Pharmacological management of bipolar disorder:a review

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Background
Bipolar disorder is a chronic recurrent neuropsychiatric disorder. The management of the different phases of the illness requires different combinations of medicines and other treatment strategies.

Aims
To synthesize the current evidence for management of bipolar disorder.

Methods
We searched the MEDLINE, Cochrane database of systematic reviews and the Database of Abstracts of Reviews of Effects (DARE) for recent systematic reviews and meta-analysis between 1995 and 2010. Original articles of relevant randomised controlled trials (RCT) were accessed.

Results and conclusions
For treatment of acute mania lithium, valproate and carbamazepine are more effective than placebo but they have no superiority over antipsychotics.

There is evidence from RCTs that second generation antipsychotics (SGA) are more effective than placebo. Haloperidol may be more effective than SGA in treatment of acute mania. Combination of antipsychotic and mood stabiliser is more effective than mood stabiliser monotherapy alone.

In treatment of acute bipolar depression the current evidence is inadequate to support the use of lithium as monotherapy. The most effective treatment is combination of a mood stabiliser and an antidepressant which also minimises manic switches. FDA has approved olanzapine-fluoxetine combination and quetiapine monotherapy. Lamotrigine is also effective in the treatment of acute bipolar depression.

For prophylaxis lithium, valproate and carbamazepine are effective while lamotrigine is primarily effective in preventing depressive episodes. Lithium is more effective in preventing manic than depressive episodes. Evidence for efficacy of antipsychotics in prophylaxis is limited.

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Introduction

The current nosological concept of bipolar disorder could be traced back to works of Falret in the 19th century and of Kraeplin in the early 20th century (1). Over a hundred years later, it is still considered to be a serious mental illness associated with significant morbidity and mortality. Bipolar disorder is a chronic recurrent neuropsychiatric disorder. The management of the different phases of the illness requires different combinations of medicines and other treatment strategies. It is perhaps the most difficult psychiatric disorder to treat but one where outcome can depend significantly on the treatment skills of the clinician. However, unfortunately, the evidence base regarding treatment is less than satisfactory. There is little consensus about the management of bipolar disorder. This review attempts to evaluate the current evidence regarding the pharmacological management of bipolar disorder.

Methods

We searched the MEDLINE, Cochrane database of systematic reviews and the Database of Abstracts of Reviews of Effects (DARE) for systematic reviews and meta-analyses on management of bipolar disorder between 1995 and 2010. We also accessed original articles of relevant randomised controlled trials (RCT). This review is based on evidence provided, mostly, by RCTs and the synthesis of data from such trials in meta-analyses and systematic reviews.

Results

TREATMENT OF ACUTE MANIA

Mania and hypomania are the unique and characteristic clinical conditions that distinguish bipolar disorder from all other recurrent mood disorders. Because of the risks associated with overactivity, agitation, disinhibition and impaired judgement mania is considered a psychiatric emergency. Therefore treatment must aim at rapid control of symptoms and a quick resolution of the manic phase which also minimises the social impact of the disease.

Lithium, anticonvulsants and antipsychotics are used in treatment of mania while benzodiazepines are considered an important adjunct treatment. We will consider the evidence for the effectiveness of each type of medication. For mania a 50% reduction in symptoms on the Young Mania Rating Scale (YMRS) is reported as a clinical response in most RCTs.

Lithium

John Cade first described the efficacy of lithium in treating mania. So far, a total of 29 published or

presented studies have evaluated the acute antimanic efficacy of lithium (2). Bowden et al compared lithium against placebo in two randomised placebo-controlled studies and showed that the response rate was around 49% for lithium and 25% for placebo (3,4). Four recent studies where lithium was used as the comparator drug found lithium to be superior to placebo. These studies however have not been published (2). Lithium has been compared with chlorpromazine or haloperidol in 11 studies, olanzapine in one study, risperidone in one study and carbamazepine in five studies (2,5,6). One systematic review found that lithium increased the proportion of people who had a remission of manic symptoms at three weeks compared with chlorpromazine. There was no significant difference in symptoms at three to six weeks in patients treated with lithium compared with those treated with haloperidol, olanzapine, valproate, or clonazepam. Lithium was less effective than risperidone in reducing manic symptoms at four weeks (7). A Cochrane review of three RCTs comparing lithium and valproate found no significant difference in clinical response between valproate and lithium (8).

