

## Treatment of the depressive phase of bipolar affective disorder: a review

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### Abstract

Bipolar disorder is a chronic mood disorder which usually has its onset in adolescence and young adulthood. The disorder is typified by a remitting and relapsing course. While remissions are often partial in nature, relapses are frequent and manifested as manic, mixed, hypomanic and depressive episodes. Rapid cycling is a particularly disabling form of bipolar disorder, characterised by four or more episodes in a 12-month period. Bipolar disorder inevitably causes impairment in social and occupational functioning. Many patients experience severe hopelessness and suicidal ideation and the disorder is associated with one of the highest mortality rates of all psychiatric disorders. The treatment of bipolar depression is particularly challenging and numerous patients achieve incomplete benefit even with complex psychopharmacological strategies. In recent years, many new pharmacological options have become available for the treatment of bipolar depression and the field has seen significant progress. In order to achieve better outcome for the patients, it is mandatory that treating physicians have an up to date knowledge of recent advances in the management of this condition.

**Keywords:** Bipolar disorder, Rapid cycling, Mood stabilisers, Second-generation antipsychotics.

### Introduction

Bipolar disorder (BD) is a chronic condition with the lifetime prevalence estimated at around 4% for all types of this disorder.<sup>1</sup> In the United States, National Comorbidity Survey found that 1% of the population met lifetime prevalence criteria for bipolar I (presence of at least one manic or mixed episode), 1.1% for bipolar II (major depressive episodes with at least 1 hypomanic episode), and 2.4% for sub-threshold symptoms such as one or two features over a short period of time.<sup>2</sup> Prevalence is similar in men and women and, broadly, across different cultures and ethnic groups.<sup>3</sup> Late adolescence and early adulthood are peak years for the onset of bipolar disorder.<sup>4</sup>

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The basis of the current conceptualisation of manic-depressive illness can be traced back to the 1850s. On January 31, 1854, Jules Baillarger described to the French Imperial Academy of Medicine a biphasic mental illness causing recurrent oscillations between mania and depression, which he termed "folie à double forme" (dual-form insanity). Two weeks later, on February 14, 1854, Jean-Pierre Falret presented a description to the Academy on what was essentially the same disorder, and was designated "folie circulaire" (circular insanity) by him.<sup>5</sup> These concepts were developed by the German psychiatrist Emil Kraepelin (1856-1926) who, using Kahlbaum's concept of cyclothymia, categorised and studied the natural course of untreated bipolar patients. He coined the term 'manic-depressive psychosis', after noting that periods of acute illness, manic or depressive, were generally punctuated by relatively symptom-free intervals where the patient was able to function normally.<sup>6</sup> Sub-classification of bipolar disorder was first proposed by German psychiatrist Karl Leonhard in 1957. He was also the first to introduce the terms "bipolar" (for those with mania) and "unipolar" (for those with depressive episodes only).<sup>7</sup>

There is no clear consensus as to how many types of bipolar disorder exist. In Diagnostic and Statistical Manual of Mental Disorders (4th Edition; text revision) (DSM-IV TR) and International Classification of Disease (ICD-10), bipolar disorder is conceptualised as a spectrum of disorders occurring on a continuum.<sup>8</sup> The DSM-IV TR lists 3 specific subtypes (Bipolar I, Bipolar II and Cyclothymic disorder) and 1 non-specified diagnosis (Bipolar disorder NOS). The course specifier, "rapid cycling," is applied to any of the sub-types where there are four or more affective episodes (manic, mixed, hypomanic or depressive) during a 12-month period. The presence of rapid cycling is associated with worse prognosis in spite of best possible attempts at management, which is manifested as increased morbidity and mortality from attempts at self-harm.<sup>9</sup> In addition, patients with rapid cycling tend to suffer from more comorbid disorders which increase the burden of impairment in psychosocial spheres of life.<sup>10,11</sup> Adolescents and women suffering from bipolar disorder, with onset during the post-partum period, are more often affected with rapid cycling.<sup>12</sup>

