 1996 to 2001 reported serious rash in 0% with lamotrigine, 0.1% (n = 1) with placebo, and 0% with comparators (Calabrese 2002). Across all bipolar disorder studies with 2,272 patients on lamotrigine, serious rash was observed in three patients for an overall rate of 0.1% (lamotrigine package insert). One of these three patients experienced a mild Stevens-Johnson syndrome on adjunctive lamotrigine and did not require hospitalization.

In a randomized trial Usual Care Precautions were compared with Dermatologic Precautions (UCP plus additional specific precautions intended to decrease the risk of rash) for 12 weeks (Ketter 2006). Lamotrigine was added (target dose 200mg/day) to ongoing medication with a slow up titration.

Usual Care precautions were:
1. not exceeding the initial dose or dose-escalation schedule
2. if a rash developed during the study the patient contacted the investigator immediately
3. lamotrigine was stopped in case of rash.

Patients in the Dermatologic Precautions group were, besides UCP, advised not to:
4. take new medications or foods, use new cosmetics, deodorants, detergents or
fabric softeners
5. stimulate the immune system through excessive sun exposure
6. participate in activities that might lead to exposure to poison oak or poison ivy
7. receive any immunizations

1175 patients were included. In both groups there were no reports of serious rash. The rate of non-serious rash was low for UCP as well as for DP (8.8% and 8.6% respectively, OR 0.99), which is comparable with rates of rash in previous studies. Clinical response was 50% with 29% remission over both groups (according to the Clinical Global Impressions Bipolar version).

A German registry that documents the incidences of serious rash has been in place since 1990 and ascertains hospitalized cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) related to antiepileptic drug use (Rzany 1996). Reported cases are confirmed by a registry physician and reviewed by a dermatological expert committee ensuring high diagnostic accuracy. The incidence of serious rash rising to the level of SJS/TEN diagnosis in the German registry was 0.02% from 1993-2001 (Messenheimer 2002).

Risk of rash is noted to be higher in pediatric patients and may be increased by co-administration of divalproex sodium or exceeding the recommended initial dose or dose escalation schedule for lamotrigine. Women may be at increased risk for rash compared with men, with a relative risk of 1.8 (Wong 1999).

Other side effects and tolerability

Lamotrigine is known to be generally well tolerated in the treatment of epilepsy (Choi 2003). A great deal of data generated by the 18-month lamotrigine maintenance trials (Bowden 2003 and Calabrese 2003) confirms clinical experience and epilepsy management reports of lamotrigine’s favorable side effect profile in the treatment of bipolar patients. In 280 patients on maintenance lamotrigine during double-blinded treatment in both trials combined, only 23 (8.2%) discontinued study participation prematurely due to an adverse event; 7.9% of placebo treated patients experienced adverse events that led to
end of study (15 of 191). Over the 18 months randomized phase, lamotrigine treated patients exhibited a 4.9 pound mean decrease in body weight, compared to a 2.6 pound mean weight gain in the placebo group. In a combined analysis of both studies, the incidence of mania/ hypomania/ mixed episodes reported as adverse events was 5% for patients treated with lamotrigine, 4% for patients treated with lithium, and 7% for patients treated with placebo. In general, lamotrigine exhibits placebo level rates of treatment-emergent adverse events and is better tolerated than lithium (Calabrese 2003). Table 1 lists treatment-emergent adverse events for the combined maintenance studies during randomized phase.

**Table 1.** Adverse events observed during randomized phase of lamotrigine maintenance studies (in percent)*

<table>
<thead>
<tr>
<th>Event</th>
<th>Lamotrigine (n = 227)</th>
<th>Placebo (n = 190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Somnolence</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Back pain</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Benign rash</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Cough exacerbation</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

* Adverse events listed had incidence > 5% and were numerically greater than placebo. [Bowden 2003; Calabrese 2003; Data on file, GlaxoSmithKline]
Clinical applications for lamotrigine

Bipolar depression

For the management of acute bipolar depression, the APA Practice Guidelines of 2002 recommended lamotrigine as a first-line option with moderate clinical confidence (Hirschfeld 2002). Since then other options have become available, especially quetiapine and the combination of olanzapine plus fluoxetine. With the data that became available after the 2002 guideline, lamotrigine has a place in the treatment of acute bipolar depression, especially in patients experiencing a depressive episode despite adequate treatment with lithium. In these patients lamotrigine can be recommended as add-on therapy with substantial clinical confidence.

Dosing should follow published titration schedules to minimize the risk of rash, with a minimum dose of 50 mg/day and a target dose of 200 mg/day for most patients (table 2). There is no pharmacokinetic interaction with lithium, However, in bipolar patients experiencing a breakthrough depression on carbamazepine or valproate, lamotrigine should be added while keeping in mind pharmacokinetic interactions that may affect dosing: double dose of lamotrigine in combination with carbamazepine, half the dose in combination with valproate.