Anticonvulsants

Efficacy of valproate over placebo was reported for the first time in 1991(9). A Cochrane review of valproate for acute mood episodes in bipolar disorder reports 10 RCTs comparing valproate with other interventions (8). Three trials comparing valproate with placebo found valproate to be more efficacious. Three trials comparing valproate and lithium found no significant difference. Favourable response to valproate was associated with high pre-treatment depression scores, suggesting that treatment with valproate alone may be particularly effective in manic patients with mixed affective states (1). Valproate has a more rapid onset of action, compared to lithium, as valproate's wide therapeutic window allows loading treatment strategies (9). One RCT found no difference between valproate and carbamazepine. Two RCTs found valproate was less effective than olanzapine (8). Non-placebo controlled studies have shown that valproate is equal in efficacy to haloperidol (1).

Valproate has been recommended as the preferred choice in patients with numerous (>8) episodes in history or in patients with more than four depressive episodes (9). It is also reported that valproate is effective in treating rapid cycling manic patients (1).

Immediate release carbamazepine is effective in acute mania (10). Two large, three week, double-blind, placebo-controlled, randomised trials found extended release carbamazepine monotherapy was more effective than placebo in treatment of acute mania in patients with bipolar 1 disorder (11). Two RCTs found carbamazepine to be as effective as lithium (12,13).

Several RCTs of other anticonvulsants namely lamotrigine, topiramate and gabapentin for treatment of acute mania have not been found to be superior to placebo (10).

Antipsychotics

A meta-analysis of second generation antipsychotics (SGA) for treatment of acute mania reports on 24 RCTs (14). Twelve trials compared the effects of aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone vs. placebo in the treatment of acute mania. All second generation antipsychotics were significantly superior to placebo in treating acute manic symptoms (14). The number of RCTs that show superiority of individual SGAs over placebo are two for olanzapine, three for risperidone, two for quetiapine, two for ziprasidone and three for aripiprazole (9,14-16).

Few studies have compared efficacy of SGAs with other medication. One RCT has shown that quetiapine up to 800 mg/day was superior to placebo (53.3% vs. 27.4%) but inferior to lithium. In another trial, haloperidol doses up to 8 mg/day was superior to quetiapine up to 800 mg/day at week 3 but not at week 12. A study of ziprasidone which also had a haloperidol arm, showed significant superiority of ziprasidone over placebo but significantly lower efficacy vs. haloperidol (up to 30 mg/day) at the 3 week and 12 week endpoints (17).

The SGAs showed no superiority in improving manic symptoms compared with haloperidol (14). Results for the individual SGAs were diverse. Olanzapine and quetiapine reduced manic symptoms less effectively than haloperidol (18). Aripiprazole was less efficacious in terms of a higher rate of dropouts due to inefficacy, but effectiveness criteria such as rates of global dropout and dropout due to adverse events were superior compared with haloperidol (14,19).

Clozapine has not been extensively studied with regards to its effectiveness in bipolar disorder. There are no RCTs but a few small sample, open-label studies suggest that clozapine may be effective in the treatment of acute mania (17).

Monotherapy versus co-therapy

A systematic review of eight randomised trials have found that adjunctive treatment with quetiapine, haloperidol, risperidone or olanzapine was associated with a significant reduction in YMRS scores compared with mood stabiliser monotherapy (20).

Combined therapy with olanzapine and either valproate or lithium is more effective than treatment with either mood stabiliser alone (21). Treatment with lithium or divalproate and quetiapine in one RCT and risperidone in two RCTs found co-therapy is superior to mood stabiliser monotherapy (22-24). One study also found combination of haloperidol and mood stabiliser was more effective than mood stabiliser monotherapy.

