Review Article

Antidepressant monotherapy for bipolar type II major depression


Objectives: Bipolar type II (BP II) disorder is thought to be distinct from BP I disorder on genetic and biological grounds, and it is not merely a milder form of the illness. It affects 1.5–2.5% of the US adult population, and is characterized by highly recurrent depressive episodes with a substantial morbidity from alcoholism and non-affective psychopathology, and a higher suicide rate than either BP I or unipolar depression. Treatment recommendations for BP II depression are based upon concerns over drug-induced manic-switch episodes, and suggest using either a mood stabilizer alone or a combination of an SSRI plus a mood stabilizer. Recent evidence, however, indicates that the rate of manic switch episodes may be modest in BP II patients. Recent studies have provided evidence that antidepressant monotherapy may be an effective initial and long-term treatment for BP II major depression with a low manic-switch rate.

Methods: In this article, we review the recent literature on BP II disorder, with a focus on the treatment of BP II major depression.

Results: We present a summary of data from recent studies by our group and others indicating that antidepressant monotherapy for BP II depression may be safe and effective with a low manic-switch rate.

Conclusion: Antidepressant monotherapy may be beneficial for some patients with BP II major depression.

Jay D Amsterdam and David J Brunswick
Department of Psychiatry, Depression Research Unit, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Key words: antidepressant – bipolar II disorder – mood stabilizer – treatment

Introduction

Incidence and epidemiologic factors

There has been a growing awareness of the prevalence and importance of bipolar type II (BP II) disorder. The financial impact of BP II disorder (in terms of medical costs and lost productivity) is considerable and has been estimated to be about $20 billion annually (1). Despite this, most BP II patients receive an incorrect diagnosis of recurrent unipolar depression (2). As a result, Goodwin and Ghaemi (3) have estimated that the apparent incidence of BP II major depression can vary widely depending upon the ascertainment method used. Community-based epidemiologic studies have found a prevalence rate of 1.5–2.5% for BP II disorder (1, 4, 5). However, estimates vary widely. Two recent clinical surveys have estimated that approximately 40% of patients with a diagnosis of major depression may have BP II disorder (6, 7). This is consistent with a vast underdiagnosis of BP II disorder. In this regard, in two recent office-based surveys, 40–45% of patients diagnosed with BP II major depression had previously been diagnosed as recurrent unipolar MDE (3, 8). Thus, BP II disorder may characterize a high proportion of affectively ill patients seen in physician’s offices. It would appear that BP II depression represents the most common expression of BP disorder (2).

Clinical characteristics

Bipolar II disorder was initially described in 1976 (9). As defined in DSM-IV, it is characterized by a preponderance of depressive episodes with a lifetime history of one or more hypomanic episodes.
Antidepressant monotherapy for bipolar type II major depression

As part of a study examining the relative efficacy of long-term, relapse-prevention therapy in BP disorder, Prien et al. (22) reported the presence of drug-induced mania in 67% of 44 BP I depressed patients taking imipramine, 12% of patients taking lithium, and 33% of patients taking placebo. A larger study in 117 remitted BP I patients taking either imipramine, lithium or a combination of lithium and imipramine, found manic episodes in 53% of imipramine-treated patients, 26% of lithium-treated patients and 28% of patients receiving the combined therapy (23).

Wehr and Goodwin (24) reported accelerated ‘cycling’ during TCA treatment in five rapidly cycling, female BP I patients. In a subsequent study, Sachs et al. (25) compared add-on therapy with bupropion versus desipramine to a mood stabilizer in 19 BP I depressed patients. They observed a 55% manic switch rate with desipramine and 11% with bupropion. Based upon these limited, controlled data, many clinicians prescribe bupropion for the treatment of BP I and BP II depression.

More recently, Bottlender et al. (26) suggested that the concurrent use of a mood stabilizer may reduce the likelihood of a manic switch in BP I patients. However, controlled studies on this issue are limited in number. In a naturalistic study, Boerlin et al. (27) found a similar (~20%) rate of hypomanic switch episodes in 13 BP patients on a combination of a mood stabilizer plus an antidepressant and 14 BP patients on a mood stabilizer alone. In contrast, in a controlled lithium discontinuation study on BP I and BP II patients, established on maintenance lithium therapy, Fadda et al. (28) found that 20 of 38 (53%) BP I patients, and none of 26 BP II patients developed a manic episode following lithium discontinuation.