There are several childhood precursors in children who later receive BD diagnosis. The abnormalities may range from subtle mood fluctuations to full major depressive episodes, and the existence of disruptive behaviour disorders including attention-deficit hyperactivity disorder (ADHD).<sup>13</sup> During the depressive phase of the disorder, coexistence of other psychiatric conditions poses diagnostic and management challenges and adversely affects the prognosis. Panic disorder, generalised anxiety disorder, social phobia, obsessive compulsive disorder (OCD), substance use disorders, and eating disorders are frequently comorbid with the depressive phase of bipolar affective disorder.<sup>14</sup>

The prognosis of BD depends on the length of affective episodes, presence of rapid cycling, and existence of sub-threshold symptoms between episodes. Major depressive episodes and sub-clinical depressive symptoms unfavourably influence the outlook and represent the major source of morbidity.<sup>15</sup> In spite of the fact that the patients spend much more time experiencing depressive symptoms as opposed to manic symptoms, the treatment of the former is difficult and complicated. The purpose of this review is to highlight current trends in the treatment of BD by describing the agents that have been found effective as mood stabilisers in the depressive phase of BD.

## Pharmacotherapy of Bipolar Depression

### Lithium Salts

The efficacy of lithium salts in the treatment of BD was discovered serendipitously by Australian psychiatrist John Cade in 1949. The Danish psychiatrist, Mogen Schou, conducted controlled trials of this drug in 1970, establishing its role as a mood stabiliser. It is useful in treating the manic phase of BD, usually in combination with an anti-psychotic, and as monotherapy in the maintenance phase. Its efficacy in treating bipolar depression and mixed states is less well-ascertained. Although the drug's usefulness is well known, there are serious problems with side-effects, teratogenic potential, narrow therapeutic index, and toxicity in overdose.<sup>16</sup> Because of these disadvantages, in particular its potential lethality in overdose, there has been a persistent effort to find other drugs for the treatment of BD.

### Carbamazepine

The anti-epileptic potential of this drug was discovered by Swiss chemist, Walter Schindler in 1953. It stabilises the inactivated state of the voltage-gated sodium channels, making fewer of these available to subsequent opening, and leaving the affected neurons less excitable. Food and Drug Administration (FDA) has approved its use in the manic and mixed phases of BD. It is also used in the

maintenance phase of bipolar affective disorder, though in this respect its efficacy is perhaps inferior to that of lithium. The drug is often used in treating bipolar depression. Nevertheless there is absence of data from good-quality controlled trials. The main drawbacks are its hepatic enzyme inducing potential, neurological side-effects, liability to cause syndrome of inappropriate secretion of antidiuretic hormone (SIADH), idiosyncratic skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis), aplastic anaemia (rarely), and neural tube defects in the foetus.

### Extended-release Carbamazepine

In 2004, an extended release formulation of carbamazepine was approved by the United States FDA for the acute treatment of manic and mixed episodes associated with BD type I. In two randomised, placebo-controlled, double-blind monotherapy trials, the drug showed significant onset of effect within 7 days, an incremental response of about 25% over placebo and a moderate effect size of 0.61 with no treatment-emergent depression.<sup>17</sup> It allowed twice daily dosing and minimised plasma carbamazepine fluctuations. The drug has been used off-label as maintenance treatment and for bipolar depression, both as monotherapy and in combination with other mood-stabilisers and 2nd generation antipsychotics.

### Oxcarbazepine

Oxcarbazepine is a structural derivative of carbamazepine, with a ketone in place of the carbon-carbon double bond on the dibenzazepine ring. Used primarily as an anti-convulsant, it has been found to reduce anxiety and enhance mood; data from a range of studies has underscored its potential as a mood stabilizer.<sup>18</sup> The drug appears to be efficacious in the treatment of bipolar depression, and as a prophylactic agent in the maintenance phase. Its unique structure is apparently responsible for causing less liver enzyme stimulation, fewer neurological side-effects and a reduction in the liability of causing Stevens-Johnson syndrome and aplastic anaemia. In addition, the teratogenic potential of oxcarbazepine comes out to be not as much as carbamazepine. However, it retains the likelihood of causing SIADH.