Benzodiazepines

Clonazepam and lorazepam are used in the treatment of acute mania but trial results are conflicting. A meta-analysis suggests that clonazepam is efficient and safe

in the treatment of acute mania (25). The results remain inconclusive for lorazepam. According to the ranking of treatments, haloperidol was the most efficient drug, followed by clonazepam, lithium and lorazepam (25).

Treatment of acute bipolar depression

Bipolar depression is more refractory to treatment than unipolar depression and its treatment may increase risk of switch in mood. In bipolar patients the time spent being depressed is about three times more than being manic or hypomanic (9). They also spend a considerable time in sub threshold depression (9). Until recently it was assumed that treatment of unipolar and bipolar depression was similar. But recent evidence suggests otherwise. Treatment of bipolar depression is also complicated because of the many classes of drugs used.

We will consider the evidence for the effectiveness of antidepressants, mood stabilisers and antipsychotics in the treatment of acute bipolar depression. Randomised trials report two main outcome measures. Clinical response is defined as a 50% reduction in symptoms on the Montgomery-Asberg depression rating scale (MADRS) or the Hamilton rating scale for depression (HRSD). Remission is defined as MADRS score ≤12 or HRSD score < 9. In clinical practice remission is a more acceptable endpoint than reduction of symptoms.

Lithium

Unlike in mania the evidence for the effectiveness of lithium in the depressive phase is limited. Eight of nine controlled trials, with a total of 145 patients found that lithium was superior to placebo for the acute treatment of bipolar depression (26). The studies are small and underpowered and contain a mixture of bipolar and unipolar patients. A recent RCT comparing quetiapine 300 mg or 600 mg /day and lithium 600-1800 mg/day with placebo found that lithium was not significantly better than placebo in achieving response or remission in acute phase of bipolar depression (27). One explanation is that lithium has a slow onset of action and the trial duration of 8 weeks may have been inadequate for lithium to exhibit a significant effect. An open label trial of patients randomised to receive lithium or lamotrigine found both groups showed significant improvement at 16 weeks (28). We could not find any published RCTs comparing efficacy of lithium with new generation antidepressants. The current evidence is inadequate to support the use of lithium as monotherapy in the treatment of the acute phase of bipolar depression.

Other mood stabilisers

Van Lieshout et al carried out a meta-analysis on the effectiveness of mood stabilisers in treatment of acute depressive episodes (29). This review analysed 12 RCTs comparing mood stabilisers with placebo. This included five lamotrigine, one carbamazepine, two valproic acid, two olanzapine and two quetiapine RCTs (21,30-37). Participants randomised to mood stabiliser monotherapy were more likely to demonstrate clinical response than placebo. Only four studies provided remission data (21,31,32,34). These studies reported that rates of remission for olanzapine or quetiapine monotherapy were more than for placebo. An open label study comparing lithium 900 mg/day with lamotrigine 200 mg/day found comparable response and remission rates (28).

Atypical antipsychotics

Five RCTs have assessed efficacy of antipsychotics in treating acute phase of bipolar depression (38). These include two trials with quetiapine, two with aripiprazole and one with olanzapine which assessed olanzapine monotherapy and olanzapine–fluoxetine combination. All atypical antipsychotics demonstrated significant efficacy from week one and maximal effect size was at six weeks (29). The FDA has approved the olanzapine-fluoxetine combination and quetiapine monotherapy for the treatment of acute bipolar depression.

Lamotrigine

A meta-analysis reports that lamotrigine is effective in the treatment of the depressive phase of bipolar disorder (39). This is based on analysis of all randomised controlled trials conducted by GlaxoSmithKline. Duration of the trials was 7-10 weeks. Lamotrigine was superior to placebo in individuals with severe depressive symptoms at randomisation but not in people with moderate symptom severity. One RCT reported that for patients not responding to lithium adding on lamotrigine was more effective and safer than adding a placebo (40).

