Antiepileptic drugs in the treatment of Bipolar Disorder

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Introduction

Antiepileptic drugs (AEDs) were first shown to be effective in mania nearly 40 years ago (1973 carbamazepine; 1975 valproate) (1;2). The discovery that carbamazepine and valproate are effective for mania encouraged interest in other antiepileptic agents as potential treatments. Although the exact mechanism of action of the AEDs in Bipolar Affective Disorder (BPD) is not fully understood, these drugs have provided a successful means of treating and managing a very complex illness. This review aims to summarise the effect of five of the most commonly used AEDs for acute mania, bipolar depression, prophylaxis of BPD, and rapid cycling BPD.

Valproate

Acute mania

Valproate has been fairly widely studied in the treatment of mania both as a single agent (3;4) and as an adjunct to lithium (5) or antipsychotic drugs (6). A selection of the randomised controlled trials (RCTs) of valproate in the acute treatment of mania were included in a recently published multiple treatment meta-analysis by Ciprani (7). This meta-analysis places valproate at 9th position out of 14 possible interventions for the treatment of acute mania when considering both efficacy and tolerability together (7). Valproate was found to be more effective than lamotrigine (10th), placebo (11th), topiramate (12th), and gabapentin (13th). Antipsychotics, lithium, and carbamazepine, however, were all considered more effective than valproate (7).

Bipolar Depression

Two meta-analyses containing 4 RCTs concluded that valproate is effective for the treatment of acute bipolar depression (8;9). The first meta-analysis reported a number needed to treat (NNT) of 5

(8) (response), while the second reported a NNT of 7 (9) (remission). These meta-analyses should be interpreted with caution because there were only 142 participants when all RCTs were combined. Larger trials are therefore needed to assess the true clinical effectiveness of valproate for the acute treatment of bipolar depression. Although there is evidence which supports the use of valproate for the treatment of bipolar depression, it is probably not a first-line agent. The Maudsley Prescribing Guidelines recommend using quetiapine as a first-line agent and valproate or lithium as a second-line agent (10).

Prophylaxis

Valproate is effective in the prophylaxis of BPD, but may be less effective than other treatments (5;11). Lithium monotherapy was compared with valproate monotherapy and combination treatment of valproate and lithium in a non-randomised cohort study. There was no statistical difference between combination treatment and lithium monotherapy. However, both were significantly better than valproate monotherapy for preventing an affective relapse (11). This confirmed a previous finding in the BALANCE study, which was conducted over 2 years and also showed that lithium monotherapy was equivalent to combination therapy and that both were superior to valproate monotherapy at preventing any mood episode (5). In contrast to these studies, a 47 week RCT comparing olanzapine with valproate found no difference in relapse rates between the two treatment arms (12). Valproate is therefore a suitable prophylactic agent for patients intolerant to or unwilling to use lithium, which is still considered the gold standard (5;11).

Rapid cycling

Combination therapy (13) with lithium and valproate is the first-line treatment choice for rapid cycling BPD (10;14). Despite no available trials that prove combination superiority, this has become the accepted standard in the treatment of this condition. In a 6-month double-blind maintenance study in patients with rapid cycling BPD and co-occurring substance abuse or dependence, there was no significant difference in time to relapse for any mood episode between lithium monotherapy or combination lithium and valproate therapy (15). Studies of monotherapy in rapid cycling BPD also show no difference in efficacy. In a 20-month maintenance trial of lithium versus valproate monotherapy (following previous acute mood stabilisation with lithium and valproate combination therapy) neither monotherapy agent differed in time to additional treatment for a mood episode (16). Patients with rapid cycling BPD usually spend more time in the depressive rather than manic phase (10). A 12-month open-label trial comparing valproate with quetiapine monotherapy found no significant difference in effectiveness (measured by study discontinuation) (17). There were some minor differences in outcomes for those on quetiapine. These patients showed fewer days with moderate to severe depressive symptoms (17). No difference was observed, however, between the treatments for mania (17). Rapid cycling patients have a worse prognosis for response to treatment compared with non-rapid cycling patients (18). The recommendation for combination treatment is based on expert opinion (10;13;14).

Lamotrigine

Acute mania

There are 3 RCTs of lamotrigine in Cipriani's meta-analysis on the treatment of acute mania which all showed negative results (7). Lamotrigine was ranked behind placebo in 12th position for efficacy and tolerability (7). The slow titration requirements for lamotrigine render this treatment option inappropriate for the treatment of acute mania. It takes at least 6 weeks (19) to reach a suitable dose, during which time other treatments would have been more successfully started.

