The Place of Antidepressant Medication in the treatment of Bipolar Affective Disorder

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Abstract

In patients with bipolar disorder, the use of antidepressants without mood stabilisers has been thought to have the potential to induce mania, mixed affective states and rapid cycling bipolar disorder. Since both mixed states and rapid cycling are associated with an increased risk of suicide, the use of antidepressants in the treatment of bipolar disorder has been questioned. In this paper the evidence and the guidelines for the use of antidepressants in the management of depressive episodes in bipolar disorder are reviewed. The evidence suggests that the risk of mania is not significant with the use of certain antidepressants. However, there is emerging evidence that antidepressants have limited effectiveness in treating bipolar depression. We suggest antidepressants should not be the first choice of treatment for depressive episodes in bipolar disorder and if used should always be given in combination with mood stabilisers. Other compounds such as quetiapine and lamotrigine appear to be of more use in the treatment of bipolar depression.

Key words: antidepressants, bipolar disorder, mood stabilisers, quetiapine, lamotrigine.

Concerns have been raised about the consequences of using antidepressants to treat patients with bipolar disorder. Antidepressants have the potential to induce mania, mixed affective states and rapid cycling bipolar disorder in patients with bipolar disorder who are not concomitantly treated with mood stabilisers. Since both mixed states and rapid cycling bipolar disorder are related to an increased risk of suicide, this use of antidepressants in the treatment of bipolar has been challenged (1). Such theories also suggest potential hazards in the treatment unipolar depression with antidepressants when bipolar disorder has not been excluded. Moreover, Bipolar III disorder has been described as mania induced by the use of antidepressants in the treatment of a patient who had previously been considered to have unipolar depression (2). An important question is, therefore, whether antidepressants are effective in the treatment of bipolar depression and whether there is an alternative agent, such as a mood stabiliser, with greater efficacy. Second, it is important to consider whether antidepressants can be used for short-term treatment in bipolar depression without the induction of mania.

Several studies have considered the efficacy of antidepressants in the treatment of bipolar disorder. In 2004 Gijsman et al. (3) carried out a systematic review of randomised controlled trials (RCTs) on the use of antidepressants in bipolar depression; they concluded that antidepressants were more effective than placebo in the treatment of bipolar depression. In particular, Tohen et al. (4) found the olanzapine and fluoxetine combination (OFC) to be effective and this was licensed by the FDA for treatment of bipolar depression in America in 2003 (5). However, other studies have found that, when compared to the use of a mood stabiliser or an atypical antipsychotic, antidepressants have no additional benefit in bipolar disorder. In the STEP-BD study (Systematic Treatment Enhancement Program for Bipolar Disorder) (6) all participants commenced the study on an optimum dose of a mood stabiliser, i.e. lithium, valproate or carbamazepine, and were then randomised into groups receiving paroxetine, bupropion or placebo. Results demonstrated that the addition of an antidepressant to a mood stabiliser did not offer any additional benefit when compared to a mood stabiliser alone. The authors therefore suggested that a mood stabiliser should be the first-line treatment for acute bipolar depression in the outpatient setting. In the EMBOLDEN 2 study (7) acutely depressed bipolar patients were treated with paroxetine, quetiapine or placebo. Based on the Montgomery–Åsberg Depression Rating Scale (MADRS) score there was a significant improvement in the quetiapine-treated group compared to the placebo-treated group but not in the paroxetine-treated group, suggesting that

atypical antipsychotics may be of more benefit than antidepressants.

More recently a meta-analysis by Sidor & McQueen (8), covering 2373 patients (including those from the STEP-BD and EMBOLDEN 2 studies), concluded that antidepressants did not provide statistically significant benefits when compared to placebo or other current standard treatments for bipolar depression. This conclusion is further supported by a meta-analysis of 68 studies by Amit & Weizman (9) which concluded that the majority of well-designed studies did not find a significant benefit from using any class of antidepressant in bipolar disorder of any subtype.