Table 2. Recommended Lamotrigine dosing schedule

<table>
<thead>
<tr>
<th>Concomitant medication?</th>
<th>Week 1 &amp; 2</th>
<th>Week 3 &amp; 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not on divalproex or carbamazepine</td>
<td>25 mg qd</td>
<td>50 mg qd</td>
<td>100 mg qd</td>
<td>200 mg qd</td>
<td>200 mg qd</td>
</tr>
<tr>
<td>On divalproex</td>
<td>25 mg qod</td>
<td>25 mg qd</td>
<td>50 mg qd</td>
<td>100 mg qd</td>
<td>100 mg qd</td>
</tr>
<tr>
<td>On carbamazepine or phenytoin</td>
<td>50 mg qd</td>
<td>100 mg qd</td>
<td>200 mg qd</td>
<td>300 mg qd</td>
<td>300 mg qd</td>
</tr>
</tbody>
</table>
**Mania / mixed states**

Lamotrigine monotherapy is not recommended for the acute management of mania or mixed states associated with bipolar I disorder. Despite limited case reports and early data suggesting that lamotrigine may possess anti-manic properties, further study has led to the conclusion that lamotrigine has only mild to moderate efficacy in mania and should not be reliably used as monotherapy in these urgent above baseline mood disturbances. The addition of lamotrigine to other first-line antimanic agents, such as lithium, divalproex, olanzapine, or quetiapine may hasten or complete recovery from acute manic or mixed states. Lamotrigine should definitely be considered as an initial adjunctive treatment for these bipolar I patients to address the need to prevent future mood episodes after recovery from the current manic or mixed episode. Again, dosing guidelines should be followed as indicated previously and in the package insert to avoid increased risk of rash.

In bipolar II patients experiencing acute hypomania, lamotrigine can be used as a monotherapy or in conjunction with another mood stabilizer such as lithium. One effective strategy is the prescription of lamotrigine plus a short-term atypical antipsychotic

**Maintenance therapy**

Lamotrigine is indicated by the US FDA and the EMEA for the maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes. It should therefore be considered in the treatment of all bipolar patients due to the inherent natural tendency for the illness to be chronic and recurrent.

Maintenance monotherapy with lamotrigine can be considered in those individuals with non-bipolar I illness, milder forms of bipolar II disorder with predominant depressive course, and in other bipolar spectrum disorders such as cyclothymic or hyperthymic personalities. In theory, lamotrigine monotherapy could also be considered as a maintenance therapy after successful ECT for either unipolar or bipolar depression. In most patients, lamotrigine should be part of a combined pharmacological strategy to prevent relapse. Although lamotrigine
has been demonstrated an effective maintenance treatment for bipolar I disorder, its ability to prevent manic episodes was considerably less robust than its antidepressant ability. A comprehensive bipolar maintenance medication treatment plan must address prevention of depressive and manic phases, and lamotrigine is only moderately effective in the delay of manic episodes necessitating use of other mood stabilizers with a complementary efficacy profile, such as lithium, divalproex or atypical antipsychotics.

Use in women

There have been reports of lamotrigine serum concentrations decreasing in women after starting oral contraceptives and increasing after oral contraceptives were discontinued (Sidhu 2005). Dosage adjustments may have to be made in women taking lamotrigine during times of oral contraceptive initiation or termination, although no known link exists between blood levels and therapeutic effects for affective disorders.

Lamotrigine carries a Category C FDA warning for use during pregnancy. Pregnant women maintained on lamotrigine during pregnancy should have blood levels of lamotrigine checked monthly as its clearance increases significantly as pregnancy progresses. A preconception determination of lamotrigine blood level in a stable bipolar woman may provide a target dose range to maintain during pregnancy. Clearance of lamotrigine drops quickly after delivery, requiring dosage reduction in most postpartum patients. Breast-feeding is not recommended to nursing mothers on lamotrigine since significant levels of lamotrigine are present in breast milk and long term effects of exposure to neonates is unknown. Although there are some reports of an increased risk for isolated cleft palate or lip deformity after exposure to lamotrigine monotherapy during the first trimester of pregnancy (Holmes 2008) the overall risk for major birth defects appear to be similar to that of the general population (Cunnington 2005).
Summary

The discovery of lamotrigine’s positive effects on mood in epilepsy patients led to its investigations in and eventual approval for treating bipolar I disorder. Although the exact mood stabilizing mechanism of action for this novel anticonvulsant is unknown, it is thought to work by inhibiting voltage-sensitive sodium currents, in this manner stabilizing neuronal membranes and as a result modulating the presynaptic transmitter release of excitatory amino acids such as glutamate. It is approved for maintenance treatment of bipolar disorder to prevent depressive episodes. In addition, it deserves a place in the treatment of acute bipolar depression, with the strongest evidence as add-on treatment to lithium (this thesis). Lamotrigine is well tolerated, the major risk is a severe rash, and it requires careful dose monitoring.
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Chapter 2

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