### Divalproex Sodium

This consists of a compound of sodium valproate and valproic acid in a 1:1 molar relationship in an enteric coated form. It has FDA approval for the treatment of manic episodes associated with BD type I. However, the drug is successful in the pharmacotherapy of mixed episodes and rapid cycling.<sup>19</sup> It is often used in

combination with other mood stabilisers and anti-psychotics for these indications. The drug has been used as monotherapy for prophylaxis, and in combination with anti-depressants for the treatment of BD. The rationale for the latter strategy is that divalproex sodium reduces the chance of switch into manic/mixed/hypomanic phases, and, hence, prevents destabilisation of mood which is apt to occur with anti-depressant monotherapy.

There are a number of serious issues with divalproex sodium. This drug has a marked teratogenic potential, and can induce such anomalies as anencephaly and spina bifida; the mechanism of neural tube defects is presumably secondary to its antagonism of folate metabolism.<sup>20</sup> It has a liability of causing weight gain, central nervous system (CNS) adverse effects, hepatic injury, pancreatitis (rarely), thrombocytopaenia, and, in females of reproductive age, endocrine dysfunction resulting in irregularities of menstruation and induction of polycystic ovary syndrome. The drug is also known to cause urea cycle abnormalities, hyperammonia and encephalopathy.<sup>21</sup> It is associated with fatigue, drowsiness, tremors, as well as altered mental status and hallucinations. Dermatologic side effects include hair loss and acne; gastro-intestinal side effects consist of dyspepsia, nausea and vomiting.

It has important drug interactions with other anti-convulsants. It inhibits the metabolism of the active metabolite of carbamazepine, prolonging the effects of this drug and delaying its excretion. Sodium valproate reduces the apparent clearance of lamotrigine, such that the latter's dosage for co-administration with valproate must be reduced to half the monotherapy dosage. Combining valproic acid with clonazepam can lead to profound sedation and increases the risk of absence seizures in patients susceptible to these. Valproic acid also decreases the clearance of tricyclic anti-depressants, amitriptyline and nortriptyline. Aspirin may decrease the clearance of valproic acid, leading to higher than intended levels of the anti-convulsant. The drug decreases the intestinal absorption of folate and should be avoided, if possible, in pregnancy because low serum folate levels are implicated in causing neural tube defects in the foetus.

### Lamotrigine

This anti-convulsant first received FDA approval in 1994 for the treatment of partial seizures. In 2003, lamotrigine got approval as maintenance treatment for the prevention of mood episodes in BD type I. However, its efficacy was primarily in the reduction of recurrent depressive episodes. It produced no outcome as an anti-manic agent and was ineffectual in the management of

rapid cycling. It was superior to conventional anti-depressants because it could treat BD without triggering mania, hypomania, mixed states, or rapid cycling. In a meta-analysis conducted in 2008, it was found that lamotrigine was less successful in treating severe acute depression with number needed to treat (NNT) being 7 as compared to less-severe bipolar depression where the NNT was 11.<sup>22</sup>

Lamotrigine is a broad-spectrum anti-epileptic. Its mechanism of action appears to be mediated by stabilisation of presynaptic voltage-gated sodium channels resulting in a decrease in glutamate release. Between 5-10% of patients taking lamotrigine will develop a skin rash, but only 1 in a thousand patients will develop a serious rash. Side-effects such as rash, fever and fatigue are grave, as these may indicate incipient Stevens-Johnson syndrome, toxic epidermal necrolysis, Drug Reaction or rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome or aseptic meningitis.<sup>23</sup> Rash and other skin reactions are more common in children, so this medication is often reserved for adults. There is also an increased incidence of these eruptions in patients who are currently on, or recently discontinued, a valproate-type anti-convulsant drug, as these medications interact in such a way that the clearance of both is decreased and the effective dose of lamotrigine is increased.

### Topiramate

This is a novel anti-convulsant and is used in the treatment of a wide variety of seizures in children and adults. It is used off-label in a range of neuropsychiatric conditions, including treatment-resistant mood disorders, eating disorders, substance use disorders, post-traumatic stress disorder and borderline personality disorder. The neurological conditions that show response to this drug are typical and atypical migraine, cluster headache, essential tremor, neuropathic pain, and idiopathic intracranial hypertension among others. Bipolar patients who suffer from persistent depressive, dysthymic, or dysphoric mixed phases pose a therapeutic challenge; one remedial option for such patients is a trial of topiramate.<sup>24</sup> This drug is a valid choice for bipolar patients who suffer from the above-mentioned psychiatric and neurological comorbidities.