Antidepressants

A systematic review of antidepressants in treatment of acute bipolar depression considered 12 RCTs with a total of 1088 patients (41). Four RCTs of fluoxetine, deprenyl and tranylcypromine found antidepressants to be more effective than placebo. However 75% of these patients were taking concurrent mood stabilisers or antipsychotics. Two RCTs reporting remission found that patients treated with an antidepressant (paroxetine, imipramine, or fluoxetine) were more likely to reach remission than those who were not taking an antidepressant. In these two trials all patients were taking either lithium or olanzapine. There was no evidence of an increased risk of switching to a manic episode in the trials. The review made important observations. There is no strong reason to avoid antidepressants for patients with bipolar depression. This is at odds with the recommendation in the American Psychiatric Association guidelines to use lithium or lamotrigine as a first-line of treatment for bipolar depression. For patients already taking a mood stabilizer, adding an antidepressant as a first-line treatment was recommended. For patients not taking a mood stabilizer but with a history of mania, the current consensus is to use antidepressants in combination with an antimanic agent or a mood stabiliser (41).

Prevention of mania and depression in bipolar disorder

The risk of relapse is very high in bipolar disorder and it stays high even after years of being well if medication is discontinued. Relapse is devastating to the individual and contributes to the disability caused by bipolar disorder, which is in the top ten leading causes of disability.

Lithium

A systematic review of five RCTs (770 participants) that compared lithium with placebo found that lithium was more effective than placebo in preventing manic relapses but not as effective in preventing depressive relapses (7). They concluded that lithium treatment reduces the risk of relapse in bipolar disorder and the preventive effect is clear for manic episodes, although it is equivocal for depressive episodes (7).

Lamotrigine

Two 18 month, randomised, double-blind trials have compared lamotrigine, lithium, and placebo as maintenance treatment in a total of 1315 recently manic or depressed patients with bipolar 1 disorder (42). Both lamotrigine and lithium significantly prolonged the time to intervention for any mood episode compared with placebo. Lamotrigine was primarily effective against depression and lithium was primarily effective against mania.

Valproate

Although several open labeled studies have shown valproate to be effective in prophylaxis the only RCT comparing efficacy of divalproex, lithium and placebo did not find a significant benefit of valproate in the primary outcome measure of time to any mood episode (43).

Carbamazepine

Early studies have shown evidence of effectiveness of carbamazepine over placebo. For patients with a history of classical euphoric mania, lithium was superior to carbamazepine (44). A recent RCT found lithium to be superior in prophylactic efficacy to carbamazepine in bipolar patients not previously treated with mood stabilisers (45).

Atypical antipsychotics

RCT evidence of efficacy of SGAs in prophylaxis is only available for olanzapine (46). Combination of olanzapine with lithium or valproate did not provide a significant advantage in preventing an episode compared to mood stabiliser monotherapy (47). A RCT comparing olanzapine and lithium in prophylaxis over one year found olanzapine was as effective as lithium in preventing relapses (48). Compared with lithium, patients on olanzapine had significantly lower risks of manic episodes and mixed episodes but lithium was superior in preventing depressive episodes.

Rapid cyclers

Dunner and Fieve found that patients with four or more episodes per year were less responsive to lithium than those with fewer episodes, and coined the term "rapid cycler" for this subgroup (46). Lithium appeared to prevent new manic episodes in rapid cycling patients but it had no effect on new depressive episodes. In other small open trials in rapid cycling patients a small prophylactic effect of lithium was again observed (although it was inferior to the active comparator, lamotrigine). For lamotrigine, although RCT data is available its effectiveness in rapid cyclers is not established (46). The evidence for a prophylactic efficacy of carbamazepine in rapid cycling is contradictory. The only controlled study comparing lithium and carbamazepine did not find any superiority for carbamazepine. There is some evidence for prophylactic efficacy of clozapine in rapid cycling patients but the methodology of these studies is questionable (46).

Pharmacotherapy in lactating women

Evidence of effectiveness and safety of medication in lactation is scarce. They are mostly uncontrolled studies and case reports. A review found 11 cases of lithium use, 39 cases of valproate use and 50 cases of carbamazepine use during breast feeding. Though these reports favour use of carbamazepine and valproate over lithium, the quality of data is not adequate to make any recommendations (49).