When considering whether the use of antidepressants in bipolar disorder increases the occurrence of a switch to mania/hypomania, the evidence suggests that there is no significantly increased risk with at least some types of antidepressants, such as the selective serotonin re-uptake inhibitors (SSRIs) or bupropion. Goldberg et al. (10) found that bipolar patients who have an earlier onset of illness and have a strong family history of bipolar illness are at a higher risk of developing antidepressant-induced manias. However, Gijsman et al. (3) found that antidepressants were not associated with an increased rate of mania when compared to placebo. Furthermore, the results of the STEP-BD study suggested that there is no increase in hypomanic or manic switch when paroxetine or bupropion are added to a mood stabilizer during a depressive phase (6). Sidor & McQueen (8) come to a similar conclusion in their meta-analysis, as did Amit & Weizman (9), who found that there was no significant increase in the rate of manic/hypomanic switch when patients were treated with antidepressants, especially if they were already taking a mood stabiliser. Taking these two aspects together, it appears that, although antidepressants do not increase the risk of a switch to mania/hypomania their clinical efficacy is doubtful. This is reflected in the available guidelines for the treatment of bipolar disorder, where agents other than antidepressants are generally preferred for the treatment of depression in bipolar disorder. The following recommendations for the treatment of bipolar depression are based on tables recently published in the Maudsley Guidelines (11), from which the information has been extracted.

1. Quetiapine should be the drug of choice in bipolar depression, with limited evidence for the use of valproate and lithium.

2. If antidepressants are needed, SSRIs are the preferred option. Alternatively, bupropion has been used in previous trials and is not associated with a switch to mania. Venlafaxine can also be used though it is associated with a higher risk of a switch to mania. Monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants should be avoided. None of the antidepressants is recommended for prophylactic use against depression.

3. Antidepressants as monotherapy should be avoided, especially in bipolar I disorder, due to inefficacy and potential risk of a switch to mania.

4. The combination of olanzapine and fluoxetine is more effective than either individually (or lamotrigine) and also offers a prophylactic effect.

5. Lamotrigine has been shown to be effective in acute bipolar depressive episodes and has a modest protective effect against future depressive episodes. Titration of the dose is necessary. However, it can be used to augment treatment in patients who are already on lithium or as an alternative to lithium in pregnancy.

The BAP (British Association for Psychopharmacology) guidelines (12) for managing acute depression in bipolar disorder divides its advice on the basis of whether patients are already on long-term therapy. In patients not already on long-term therapy, the guidelines suggest lamotrigine (with necessary slow titration of the dose to decrease the risk of skin rash) or quetiapine (if a rapid effect is required) as initial treatment, rather than antidepressants. According to the same guidelines, if a patient has a history of mania, antidepressants should only be used in combination with a mood stabiliser. An antipsychotic should be considered if psychotic symptoms are present. BAP also recommends electro-convulsive therapy (ECT) in acutely depressed patients with bipolar disorder if they present with a high risk of suicide, psychosis or when there is a risk to life due to severe bodily

and functional inhibition. ECT is also recommended for severe acute depression in pregnant women if they are not already on long-term treatment for bipolar disorder. In cases where symptoms are less severe, lithium or valproate may be considered. Psychological therapies such as IPT, CBT and family-focused therapies may help to reduce the duration of the acute episode.

For the treatment of an acute depressive episode in patients already on long-term therapy for bipolar disorder, the BAP guidelines (12) recommend optimisation of current medications, as well as ensuring that lithium levels are within the therapeutic range. Consideration should also be given to the prevention of a manic relapse with a mood stabiliser or antipsychotic. If the depression does not respond to treatment, augmentation or a change of treatment should be considered.

When considering the choice of antidepressant, the BAP guidelines (12) indicate that tricyclics and drugs such as venlafaxine and duloxetine carry a higher risk of manic switch than SSRIs. If there is a history of antidepressant-induced mood destabilisation then quetiapine or lamotrigine should be considered. Since the duration of acute depression in bipolar disorder is usually shorter than in unipolar disorder, antidepressants can often be discontinued after 12 weeks.

NICE Guidelines (13) and the Canadian network for mood and anxiety treatments (CANMAT) guidelines (14) have retained the use of an antidepressant as one of the options for treatment, stressing the concurrent use of a mood stabiliser.

