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DRUG BULLETIN

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Is There Evidence for New Anticonvulsants as Mood Stabilisers?

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- Since the introduction of lithium for the treatment of mania in the 1950's, it has remained the "gold-standard" for bipolar disorder management.
- The recognition of certain anticonvulsants' efficacy as mood stabilisers has led to greater treatment options for bipolar disorder patients and the introduction of newer anticonvulsants has seen this treatment option group expand.
- Unfortunately, very few randomised controlled trials are available to determine the effectiveness of newer anticonvulsants as mood stabilisers.
- Further research involving anticonvulsants, and other medications such as atypical antipsychotics, is currently required to clarify their place in the management of bipolar disorder.

Bipolar Disorder

Bipolar disorder is an illness that is characterized by a dysregulation of mood. It has been thought that the prevalence for bipolar disorder, usually quoted as approximately 1-2%[1,2], may actually be up to 4% of the population[3]. When looking at bipolar spectrum disorders, it may rise even further to a lifetime prevalence of up to 6.5%[3].

Current treatment strategies for bipolar disorder aim to control acute episodes of mania or depression and to prevent relapse. Due to the challenging nature of the illness, alternative treatment options are being sought and often a combination of medications is required to achieve maximum response.

Traditional Treatment Options for Bipolar Disorder

Lithium

The main use of lithium is in the treatment of acute mania and prophylaxis of bipolar disorder relapses, however it also has indications in other psychiatric conditions such as treatment-resistant depression, schizoaffective disorder and schizophrenia. Meta-analyses of lithium randomised controlled trials (RCTs) confirm its value in the management of acute episodes of mania and for preventing relapse[2,4].

One review (search date 2003) identified no RCTs of sufficient quality to assess lithium in people with bipolar depression[4]. An international consensus group however, concluded that despite the methodological limitations, the research supported the efficacy of lithium over placebo in bipolar depression[5].

Valproate

There is evidence that valproate is more effective than placebo in treating mania, however its role in treating bipolar depression is unclear[2]. There is only one double-blind trial looking at valproate's effectiveness in prophylaxis, where there was no difference in time to first relapse in patients on valproate, lithium or placebo[6]. Open studies however indicate prophylactic anti-manic and anti-mixed, but not antidepressant activity[2].

The only form of valproate available in Australia is sodium valproate. Overseas, it is available in three forms, sodium valproate, valproic acid and semisodium valproate (also known as divalproex sodium or divalproex semisodium). No trial directly compares the efficacy of sodium valproate to semisodium valproate in the treatment of bipolar disorder[7]. It should be noted however that semisodium and sodium valproate are both metabolised to valproic acid, which is thought to have the pharmacological activity[7,8].

Carbamazepine

Despite common use of carbamazepine in the treatment of bipolar disorder, quality randomised controlled studies comparing carbamazepine to placebo are rare[2,4,8]. It appears as efficacious as lithium in acute mania and prophylaxis[2,4,8] and may have a role in treatment of rapid-cycling patients, although studies are lacking[1,2,8].

Newer Anticonvulsants in the Treatment of Bipolar Disorder

Lamotrigine

The use of lamotrigine for bipolar disorder has increased dramatically in recent years. It is the most widely investigated anticonvulsant for the treatment of bipolar disorder and recently gained approval in the US for maintenance treatment[9]. At this stage no specific brand of lamotrigine has an indication for bipolar disorder in Australia.

From clinical trials, lamotrigine appears to be well tolerated, with the exception of the risk of rash. As rashes with lamotrigine can be potentially life-threatening, careful monitoring is essential. Lamotrigine's low incidence of weight gain[10] may offer an advantage in current clinical practice.

Mania
There are no RCTs comparing lamotrigine to placebo in the treatment of bipolar mania though two small studies show lamotrigine was as effective as lithium in acute mania[11,12]. A review however, found the results of 3 double-blind studies did not support the use of lamotrigine in mania[9].

Depression
Initial open trials, chart reviews and augmentation studies in bipolar depression indicated that lamotrigine had good response rates, which one review found ranged from 55% to 72%[13]. A large placebo controlled study in 195 patients with bipolar depression found response in 51% of patients on lamotrigine 200mg/d, 41% of patients on lamotrigine 50mg/d and 26% of patients receiving placebo[14].

Prophylaxis
Three large RCTs found lamotrigine superior to placebo for the prevention of mood episodes in bipolar I patients[15,16,17]. Secondary analysis of two of the trials suggested that lamotrigine was effective against depressive episodes but not manic relapse[15,16].

Rapid cycling
A RCT found 41% of rapid-cycling patients receiving lamotrigine were stable without relapse after 6 months, compared with 26% of patients on placebo[18]. A smaller RCT found lamotrigine superior to gabapentin and placebo in treatment-refractory (mainly rapid-cycling) bipolar patients[19].