Discussion

There is no consensus currently on what is accepted as sufficient evidence for treatment effectiveness. The World Federation of Biological Scientists suggests the following as level one evidence (9). In RCTs showing superiority to placebo, two or more double-blind, parallel-group trials are adequate. In a RCT showing superiority to or equivalent efficacy with an established comparator treatment, evidence from one trial is adequate. In a three-arm study with placebo a single trial is adequate as level one evidence (9). In the case of existing negative studies these must be outweighed by at least two more positive studies or a meta-analysis of all available studies.

These recommendations have inherent weaknesses. What is striking regarding the evidence for efficacy of treatment in bipolar disorder is the small number of RCTs. For drugs like lithium the evidence consists of studies carried out several decades ago and thus they are not of sufficient methodological quality to be included in systematic reviews or meta-analysis. Based on systematic reviews and meta-analysis many guidelines now recommend newer drugs such as olanzapine and

quetiapine for treatment of bipolar disorder over older drugs like lithium or tricyclic antidepressants (50). The absence of evidence is not necessarily evidence of an absence of effect.

Typical antipsychotics have been used extensively to treat mania since their introduction over a half a century ago, but surprisingly they have not been studied extensively. For example haloperidol has never been formally shown to be superior to placebo in a parallel-group monotherapy trial in mania (2). For chlorpromazine there is only one small, placebo controlled study done in 1967 and three randomised comparative studies against lithium, haloperidol and pimozide.

There are other limitations to current evidence. There are more RCT's comparing a drug to placebo than head to head comparisons with other drugs. Once the efficacy of a new drug has been established with placebo controlled trials we need to know if it is better or worse than currently accepted treatment.

There are limitations due to trial design. Many reports of efficacy are based on clinical response which is 50% reduction in symptoms which is not the goal in clinical practice. Duration of most trials are 6-9 weeks and this duration may not be adequate to achieve remission. This is especially important as the antidepressant action is maximized weeks after initiating treatment. The dose used in trials may be less than that used in clinical practice. This can have a significant impact on the outcome of a trial as many drugs are known to exhibit a dose response relationship.

Publication bias may result in fewer studies with negative findings being published. Many RCTs are sponsored by pharmaceutical companies and there is concern that some pharmaceutical company sponsored trials are biased.

Fountoulakis et al recently reviewed treatment guidelines for bipolar disorder (17). Their investigation revealed that guidelines for the treatment of bipolar disorder vary significantly across committees or specialist groups. For the treatment of acute mania, some guidelines recommend monotherapy with a mood stabiliser or a second generation antipsychotic drug as first-line treatment, whereas others recommend a combination of a mood stabiliser and antipsychotic.

While this review looked at recent evidence from systematic reviews and meta-analysis it did not undertake a systematic search of databases for RCTs. Therefore it is possible that some evidence has been missed. As discussed above our review mainly analysed evidence from RCTs so evidence from other types of studies have not been included. We also did not review safety and tolerability of drugs, two other aspects which need to be considered along with efficacy in deciding on treatment.

Conclusions

For treatment of acute mania, lithium, valproate and carbamazepine are more effective than placebo but they have no superiority over antipsychotics. There is evidence that SGAs are more effective than placebo. Haloperidol may be more effective than SGAs in treatment of acute mania. However combination of an antipsychotic and a mood stabiliser is more effective than mood stabliser monotherapy alone.

In the treatment of acute bipolar depression the current evidence is inadequate to support the use of lithium as monotherapy. The most effective treatment is combination of a mood stabiliser and an antidepressant which also minimises manic switches. The FDA has approved the olanzapine-fluoxetine combination and quetiapine monotherapy for the treatment of acute bipolar depression. Lamotrigine is also effective in the treatment of acute bipolar depression.

For prophylaxis, lithium, valproate and carbamazepine are effective while lamotrigine is primarily effective in preventing depressive episodes. Lithium is more effective in preventing manic than depressive episodes. Evidence for efficacy of antipsychotics in prophylaxis is limited.

Declaration of interest

RH and Vde S have received educational grants from Sun Pharmaceutical Company.

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