In 2010, the Psychopharmacology Algorithm Project at Harvard South Shore program (PAP HSS) (15) bipolar depression algorithm presented a slightly different route for management but still did not favour antidepressants as a first-line treatment. It was suggested that the first action following diagnosis should be to assess whether ECT is required. If ECT is not necessary then a pharmacological route is suggested. If the patient has psychotic symptoms, an antipsychotic should be considered. The next level is either to initiate or optimise treatment with mood stabilisers (lithium is the preferred agent in these guidelines). It is noted that patients with rapid cycling mood disorder may need a combination of mood stabilisers. If this is ineffective, quetiapine or lamotrigine should then be considered. Only if all three fail and the risk of mood destabilisation is low, should the use of antidepressants be considered. PAP HSS acknowledged the possible risk of antidepressants causing manic switch and long-term mood destabilisation. The guidelines suggested that bupropion is associated with the lowest risk followed by sertraline, while venlafaxine is associated with the highest risk.

Finally, the World Federation of Societies of Biological Psychiatry (WFSBP) in its updated guidelines in 2010 (16) stated that quetiapine at 300 mg per day is an effective treatment for bipolar I and II depression but that the olanzapine/fluoxetine combination (OFC) is also effective. Fluoxetine, and other antidepressants to a lesser degree, were advised when used in combination with either a mood stabiliser or lamotrigine or as an addition to lithium in patients with a poor response.

Taken together, the various guidelines include antidepressants in their recommendations for the treatment of acute depression in bipolar disorder but generally this is not as a first-line treatment. Importantly, NICE guidelines suggest that the emergence of mixed agitated states, mood cycling and treatment-emergent affective switch due to antidepressants in bipolar disorder demands extreme caution in the use of antidepressants (17). Moreover, the American Psychiatric Association (APA) practice guidelines have stated that antidepressants in bipolar disorder carry the risk of mood destabilization and affective switching and as such they are contraindicated, especially in rapid cycling bipolar patients (18).

However, Grunze 2008 (19) suggests that much of the evidence surrounding the effects (both favourable and unfavourable) of antidepressants comes from small, poorly-designed studies and that, because of this, the risk of switch may have been overestimated. This is a view supported by the meta-analyses and systematic reviews cited earlier in this article which, in general, found no increased risk of switch with antidepressants. However, as these studies also call into question the efficacy of antidepressants in bipolar disorder, the guidelines on antidepressants may have to be reconsidered, not because of adverse effects but because of a lack of treatment benefit.

Some fundamental questions have arisen with regard to the management of bipolar depression. The first and most important question is whether antidepressants have any role to play in the treatment of bipolar depression. Second, if antidepressants do have a role, in what circumstances should they be used? Third, what are the risks of using antidepressants, especially in terms of affective switch to hypomania/mania and how might these risks be avoided or minimised?

Taken together, recent evidence does not favour the use of antidepressants in bipolar depression but rather encourages the use of mood stabilisers or antipsychotics as first-line treatment for an acute depressive episode. The majority of guidelines have suggested that the role of antidepressants is as an adjunct in the treatment of bipolar depression. There is conflicting evidence on whether antidepressants increase the rate of a switch to mania in bipolar disorder, with more recent evidence suggesting that they do not. However, when antidepressants are used, the concomitant use of mood stabilisers is advocated. As bipolar disorder is a remitting and relapsing disorder (with a high recurrence rate of more than 90%) (20), when an antidepressant is prescribed it is of the utmost importance to consider the response to antidepressants in any previous depressive episodes. In particular, it is important to identify whether there has been the emergence of manic or hypomanic symptoms in the past, in order to minimise the risks, on an individual basis, of using antidepressants.

GP Comment

What have I learned from this paper?

I found this paper extremely helpful because it emphasised to me, as a future GP, the importance of managing patients with depression as part of bipolar disorder differently from those patients with unipolar depression. We are much less familiar with the management of this group and it was interesting to find that first-line management is with quetiapine. This paper will change my practice in prescribing for patients with bipolar disorder affected by depression and reminded me of the importance of taking a careful history from patients with depression to elicit any previous manic or hypomanic episodes, to make sure they receive an accurate diagnosis and safe, effective treatment.

Abigail Davis, GP Trainee.

This article questions the evidence that antidepressants lead to a switch to mania or mixed state when used in bipolar disorder but argues that they should not be used alone due to lack of efficacy and potential risk. Guidelines advise anti-depressants as an adjunct to treatment, but advise mood stabilisers or antipsychotics as first-line treatment for an acute depressive episode. If an antidepressant is prescribed it is vital to consider the response to antidepressants in any previous depressive episodes and the previous emergence of any manic or hypomanic symptoms.

Dr J Hopwood, GP Trainee

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