Gabapentin

At this stage, gabapentin is not considered to be a significant option for the management of bipolar disorder by the Royal Australian and New Zealand College of Psychiatrists[2] nor is it currently listed as a treatment option in the Therapeutic Guidelines – Psychotropic[1].

Gabapentin has no known clinically significant pharmacokinetic interactions and appears to be safe to use in combination with other agents[9]. It is generally well tolerated, however some patients may experience difficulties with sedation, dizziness or weight gain.

Mania
Although a number of open trials found some efficacy of gabapentin in bipolar mania[20], two RCTs failed to support this finding[19,21].

Depression
A review found a reduction in depressive symptoms among bipolar patients in five open

clinical trials[13], however no RCTs were found that examined gabapentin's efficacy in the treatment of bipolar depression.

Prophylaxis and Rapid Cycling
There is no evidence to suggest gabapentin is of benefit in the maintenance treatment of non-rapid or rapid cycling bipolar disorder.

Topiramate

Topiramate is not currently included in treatment options for bipolar disorder as recommended by the Royal Australian and New Zealand College of Psychiatrists[2] or the Therapeutic Guidelines – Psychotropic[1].

Topiramate has been associated with sedation and paresthesias and is more often associated with weight loss than weight gain[22]. Psychiatric adverse effects, including psychosis, have also been reported, although infrequently[23].

Mania
A number of open trials had encouraging results for topiramate's use in the treatment of mania[24], although this has not been demonstrated successfully in RCTs.

A 3-week RCT, as reported in a review by Chengappa et al[23], initially did not find significant differences with topiramate compared to placebo. Only after reanalysis of the data, excluding patients who had previously been on antidepressant medication, did topiramate have significant benefits compared to placebo. Another review noted that four subsequent large unpublished RCTs failed to demonstrate efficacy of topiramate compared to placebo[24].

Depression
There is very limited information regarding topiramate's use in bipolar depression. There is one small RCT (single-blind, only rater blinded) where topiramate (N=18) was compared to bupropion (N=18) in patients in the depressive phase of bipolar disorder[25]. Patients in both groups showed comparable significant improvement from baseline.

Prophylaxis and Rapid Cycling
Despite encouraging results from a small open-label study (N=27) in women with rapid cycling bipolar disorder[26], there are no RCTs to date to confirm topiramate's efficacy in this population. Similarly, there is no sufficient evidence at this stage to suggest benefit in the maintenance phase of bipolar disorder.

Emerging Anticonvulsant Treatment Options for Bipolar Disorder

Oxcarbazepine

Oxcarbazepine is a derivative of carbamazepine and is indicated for the management of partial and generalised tonic-clonic seizures. It appears to have a more favourable adverse effect and drug interaction profile than carbamazepine and has not been associated with blood dyscrasias[22].

Due to its improved safety and interaction profile, it has been a proposed alternative for acute mania and maintenance treatment in bipolar disorder[27]. A RCT found oxcarbazepine had similar efficacy to lithium in acute mania, although small sample sizes (N=52) in the study limited the statistical power to detect differences[28].

A review outlines four other small trials[9] with encouraging results and a further open trial, chart review and case series located in the literature also had positive findings[29-31].

Although preliminary data is encouraging, further evidence is required to determine the efficacy and safety of oxcarbazepine in the treatment of bipolar disorders.

Levetiracetam

Levetiracetam, a novel anti-convulsant medication is generally well tolerated with sedation being the most commonly reported adverse effect[32].

To date, there are no RCTs examining levetiracetam's efficacy in bipolar disorder. Two small open trial results suggested antimanic effects[33,34] and three case series report improvement in a total of four patients (three of which had rapid-cycling symptoms)[35-37]. Another small open trial however, did not find a consistent pattern of improvement in patients with refractory bipolar disorder with add-on levetiracetam therapy[38].

Phenytoin

Although phenytoin has been in use as an anticonvulsant for decades, very limited research

is available examining its effectiveness in mood-stabilisation.

Only two small controlled studies were found, both with positive results[39,40]. The first study found patients on a combination of haloperidol and phenytoin (N=15) had greater improvement in manic symptoms compared to those receiving haloperidol and placebo over three to five weeks (N=15)[39]. The second study (total N=23) found phenytoin had greater prophylactic effects than placebo, when added to their existing drug therapy[40].

Atypical Antipsychotics in the Treatment of Bipolar Disorder

For years typical antipsychotics have been used in mania and the longer-term treatment of bipolar disorder, however at present, the use of atypical antipsychotics is increasing.

At this stage, in Australia, olanzapine, risperidone and quetiapine are the only atypical antipsychotics to have an indication in bipolar disorder. Olanzapine has an indication for the short-term treatment of manic episodes and also for prophylaxis, whereas risperidone and quetiapine only have indications for the short-term treatment of manic episodes. Only olanzapine is currently subsidised on the Pharmaceutical Benefits Scheme for bipolar indications.

Limitations to this bulletin unfortunately do not allow for a review of the available evidence in this area, however further research on the use of these and other antipsychotics in the management of bipolar disorder is continuing.

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