Bipolar Depression

There are 5 company-sponsored RCTs of lamotrigine which were included in a meta-analyses (20). Lamotrigine was significantly better than placebo for response to treatment as assessed by the Hamilton Rating Scale for Depression (HRSD) (21) and Montgomery-Asberg Depression Rating Scale (MADRS) (22) with NNT's of 11 and 13 respectively depending on which assessment tool was used (20). There was no difference for response between BPD I or II patients for the acute treatment of bipolar depression. In a different meta-analysis, olanzapine and fluoxetine combination therapy was significantly better than lamotrigine monotherapy at treating acute bipolar depression (23). Predictably, time to 50% reduction in MADRS was significantly shorter for the combination group compared with lamotrigine monotherapy (23), most likely attributable again to the slow titration regimen required for lamotrigine. The Maudsley Prescribing Guidelines recommend lamotrigine as a 3rd line choice for the treatment of acute bipolar depression behind quetiapine, or valproate/lithium respectively (10).

Prophylaxis

There are 2 RCTs comparing lamotrigine, lithium, and placebo maintenance treatment over an 18 month period in BPD I patients (24;25). One study included recently depressed patients, while the other included recently manic patients. The results from both studies were consistent. Both lamotrigine and lithium monotherapy are significantly better at preventing any mood episode compared with placebo. When manic and depressive episodes were separated and analysed separately, lamotrigine but not lithium was significantly better than placebo at preventing a depressive episode, but not a manic episode. Conversely, lithium but not lamotrigine was significantly better than placebo at preventing a manic episode but not a depressive episode.

Rapid cycling

There are 2 RCTs investigating maintenance treatment with lamotrigine for rapid cycling BPD. Only one study is published (26). There was no significant difference compared with placebo for time to additional pharmacotherapy and subsequent study discontinuation (26). All-cause study discontinuation, however, was significantly greater for lamotrigine with a median time of 14 weeks compared with 8 weeks for placebo (26). In addition, there was a significant difference between BPD I and II subgroups favouring a longer survival rate for BPD II patients receiving lamotrigine compared with placebo (26). Overall this study suggests that lamotrigine is a useful treatment for rapid cycling BPD II patients for preventing a relapse. In contrast to this, an unpublished study failed to find a significant difference in BPD II patients (27) which highlights the need for further research in this area.

Carbamazepine

Acute mania

Carbamazepine is probably the most effective antiepileptic for the treatment of acute mania. RCTs with placebo and carbamazepine arms have shown that carbamazepine is superior. For example, the results of a 21 day RCT with 204 BPD I patients concluded carbamazepine is more effective than placebo, with significant decreases in Young Mania Rating Scale (YMRS) (28) at days 14 and 21 (29). Similarly in a 21 day RCT with 239 BPD I patients, carbamazepine was more effective than placebo, with significant decreases in YMRS as early as day 7 (30). Both of these RCTs showed response rates for carbamazepine were twice that of the placebo arms (10). There is no statistical difference between combination treatment of olanzapine and carbamazepine compared with carbamazepine monotherapy (31). RCTs comparing carbamazepine with lithium show no statistical difference between the treatment arms (32;33). It is therefore not surprising that Ciprani's meta-analyses (7), placed carbamazepine 5th, falling just behind the main antipsychotics and ahead of all other antiepileptic agents and lithium (7). The troublesome drug interactions that carbamazepine pose make it unpopular amongst clinicians, despite its efficacy for the treatment of acute mania.

Bipolar Depression

Carbamazepine would not be a first-line treatment choice for the treatment of bipolar depression; other agents have a stronger evidence base (10). One of the largest open-label studies of carbamazepine in bipolar depression, which included 27 patients, showed that carbamazepine provided remission rates of 63% (34). Larger RCTs are required to assess the true effect of carbamazepine in bipolar depression and at present another agent, such as quetiapine, would be considered as the first-line choice (10).

Prophylaxis

Carbamazepine is generally considered an effective prophylactic agent in BPD. A meta-analysis which compared 4 RCTs to assess the effect of carbamazepine or lithium on the prophylaxis of BPD failed to show any significant difference between treatment groups both individually and from the meta-analysis (35). One RCT concluded that lithium was more effective for BPD II patients than for BPD I patients when the subgroups were separated (36). A different RCT suggested the opposite (35;37). Despite similar efficacy, lithium is considered superior to carbamazepine in reducing suicidal behaviour (10;38). Further to this, carbamazepine is also less well tolerated than lithium with numbers need to harm (NNH) of 13 (35).

Rapid cycling

Carbamazepine is not routinely recommended as a first-line treatment choice for rapid cycling BPD. The evidence base for its use is limited. One small open trial of carbamazepine suggested that it might be of use for some, but different treatments are generally required for the management of most rapid cycling patients (39). Data from a small 5-year retrospective chart and notes review failed to find any differences in outcome between lithium monotherapy and combination lithium and carbamazepine therapy (40). The data did suggest that improvement was noticed earlier with the combination group (40). As lithium and valproate combination therapy is widely accepted as the treatment of choice for rapid cycling BPD (10;14), carbamazepine might be worth considering for patients who are intolerant or nonresponsive to valproate and not receiving full therapeutic benefit from lithium monotherapy. Lamotrigine might also be considered but it does not protect against mania.