While TCAs appear to result in manic-switch episodes in a substantial percentage of BP I depressed patients (24, 29), manic-switch rates resulting from selective serotonin reuptake inhibitors (SSRIs) may be substantially lower. In this regard, Cohn et al. (30) compared fluoxetine 20–80 mg/day, imipramine 75–300 mg/day and placebo in a 6-week trial in BP I depressed patients generally not taking a mood stabilizer. After this initial treatment period, the patients were followed in open-label continuation therapy (where they were free to select either antidepressant treatment). In the initial 6-week period, only two of 30 patients (6.6%) on imipramine had a manic episode, while none of 30 fluoxetine and none of 29 placebo patients had a manic episode. Similarly, during the open-label continuation phase of the study, none of 18 fluoxetine patients had a manic episode, while

last for a minimum of 4 days. It is thought to be distinct from BP I disorder on both genetic and biological grounds, and is felt to be not merely a milder form of the illness. BP II disorder is diagnostically stable over time (10–13) and rarely evolves into BP I (manic-depressive) disorder (12).

The impact of BP II disorder in terms of morbidity, mortality and health care costs has only recently been recognized. It is frequently unrecognized and often misdiagnosed. This is largely the result of a failure to recognize prior hypomanic episodes which can frequently manifest as brief periods of irritability and agitation (rather than an enhanced sense of well-being). Misdiagnosis also results from the lack of subjective and objective symptoms (of mania), which might otherwise result in treatment intervention. Periods of increased productivity and an enhanced sense of well-being that can occur during hypomania are generally not viewed by patients or physicians as illness-related symptoms. Patients with these ‘hypothymic’ symptoms are rarely considered to be in need of treatment (14). As a result, BP II disorder is generally diagnosed only by painstaking history-taking, and usually when the patient seeks treatment for a depressive episode.

Bipolar II disorder is highly recurrent, with the majority of episodes being depression (rather than hypomania) (2, 15, 16). For example, Coryell et al. (12) reported an affective relapse rate of 70% (mostly depressive) in BP I and BP II patients during lithium maintenance; while O’Connell et al. (17) found a 44% relapse rate (mostly depressive) during a 1-year follow-up of 243 BP I and BP II patients on lithium maintenance. The high recurrence rate of BP II depressive episodes (even during lithium maintenance) can result in substantial morbidity and mortality (16, 18–20). Dunner (21) has indicated that a history of multiple suicide attempts is suggestive of BP II disorder, and that the rate of successful suicides may be higher in BP II patients when compared with BP I and unipolar major depression.

Manic switch episodes during treatment of BP major depression

The use of antidepressants for treating BP II major depression has been discouraged due to the perceived risk of drug-induced mania. However, the data on drug-induced manic-switch rates in BP II depression are surprisingly few, and most estimates are based upon data obtained using tricyclic antidepressants (TCAs) in patients with BP I disorder.
four of 25 patients (16%) who switched to fluoxetine from imipramine or placebo had a manic episode.

In contrast to BP I depression, the evidence for a high manic-switch rate during antidepressant monotherapy in BP II depression is surprisingly limited. Moreover, BP II patients rarely switch into mania (12) and are much less likely than BP I depressed patients to undergo a drug-induced manic switch (31). In an open and uncontrolled study, Kupfer et al. (32) found BP II depressed patients no more likely to develop hypomania than unipolar depressed patients receiving imipramine monotherapy 150–300 mg/day. Furthermore, even when mood induction occurred in BP II patients, it was generally mild, time-limited and did not alter the overall treatment regimen (32).