This drug is often used to counter the weight-adding effect of psychotropic drugs, e.g., second-generation anti-psychotics. Individuals with mood disorders should be routinely screened for risk factors that increase peril for metabolic syndrome. For bipolar patients with excess weight, the best-studied pharmacologic approaches are metformin and topiramate. For binge eating disorder, the

greatest evidence is for topiramate and zonisamide; for glucose intolerance, dyslipidaemia, and hypertension data supports anti-diabetic, antilipidemic and anti-hypertensive treatments.<sup>25</sup>

### **Gabapentin**

Gabapentin, an analogue of the neurotransmitter GABA, was first approved by the FDA in 1994 for use as an adjunctive medication to control partial seizures. However, this drug found its most extensive application as an analgesic for the treatment of neuropathic pain. It is a ligand for the alpha 2 delta sub-unit of voltage-gated calcium channels and decreases glutamate neurotransmission by virtue of this binding. Gabapentin is used in the treatment of a number of neuropsychiatric disorders, but all such applications remain off-label. These include anxiety disorders, refractory major depressive disorder (MDD), bipolar disorder, insomnia, stimulant use disorders, alcohol detoxification, and opioid withdrawal. Neurological conditions for which gabapentin is utilised are migraine with and without aura, neuropathic pain of various aetiologies, complex regional pain syndrome, fibromyalgia, restless legs syndrome, nystagmus, and for the control of menopausal hot flashes. It is a convincing option for bipolar patients with comorbidities such as panic disorder, social phobic disorder, generalized anxiety disorder, post-traumatic stress disorder, and substance use disorders.<sup>26</sup> In addition, gabapentin is often used in refractory patients, in conjunction with other mood stabilisers.

The drug is excreted unchanged via the kidneys, without undergoing hepatic metabolism and lacks any interaction with other anti-epileptic or psychotropic medications. It has a favourable side-effect profile and is well tolerated by the patients. It lacks abuse potential and is safe in overdose. These properties make gabapentin an attractive choice in patients with hepatic, renal and other comorbid medical conditions.

Pregabalin is an analogue of gabapentin and is similar to its predecessor in all respects, with the exceptions that it is a much more potent drug and has twice as long half-life, so that it is administered 2 times per day as opposed to gabapentin which requires to be given 3 or 4 times in 24 hours. Gabapentin enacarbil extended-release is the latest gabapentinoid to receive FDA approval. As of 2011, this drug has been approved for the treatment of restless legs syndrome. It is a gabapentin prodrug which is efficiently and rapidly converted to gabapentin during active transport throughout the length of the intestine via high-capacity monocarboxylate type I nutrient transporters unlike its predecessor, which is absorbed via low capacity transporters largely confined to the upper

intestinal region.<sup>27</sup> Gabapentin enacarbil's lack of saturable absorption allows for dose-proportional absorption and increased bio-availability. In addition, there is sustained delivery over a 24-hour period by virtue of the extended-release formulation.

### **Atypical Antipsychotics**

#### **Risperidone**

This drug received FDA approval in 1993 for the treatment of schizophrenia. The anti-psychotic effect was attributed to strong blockade of dopamine receptors in the mesolimbic circuit, while antagonism of serotonergic receptors resulted in anti-anxiety effect. In 2003, risperidone was approved for the treatment of manic and mixed states associated with bipolar disorder. This drug, like other second-generation anti-psychotics (SGAs), has been used off-label for various neuropsychiatric conditions which include ADHD, generalised anxiety disorder (GAD), OCD, depressive disorders, eating disorders, insomnia, post-traumatic stress disorder (PTSD), personality disorders, substance use and dependence disorders. In the past few years, numerous studies have been published evaluating SGAs in such off-label uses. In 2011, the US Agency for Healthcare Research and Quality (AHRQ) published a systematic review which found that there was evidence for efficacy of risperidone in some anxiety disorders, and refractory unipolar and bipolar depression, but data did not support the use of SGAs in eating disorders, personality disorders, substance dependence and insomnia.<sup>28</sup> The use of risperidone was associated with a number of serious adverse effects, the most important being weight gain, dyslipidaemia, and abnormalities of glucose homeostasis - all components of the metabolic syndrome.<sup>29</sup>