Gabapentin

Despite there being no RCTs for gabapentin in BPD, sales for gabapentin (Neurontin) increased rapidly during the late 1990's. Although not licensed, the second most common use for gabapentin was for mental health indications (41). Multiple articles including case reports and reviews encouraged the prescribing of gabapentin until negative RCTs were eventually published in 2000 (41). The first negative trial was a placebo-controlled trial of adjunctive gabapentin to existing lithium or valproate therapy for the management of mania, hypomania, or mixed states (42). Significant differences in YMRS change scores favoured the placebo arm showing that gabapentin was inferior. A second negative RCT compared gabapentin, lamotrigine and placebo in refractory mood disorders. Lamotrigine was found to be superior to gabapentin and placebo as assessed by the Clinical Global Impression scale (43) that was modified for bipolar illness (44). Following these 2 negative findings the rapid growth in gabapentin prescribing ceased and prescriptions eventually reduced (45). Two further RCTs were published in 2002 and 2006 (46;47) which again found negative results. Gabapentin was recently found to be the least effective drug in Cipriani's meta-analysis on the treatment of acute mania (7).

Topiramate

Topiramate is not effective for the treatment of acute mania (7;13;14), and is not recommended by the National Institute of Clinical Excellence (NICE) (14). There are no monotherapy RCTs that assess the efficacy of topiramate for the treatment of bipolar depression. A randomised, single-blinded study

offered weak evidence that topiramate is as effective as bupropion as an adjunct to either lithium or valproate for the treatment of bipolar depression (48). This finding has not been confirmed in a robust RCT and therefore topiramate is not recommended for bipolar depression. The prophylactic effect of adjunctive topiramate to risperidone treatment has been suggested in a long term (1 year) open, prospective observational study (49). However, prophylactic efficacy has not been confirmed in a RCT and is therefore not recommended. Topiramate has not been studied for the treatment of rapid cycling BPD and its use in this condition is therefore more experimental than evidence based.

Discussion

Although valproate is the only AED that holds a licence (50) for the use in mania, there is sufficient evidence to support the use of other AEDs. Nonetheless, acute mania is treated most efficiently with antipsychotics. When considering the AEDs, carbamazepine is perhaps the most effective, but valproate would be the first-line treatment choice because it is easier to use. Similarly with bipolar depression, antipsychotic treatment (quetiapine) would be the preferred option, followed by lithium (10). Valproate or lamotrigine would be the most suitable AED to use if quetiapine or lithium were ineffective or poorly tolerated. More than 60 years since the first report of the use of lithium in BPD (51) it remains the gold standard treatment for prophylaxis (5), but in its absence valproate would be the next best choice from the AEDs. Rapid cycling BPD is difficult to treat; 30 – 40% of cases are preceded by antidepressant exposure and worsened by treatment with antidepressants (13). NICE guidance for rapid cycling BPD is for first-line use of lithium and valproate combination treatment (14). The British Association for Psychopharmacology also recommends combination therapy (13). Valproate is the AED of choice in combination with lithium, but lamotrigine and carbamazepine also have evidence worth considering if the combination of valproate and lithium fail or are inappropriate. The role of gabapentin or topiramate in the treatment or management of BPD is limited by poor supporting data and discouraging clinical observations.

Table 1: Suggested sequence for BPD

	1st choice AED	Others with efficacy	No effect
Acute mania	Valproate	Carbamazepine	Lamotrigine, Gabapentin, Topiramate
Bipolar depression	Valproate, Lamotrigine	Carbamazepine, Topiramate?	Gabapentin
Prophylaxis	Valproate, Carbamazepine	Lamotrigine	Gabapentin, Topiramate
Rapid cycling	Valproate or carbamazepine with lithium	Lamotrigine	Gabapentin, Topiramate

GP Comment

What have I learned from this paper?

This is a very useful paper, giving clear guidance on the role of antiepileptic drugs in the treatment of bipolar disorder in its various manifestations.
As GPs we are rarely involved in the initiation of treatment for bipolar disorder with antiepileptic drugs, although of course it is helpful that we understand their use and monitoring when prescribing repeats or when we are asked about side effects.

Some antiepileptic drugs have a role both in the treatment and prophylaxis of bipolar disorder, although, generally speaking, antipsychotic drugs such as quetiapine are probably better for acute treatment and lithium remains the gold standard for prophylaxis.
Of the antiepileptic drugs, valproate is clearly the first choice for mania, although it would seem that lamotrigine might be of considerable value for treating the depressed phases of bipolar disorder. Both valproate and carbamazepine seem to have a role in prophylaxis, although lamotrigine might again be of value in preventing the depressed phases. There seems to be no good evidence for the use of gabapentin and topiramate in the treatment of bipolar disorder and these drugs should probably be avoided.
For me the most important section was in the summary where it reminded us that in BPD, particularly in rapid cycling BPD, the use of antidepressants (as opposed to antiepileptic or antipsychotic drugs) can make the situation worse. This is particularly important for GPs as this is often our fault because we prescribe before we may even have considered a diagnosis of BPD.

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