The effectiveness of SSRI monotherapy in BP depression was initially noted over 20 years ago (33), and other reports have indicated that short-term SSRI treatment is highly effective in BP II depression (30, 34–36). Recent evidence suggests that the manic-switch rates in BP II depressed patients treated with SSRIs are substantially lower than that of TCAs in BP I patients. Peet (37) estimated SSRI-induced manic-switch rates at <5%, a figure that compares with recent observations of 3.8% from our group (38).

Despite the growing literature suggesting that SSRIs may be effective in BP II major depression and have a low incidence of manic induction (38), there is still disagreement concerning the use of SSRIs in BP depression (39). Persistent fear of mania during an SSRI treatment continues to plague clinicians (40). Thus, while the most accepted treatment for BP I depression is a mood stabilizer alone or in combination with an SSRI (41), there is little consensus regarding the appropriate management of BP II depression, and most current recommendations are based on those of BP I disorder.

Current treatment guidelines for BP II major depression

Bipolar II depression is generally considered to be less responsive to antidepressant monotherapy (2) and possibly to lithium monotherapy as well (4). Nevertheless, based upon early studies of lithium prophylaxis in BP II disorder (42, 43), it is now widely believed that a mood stabilizer may be needed in the treatment of BP II depression, and that antidepressants (if they are used at all) should be limited to the lowest possible dose for the shortest possible time. Despite the relative ineffectiveness of mood stabilizer monotherapy for the acute treatment of BP II major depression (4), the use of mood stabilizer monotherapy is recommended, while the use of antidepressant monotherapy is discouraged in BP II depression.

A number of treatment algorithms have been proposed for the acute treatment of BP II major depression. These algorithms are not based upon controlled clinical trials, but all express considerable concern about the use of antidepressants in the treatment of BP depression. These concerns have been summarized by Ghaemi et al. (44) who wrote that ‘experts in the treatment of BP disorder have recommended avoidance of antidepressant treatment except in the brief, short-term treatment of severe, acute Bipolar depression in conjunction with mood stabilizing agents... There is some evidence that patients with milder variations of BP disorder, such as type II, may be at more risk of misdiagnosis as unipolar major depressive disorder and over-treatment with antidepressants resulting in a worsened rapid-cycling course.’

The American Psychiatric Association Practice Guideline for the Treatment of Patients with Bipolar Disorder (41) has recommended that BP MDE patients should begin mood-stabilizer (generally lithium) therapy, and that patients given a concurrent antidepressant should receive the lowest effective dose of SSRI for the shortest time. This algorithm makes no distinction between the treatment of BP I and BP II depression.

Similar recommendations have been made by an Expert Consensus Guideline Series based upon the recommendations of 61 American experts on BP disorder (45). However, in contrast to the APA recommendations, they suggested that antidepressant monotherapy may be considered in BP patients who have had a history of minimal hypomania (i.e. BP II depression). They recommend that antidepressant therapy be limited to SSRIs or bupropion as the first choice.

In contrast, a panel of distinguished Canadian psychiatrists recommended against the use of antidepressant monotherapy in the treatment of BP MDE, recommending instead lithium monotherapy as the treatment of choice (46). Where a combination of an antidepressant and mood stabilizer is used in BP MDE, they recommend that the antidepressant dose be reduced and withdrawn completely within 6–12 weeks of remission of depressive symptoms.

A recent guideline for the treatment of BP patients recommends that a mood stabilizer alone is the preferred initial strategy for the treatment of a first episode of mild to moderate BP depression (47). In the case of severe BP depression, a combination of a mood stabilizer and antidepressant medication is recommended. The use of an
Antidepressant monotherapy for bipolar type II major depression

Antidepressant alone is not recommended for any BP patient. This report recommended that antidepressants be used at the same target dose as that employed in the treatment of non-BP patients (except in patients with a history of antidepressant-induced mania). No distinction was made in this treatment guideline between therapy for BP I and BP II depression (47).

Despite these recommendations, many psychiatrists recognize the limitations of lithium or other mood stabilizer monotherapy for BP II depression. A substantial proportion of BP II depressed patients do not respond to mood-stabilizer monotherapy (48), and many psychiatrists feel that SSRI monotherapy may be favored over mood stabilizer monotherapy for BP MDE (49).