#### **Olanzapine**

Olanzapine, an antipsychotic with predominantly dopamine D2 and serotonin 5HT2A receptor blockade, is used as an anti-schizophrenic medication. The drug is also effective in treating acute manic and mixed episodes associated with BD type I, and has FDA approval for both indications. However, BD is a chronic, progressive disease that presents severe challenges for long-term treatment because each episode seems to increase the risk for another episode, and subsequent episodes appear to be increasingly treatment-resistant. Pharmacological treatment options are limited, and mounting evidence suggests that exposure to anti-depressants increases long-term mood instability in patients with bipolar disorders.<sup>30</sup> Considering these challenges, novel treatment options are needed, and are being investigated. A limited number of clinical trials have explored the use of SGAs to treat

depression in BD and these agents have been found to have varying efficacy in this regard with insignificant risk of causing switch into manic, mixed or hypomanic phases. Olanzapine in combination with fluoxetine received FDA approval in 2003 for the treatment of depressive episodes associated with BD. In 2004, olanzapine got approval for the long-term treatment of bipolar I disorder and, most recently, in 2009, olanzapine in combination with fluoxetine received FDA endorsement for the management of resistant depression. The drug is used off-label for anxiety-spectrum disorders, anorexia nervosa, and substance dependence.

The expansion of olanzapine's use in psychiatry is in parallel with an increase in the number of patients receiving this drug, and many are given treatment for a long duration of time. Therapy with this medication has a number of tolerability and safety issues such as metabolic adverse effects, extrapyramidal symptoms and undesirable sedative effects. Metabolic concerns such as weight gain, increase in blood glucose, triglycerides and total cholesterol levels lead to long-term consequences, which include cardiovascular disease and type 2 diabetes mellitus, and these complications cause high rates of morbidity and mortality among patients with severe mental illness.<sup>31</sup>

### Quetiapine

This SGA is used in the treatment of schizophrenia, BD and major depressive disorder. In BD, the drug is approved for the treatment of acute manic episode, bipolar depression, and for maintenance in conjunction with lithium and divalproex sodium. Quetiapine is an antagonist at dopamine D<sub>2</sub>, serotonin 5HT<sub>2A</sub>, 5HT<sub>2C</sub>, 5HT<sub>1A</sub> and histamine H<sub>1</sub> receptors.<sup>32</sup> Due to this broad range of effect, it has a marked anti-anxiety action, and is often used for the treatment of insomnia. It is not a controlled substance, and is considered to lack abuse potential by the regulating authorities.

In 2006 an extended release (XR) version of the drug was launched which has similar bioavailability but prolonged plasma levels compared with the immediate release (IR) formulation, allowing for less-frequent once-daily dosing. Clinical studies have confirmed the efficacy of quetiapine XR in relieving the acute symptoms of schizophrenia during short-term trials, and reducing the risk for relapse in long-term studies. Direct switching from the IR formulation to the same dose of the XR formulation is not associated with loss of efficacy or tolerability issues, and switching patients to quetiapine XR from conventional or other atypical anti-psychotics for reasons of insufficient efficacy or tolerability also proved to be beneficial and

generally well tolerated. In bipolar patients, quetiapine XR has also proven effective in relieving acute manic and depressive symptoms.<sup>33</sup> Adverse events with quetiapine XR in patients with either schizophrenia or bipolar disorder are similar to those associated with the IR formulation, the most common being sedation, dry mouth, somnolence, dizziness, and headache. The low propensity for extrapyramidal side effects is maintained with the XR formulation. Overall, evidence from clinical trials suggests that quetiapine XR is an effective and generally well tolerated treatment option in patients with schizophrenia and BD.<sup>34</sup>

