

Pharmaceutical treatment of acute bipolar depression

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F1000 Medicine Reports 2010, **2**:47 (doi:10.3410/M2-47)

The electronic version of this article is the complete one and can be found at: <http://f1000.com/reports/medicine/content/2/47>

Abstract

The treatment of bipolar depression is one of the most challenging fields in contemporary psychiatry. The best data concern the antipsychotics quetiapine and the olanzapine-fluoxetine combination. However, the usefulness of antidepressants in bipolar depression remains controversial; positive data are available for fluoxetine but negative results have been published for paroxetine. Accumulated knowledge so far suggests that bipolar patients need continuous administration of an antimanic agent even during the acute depressive phase. Although our knowledge is indeed limited, the development of guidelines for polypharmacy is necessary and should be done as soon as possible.

Introduction and content

The treatment of bipolar disorder is complex and full of caveats for the clinician [1-4]. An important problem in the gathering of scientific evidence lies in the low reliability and validity of diagnosis. Another problem is that specific and different treatments need to be considered separately for manic, hypomanic, mixed and bipolar depression episodes, as well as for unipolar depression. This article will comment on the available hard data (randomized trials) for the treatment of bipolar depression and suggest future directions for research.

Older studies conducted throughout the 1970s and 1980s on treatment of bipolar disorder reported positive effects for lithium [5], carbamazepine [6], amitriptyline [5], imipramine [7,8] and fluoxetine [9-11], however, the studies were small and suffered from a number of methodological drawbacks. Results from add-on studies with imipramine as an adjunctive therapy to lithium were negative [7,8,12].

Within the last 10 years, several phase III clinical studies of lamotrigine (SCA100223, SCA30924, SCA40910, SCAA2010 and SCAB2001) have demonstrated a lack of efficacy for this agent in the treatment of bipolar

disorder [13]. There were only two small studies reporting a positive effect of valproate in bipolar I patients [14,15], while on the contrary, the efficacy of the olanzapine-fluoxetine combination (OFC) against bipolar I depression has been well documented [16,17]. There has been concern about the effect of olanzapine monotherapy on the 'depressive core' of symptoms, however, it is certain that patients receiving this treatment manifest a significant improvement in symptoms 'peripheral' to those of depression, such as insomnia, anxiety and loss of appetite [18,19]. It has been reported that the OFC is more effective than olanzapine monotherapy [17] and also improves many secondary indices [20].

One study without a placebo arm suggested both paroxetine and venlafaxine could be effective for the treatment of bipolar depressed patients [21]. Another compared imipramine and paroxetine with placebo as an add-on to an ongoing lithium regimen and reported that these antidepressants were beneficial for patients with low (but not high) serum levels of lithium [22]. Other reports suggest that adding venlafaxine, sertraline or bupropion to a mood stabilizer increases the response rate [23-25]. Similar findings were reported for paroxetine [26] and citalopram [27]. Adding inositol [28] or

modafinil [29] to a mood stabilizer could also be useful in the treatment of bipolar depression.

Recent advances

During the last 3 years, there have been some important insights from newly available data. For example, recent negative data has emerged for drugs that had previously shown efficacy in older studies, such as monotherapy with lithium [30], paroxetine [31] and aripiprazole [32], and there have been equivocal results for valproate: two randomized controlled trials (RCTs) on the extended-release form of valproate reported one positive and one negative result; neither study was published (for reviews, see [33,34]).

Quetiapine was, however, reported to be effective at dosages of both 600 mg/day and 300 mg/day, and produced response rates of 58.2% and 57.6%, respectively (versus 36.1% for placebo), and remission rates of 52.9% in both the treated groups (versus 28.4% for placebo) [35]. It is important to note that quetiapine significantly improved all the Montgomery-Åsberg Depression Rating Scale (MADRS) items corresponding to the core symptoms of depression. *Post-hoc* analysis suggests 300 mg and 600 mg are equally effective; despite there being a small difference in the effect size [35,36], they both improved secondary measures including quality of life indices [37]. Similar results were obtained from two more recent RCTs [30,31]. Another study reported that an extended-release form of quetiapine at 300 mg daily was significantly more effective than placebo for bipolar I depression throughout the 8-week study, with significance observed as early as day 7 [38].