In line with this, the Harvard Psychopharmacology Algorithm has recommended that BP II depressed patients, not already taking a mood stabilizer, should be treated with an SSRI or bupropion alone (50). However, as with all the foregoing algorithms, this recommendation is not based upon controlled clinical trials.

Treatment studies

Acute fluoxetine monotherapy of BP II major depression

We examined the efficacy and safety of short-term (12 weeks) fluoxetine monotherapy in 89 BP II major depressed patients, and compared it with that of 89 unipolar depressed patients (38).

Methods. In brief, as part of a five-site, prospective, double-blind, placebo-controlled 839 patient study, we identified 89 patients meeting DSM III-R criteria for BP II major depression. This patient cohort was age- and gender-matched to 89 unipolar depressed patients for outcome comparison. The study was divided into two phases: (i) an initial, 12-week open-label, fixed-dose fluoxetine 20 mg daily treatment; and (ii) a 50-week double-blind, placebo-substitution, relapse-prevention phase for patients who remitted during the initial treatment phase.

Remission during the initial phase was defined as a reduction in the baseline HAM-D<sub>17</sub> score >50% plus a final HAM-D<sub>17</sub> score ≤7 from weeks 9–12 of treatment. Adverse events were ascertained from patient-recorded and physician-elicited reports with ‘manic switch’ rates compiled retrospectively from the adverse events database. A ‘manic switch’ was defined as any treatment emergent event symptom suggestive of a hypomanic mood change (e.g. rapid thoughts, affective lability, agitation, increased activity and enhanced energy).

Results. Fluoxetine monotherapy resulted in a similar efficacy for BP II and unipolar depressed patients. During the initial treatment phase 61% of BP II and 51% of the matched unipolar patients (p = ns) met the response criteria. A similar number of BP II and unipolar patients discontinued treatment for adverse events during the initial treatment phase. Symptoms suggestive of a hypomanic switch were observed in only 3.8% of BP II patients and in none of the unipolar patients during the initial study phase.

Long-term fluoxetine monotherapy of BP II major depression

We examined the efficacy and safety of long-term (6 month) fluoxetine monotherapy in 28 BP II patients, and compared with that of 27 unipolar patients who had remitted from their major depression during initial fluoxetine treatment (38).

Methods. We examined long-term efficacy (survival) and safety in BP II and unipolar patients who responded to fluoxetine 20 mg daily with a HAM-D<sub>17</sub> score ≤7. These patients were enrolled into one of four treatment conditions: (i) continuation fluoxetine 20 mg daily for 50 weeks; (ii) continuation fluoxetine for 38 weeks and then placebo for 12 weeks; (iii) continuation fluoxetine for 14 weeks and then placebo for 36 weeks; or (iv) continuation placebo for 50 weeks. Relapse was defined as a sustained increase in HAM-D<sub>17</sub> score ≥14 for 3 weeks, or DSM III-R criteria for major depression for 2 weeks. The presence of hypomanic symptoms were ascertained as described.

Results. Fluoxetine monotherapy was effective in long-term relapse-prevention for BP II patients who remitted from their major depression. Kaplan–Meier survival curves for the BP II (n = 28) and unipolar (n = 27) patients who received at least 26 weeks of fluoxetine maintenance therapy showed a slightly better outcome in the BP II patients (78%) versus unipolar patients (67%) (p = ns). Symptoms suggestive of a hypomanic switch were observed in only 1 (3.6%) BP II patient. These retrospective data support the contention that SSRI monotherapy may be a safe and effective treatment for BP II depression (Table 1).