### Ziprasidone

This SGA has a unique efficacy profile. It binds to dopamine D<sub>2</sub> receptors with less affinity than haloperidol and acts as an antagonist at a number of serotonin receptors, including 5HT<sub>2A</sub>, 5HT<sub>2C</sub>, 5HT<sub>1A</sub>, and 5HT<sub>1B</sub>/5HT<sub>1D</sub> receptors. Additionally, ziprasidone works as a transport re-uptake inhibitor for serotonin and noradrenaline. These properties confer ziprasidone with anti-psychotic activity, as well as antianxiety effects. The drug is licensed for the treatment of schizophrenia and manic and mixed episodes associated with BD type I. It is used off-label for bipolar depression, major depressive disorder, bipolar maintenance, OCD, and PTSD. It exhibits low levels of hyperprolactinaemia and weight gain/metabolic adverse events, and is a treatment option for obese bipolar patients and those who develop the metabolic syndrome with other SGAs.<sup>35</sup> Ziprasidone is associated with moderate extrapyramidal effects and causes slight prolongation of corrected QT interval. Its absorption is optimally achieved when administered with food. Without a meal preceding dose, the bioavailability of the drug is reduced by approximately 50%. Ziprasidone is hepatically metabolised by aldehyde oxidase; minor metabolism occurs via cytochrome P450 3A4. It has no significant interactions with other psychotropic drugs. Emerging evidence indicates that in patients with BD, ziprasidone provides valid efficacy and remarkable safety when administered alone for the treatment of manic and mixed episodes. The same applies when ziprasidone is administered in combination with lithium or valproate for the prevention of affective recurrences and relapses.<sup>36</sup>

### Aripiprazole

It is an atypical anti-psychotic licensed for the treatment of schizophrenia, manic and mixed episodes associated with BD and as an adjunct therapy for major depressive disorder. It functions as a partial agonist at dopamine D<sub>2</sub> and 5-HT<sub>1A</sub> receptors, and as an antagonist at 5-HT<sub>2A</sub> receptor. Aripiprazole use is accompanied with less extrapyramidal side effects and hyperprolactinaemia

compared to other SGAs, presumably because of partial D2 agonism. The most recent results obtained from scientific research show that dopaminergic mechanisms are involved in motivation, reward and reinforcement of substance abuse - a disorder frequently comorbid with BD. The use of aripiprazole as a partial dopamine agonist could represent a novel strategy for normalising dopamine neurotransmission in disorders such as alcoholism, stimulant and nicotine use.<sup>37</sup> In addition, aripiprazole shows less metabolic adverse effects compared to other atypical anti-psychotics and is an appealing option in adolescent BD as young people are much more concerned about physical appearance and body image which is apt to be negatively affected with weight-adding drugs. It has a long elimination half-life of 75 hours and steady state plasma levels are achieved in about 14 days. Aripiprazole appears to be a promising agent for the maintenance treatment of BD as adjunctive treatment with established mood stabilisers like lithium, valproate, carbamazepine and lamotrigine.<sup>38</sup> Women with BD present a particular management challenge. Although no methodical studies have been carried out in pregnancy and lactation, existing evidence suggests that second-generation anti-psychotics can be considered in women with severe exacerbations of mood disorders.

## Conclusion

With an increase in the understanding of different aspects of bipolar affective disorder, there have been significant advances in the management of the depressive episodes. Evidence from a number of studies shows that anti-depressant monotherapy is mood destabilising and can induce mixed manic and hypomanic episodes and rapid cycling. As such, if anti-depressants are used in the management of bipolar depression, then this strategy should be employed in conjunction with mood stabilizers, and the latter agents are the mainstay in the treatment of this condition. There has been a steady increase in the use of anti-convulsants in the treatment of bipolar depression. The availability of anti-epileptics with novel mechanisms of action, better pharmacokinetic profiles and fewer drug interactions are some of the factors promoting the use of these agents in bipolar depression. The therapeutic role of second-generation anti-psychotics is well-established in the management of bipolar depression. Modern psychopharmacological options are safer and better tolerated, but no single drug has been shown to successfully treat all manifestations of depressive symptoms in bipolar affective disorder. As such, these agents are most often used in combination to achieve better outcomes. As newer drugs are added to the armamentarium, it is hoped that patients suffering

from this chronic and difficult-to-treat condition will get better relief and the burden that bipolar depression places on the sufferers and their families will diminish.

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