In a recent double-blind, placebo-controlled study, adding an antidepressant (either bupropion or paroxetine) to a mood stabilizer in 179 bipolar depressed patients was not significantly more beneficial than placebo after 26 weeks of treatment, and the recovery rates (23.5% in the antidepressant group versus 27.3% in the placebo group) and switch rates to mania were similar [39]. Thus, this study does not support the usefulness of adjunctive antidepressant therapy. However, these data should be read with caution because although paroxetine played a significant role in the design, it has since been shown to be no more effective than placebo [31]. A more recent study reported that adding lamotrigine to lithium was more effective than placebo in patients with bipolar depression [40]. Another recent 8-week trial studied 52 incomplete responders treated with carbamazepine or oxcarbazepine (600-1200 mg daily) during maintenance treatment with lithium [41]. Although this trial focused on patients in the 'maintenance' phase, the design and the results are

more relevant to the acute depressive phase because the study sample included depressed patients. Both groups improved with the addition of either drug but those receiving oxcarbazepine improved significantly more in terms of their MADRS and Hamilton Depression Rating Scale (HDRS)-21 scores [41]. Another study reported that adding venlafaxine, sertraline or bupropion to a mood stabilizer increases the response rate [23].

Several reviews and meta-analytic studies of the literature are currently available. Some suggest that only quetiapine – and to a lesser extent, olanzapine – show efficacy as a monotherapy for bipolar depression [42-44]. However, two meta-analyses of four randomized placebo-controlled trials (of 6 and 8 week duration) with a total sample size of 142 patients suggested that divalproex could also be efficacious in acute bipolar depression, with response rates of 39.3% for divalproex versus 17.5% for placebo. Remission rates were 40.6% versus 24.3%, respectively [33], with an effect size *d* equal to 0.35 [34]. The meta-analysis of the five 'negative' trials of lamotrigine monotherapy (1072 patients) reported that lamotrigine was superior to placebo in people with an HDRS score of greater than 24 but not in people with an HDRS score of less than or equal to 24 [45]. The meta-analysis of data on paroxetine and monoamine oxidase inhibitors (MAOIs) in 52 patients confirmed that the effectiveness of paroxetine was unacceptably low, but rates of recovery with MAOIs were significantly higher than the recovery rate with paroxetine [46].

Implications for clinical practice

Classically, the treatment of bipolar illness includes the use of the so-called mood stabilizers (lithium and specific anticonvulsants), antipsychotics, and antidepressants. Recent data dispute the efficacy of some of these agents against bipolar depression. Only quetiapine and the OFC are currently considered to be effective and thus have been approved for the treatment of acute bipolar depression [17,47,48]. Typical antipsychotics (haloperidol, chlorpromazine and perphenazine) seem to have some efficacy against acute mania but they also seem to predispose patients to manifest dysphoria or depression [49,50]. The dispute concerning the usefulness of antidepressants continues; clinicians should be cautious in their use and avoid prescribing them as monotherapy [1]. It is important to bear in mind that the only positive data available for the use of antidepressants in treating bipolar disorder are for fluoxetine; strong negative data still exist for paroxetine. Since, in real life, the majority of bipolar patients do not do well on monotherapy, several combination therapies and add-on agents have been tested [23,40,41] that the clinician should become familiar with.

Some of the recommendations above are in relative contrast to everyday clinical practice where clinicians do not tailor their choice of antidepressant to a specific type of depression and tend to use typical antipsychotics against mania. The chronicity of bipolar depression and its relative refractoriness to treatment might be the cause of this discrepancy. However, treating patients as if there is a 'class effect' for drugs might iatrogenically worsen the long-term course of the illness in some patients.

When the clinician is treating a depressed bipolar patient, it is clear that the first step should be the use of agents with proven efficacy (from placebo-controlled double-blind studies) against this condition. However, it is likely that most patients will fail with such a treatment and the clinician will be left with no hard data to rely on. In this case, the clinician should avoid treatments with a proven worsening effect on the long-term outcome of the disease. Additionally, psychoeducation could constitute a useful tool to treat bipolar depression, along with family-focused psychoeducation and cognitive-behavioral therapy [51].

Abbreviations

HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MAOI, monoamine oxidase inhibitor; OFC, olanzapine-fluoxetine combination; RCT, randomized controlled trial.

Competing interests

The author has received support comprising travel and accommodation expenses from various pharmaceutical companies in order to participate in medical congresses. He has also received honoraria for lectures from AstraZeneca, Janssen-Cilag, Eli Lilly and a research grant from the Pfizer Foundation. He is member of the board of Wyeth for desvenlafaxine and Bristol-Myers Squibb for aripiprazole in bipolar disorder.

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