Venlafaxine monotherapy in BP II major depression

We examined the safety and efficacy of acute (6-week) and long-term (3-month) relapse-prevention venlafaxine monotherapy in BP II and unipolar patients with DSM-IV major depression (51, 52). This was a
Table 1. Venlafaxine monotherapy in BP II and unipolar major depression

<table>
<thead>
<tr>
<th></th>
<th>Weekly HAMD21 scores</th>
<th>Weekly MADRS scores</th>
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<tbody>
<tr>
<td></td>
<td>BP (n = 16)</td>
<td>UP (n = 26)</td>
</tr>
<tr>
<td>Week 1</td>
<td>22 ± 6</td>
<td>20 ± 5</td>
</tr>
<tr>
<td>Week 2</td>
<td>16 ± 8</td>
<td>19 ± 8</td>
</tr>
<tr>
<td>Week 3</td>
<td>11 ± 5</td>
<td>16 ± 7</td>
</tr>
<tr>
<td>Week 4</td>
<td>11 ± 5</td>
<td>12 ± 8</td>
</tr>
<tr>
<td>Week 6</td>
<td>9 ± 7</td>
<td>10 ± 6</td>
</tr>
</tbody>
</table>

Values are represented as mean ± S.D.  
p-values are bipolar (BP) versus unipolar (UP).

Methods. In brief, patients met DSM-IV criteria for MDE and had a baseline HAM-D21 score ≥20. Following a 1-week placebo lead-in period, patients were randomized to either once or twice daily venlafaxine dosing starting at 37.5 mg daily and increasing to 225 mg daily during weeks 4–6. Responders with a final reduction in HAM-D21 score > 50% continued in double-blind therapy for an additional 3 months.

Results. A total of 48 patients were enrolled into the study over a 6-month period. Of these, 42 (88%) of the patients (16 BP II and 26 unipolar) completed the 6-week trial. Completer analyses demonstrated a significant overall reduction in HAM-D21 and Montgomery Asberg Depression Rating Scale (MADRS) scores (p < 0.001).

There was similar overall efficacy among the BP II and unipolar depressed patients. Moreover, the BP II patients appeared to have a more rapid decline in mean HAM-D21 (ANOVA; p = 0.03) and MADRS (p = 0.02) scores by week 3. There were no episodes of manic induction detected in any patient during the acute (6-week) or relapse-prevention (3-month) phase.

Table 2. Venlafaxine monotherapy in BP II and unipolar depressed women

<table>
<thead>
<tr>
<th></th>
<th>Weekly HAMD21 scores</th>
<th>Weekly MADRS scores</th>
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<tbody>
<tr>
<td></td>
<td>BP (n = 15)</td>
<td>UP (n = 16)</td>
</tr>
<tr>
<td>Baseline</td>
<td>24 ± 3</td>
<td>23 ± 3</td>
</tr>
<tr>
<td>Week 1</td>
<td>20 ± 6</td>
<td>21 ± 5</td>
</tr>
<tr>
<td>Week 2</td>
<td>17 ± 8</td>
<td>18 ± 8</td>
</tr>
<tr>
<td>Week 3</td>
<td>13 ± 7</td>
<td>16 ± 7</td>
</tr>
<tr>
<td>Week 4</td>
<td>12 ± 7</td>
<td>12 ± 6</td>
</tr>
<tr>
<td>Week 6</td>
<td>11 ± 9</td>
<td>11 ± 7</td>
</tr>
</tbody>
</table>

Values are represented as mean ± S.D.  
p-values are bipolar (BP) versus unipolar (UP).

Venlafaxine monotherapy in BP II depressed women

Gender differences in the presentation, course and outcome of BP disorder in women have been reported. For example, women with BP I disorder may be more likely to have recurrent depressive episodes (53), develop rapid cycling (54, 55), have dysphoric mania (56) and drug-induced manic-switch episodes (29, 57). Therefore, we specifically examined the comparative safety and outcomes of venlafaxine monotherapy in women with BP II and unipolar depression (58).

Methods. The methods are as described in Ref. (38). In brief, 15 women with BP II depression (mean ± SD age 37 ± 12 years) and 17 women with unipolar depression (41 ± 12 years) were treated with venlafaxine, starting at 37.5 mg/day and increased to a maximum of 225 mg/day for 6 weeks. Responders were continued for an additional 3 months of relapse-prevention therapy.

Results. A total of 31 women (15 BP II and 16 unipolar) received venlafaxine for >1 week and 28 (14 BP II and 14 unipolar) women completed the initial 6-week trial. Efficacy was similar among BP and unipolar-depressed women (Table 2). BP II depressed women showed a slightly more rapid improvement on the Clinical Global Impression,
Antidepressant monotherapy for bipolar type II major depression

Improvement (CGI/I) scale by day 21 of treatment (p = 0.076), while the percentage of patients with a ≥50% reduction in baseline HAM-D21 score was similar in BP and unipolar women.

Two BP II (13%) and three unipolar (18%) women discontinued treatment because of adverse events or lack of efficacy (p = ns). No episodes of drug-induced hypomania or rapid cycling were observed in the BP women during the initial or long-term study phase.

Discussion

Expert panels have recommended the following treatment approaches for BP II depression: (i) avoid the use of antidepressant monotherapy; (ii) initiate antidepressant therapy with a mood stabilizer alone (mild depression), or with a combination of a mood stabilizer and SSRI (severe depression); (iii) limit antidepressant agents to either an SSRI or bupropion, and avoid the use of a TCA; and (iv) initiate an SSRI or bupropion therapy at the lowest effective dose for the shortest possible duration (severe depression) (41, 59). Most of these recommendations are based upon data derived from the BP I depression literature, and none are the result of adequately powered and controlled, prospective clinical trials.

In clinical practice, however, most of these guidelines are not followed. Patients and physicians shun the diagnosis of BP disorder, or patients refuse to take long-term mood stabilizer therapy or demonstrate reduced compliance in taking multiple psychotropic medications. Moreover, non-adherence to therapy substantially increases with treatment duration. Finally, the diagnosis of BP II disorder is often overlooked, and antidepressant monotherapy is repeatedly prescribed for acute BP II depression.

In contrast to the expert recommendation that antidepressants other than an SSRI or bupropion be avoided in BP II depression (especially the use of TCAs), there is substantial evidence from controlled trials that TCAs, as well as MAO inhibitors, may be highly effective in BP major depression. For example, Himmelhoch et al. (60) found the antidepressant efficacy of tranylcypromine to be superior to imipramine in BP I and II depressed patients on mood stabilizers. In this study, the side effect burden with tranylcypromine was similar to that of imipramine. We have also reported MAO inhibitor monotherapy to be effective, and without manic induction, in up to 50% of patients with treatment-resistant BP II depression (61).

Similarly, Kupfer (16) reported only a 4% hypomanic switch rate in BP II depressed patients treated with imipramine monotherapy >225 mg daily – suggesting that the previously reported high rates of TCA-induced manic-switch episodes may be limited to patients with BP I disorder. These observations comport well with more recent data from our group in BP II patients treated with fluoxetine (38) and venlafaxine (51, 58).

Finally, what is the optimal time duration for the use of antidepressant treatment of BP II depression? Current recommendations indicate that patients with severe BP II depression might be treated with an SSRI (in combination with a mood stabilizer) at the lowest effective dose for the shortest possible time before discontinuing the SSRI. In this regard, there are few data in the literature to indicate that ‘low dose’ antidepressant therapy (alone or in combination with a mood stabilizer) are effective for BP major depression, or that rapid discontinuation of antidepressant therapy for an illness with highly recurrent depressive episodes is more effective than continuation therapy. In contrast, available data suggests that continuation SSRI therapy may be more beneficial in long-term prevention of BP II depression relapse, suggesting that continuation SSRI therapy may be equally beneficial in BP II and unipolar depressives (38).

Conclusion

Bipolar II major depression appears to be a diagnostically distinct disorder, and not merely a more mild form of manic-depressive illness. It appears to represent a valid, distinct, highly recurrent and often psychosocial malignant subtype of BP disorder (62). To date, there is no consensus on treatment approaches for BP II depression, and most recommended treatment algorithms are not based on empirical evidence and may lead to poor outcomes. Based on our preliminary findings in studies with fluoxetine and venlafaxine monotherapy of BP II depression (38, 51, 58), and a careful review of the literature on this subject, we suggest that antidepressant monotherapy may be safe and effective therapy for most patients with BP II depression.

Acknowledgements

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Antidepressant monotherapy for bipolar type II major depression


