Review Article

Management of Bipolar II Disorder

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ABSTRACT

Bipolar II disorder (BP II) disorder was recognized as a distinct subtype in the DSM-IV classification. DSM-IV criteria for BP II require the presence or history of one or more major depressive episode, plus at least one hypomanic episode, which, by definition, must last for at least 4 days. Various studies found distinct patterns of symptoms and familial inheritance for BP II disorder. BP II is commonly underdiagnosed or misdiagnosed. Making an early and accurate diagnosis of BP II is utmost importance in the management of BP II disorder. The clinician should have this diagnosis in mind when he is facing a patient presenting with mood problems, particularly unipolar depression. Quetiapine and lamotrigine are the only agents with demonstrated efficacy in double-blind RCT. Although the evidence for the use of lithium in long-term therapy is largely based on observational studies, the many years of close follow-up, comparatively larger subject numbers, and 'harder' clinically meaningful with bipolar disorder outcomes measures, enhance our confidence in its role in treating BP II. With respect to short-term treatment, there is some limited support for the use of risperidone and olanzepine in hypomania and for fluoxetine, venlafaxine and valproate in treating depression. The current clinical debate over whether one should use antidepressants as monotherapy or in combination with a mood stabilizer when treating BP II depression is not yet settled. There is a need for large, well-designed RCTs to cast more definitive light on how best to manage patients with BP II disorder.

Key words: *Bipolar, disorder, antidepressants, depression*

MANAGEMENT OF BIPOLAR II DISORDER

The term bipolar II (BP II) was first used about 30 years ago to differentiate patients with recurrent depressive episodes and hypomania from those with classic bipolar disorder, ie, bipolar I (BP I), which is characterized by both depressive and manic episodes, and from those with recurrent major depression.[1] Later, the BP II disorder was recognized as a distinct subtype in the DSM-IV classification (APA. 1994). DSM-IV criteria for BP II requires the presence or history of one or more major depressive episode, plus at least one hypomanic episode, which, by definition, must last for at least 4 days. Various studies found distinct patterns of symptoms and familial inheritance for BP II disorder.[2] Preliminary imaging[3] and biochemical[4] studies that have separately examined subjects with BP I and BP II disorders have found differences in these groups which further support the view that BP II disorder is a discrete diagnostic entity.

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The National Comorbidity Survey Replication[5] that included 9,282 subjects reported a lifetime prevalence of BP II of 1.1% (12-month prevalence 0.8%). The mean age of onset was 20.3 years. Only a minority (15.4%) of subjects with BP II in the community received appropriate medication (defined as lithium/valproate, anticonvulsants, or antipsychotics). Major part of the treatment was given owing to their comorbid disorders. Other epidemiological studies have reported

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a lifetime community prevalence of about 5%, and that 50% of depressed outpatients have BP II.[6] A 1-year naturalistic follow-up of patients with BP I (n=405) and with BP II (n=102) confirmed that patients with BP II are symptomatic approximately 50% of the time.[7] The authors pointed out that patients with BP I and BP II had the same tendency toward mood instability. Therefore, accurate diagnosis of the BP II condition is very important so that appropriate treatment can be given.

There seems to be considerable agreement that bipolar disorder, including BP II, is commonly underdiagnosed or misdiagnosed.[8-11] A study showed that it takes on average 12 years before patients who seek mental health services are appropriately diagnosed with BP II or BP NOS (periods for BP I and unipolar depression were 7 and 3.3 years, respectively).[8,9] There are two important factors that may account for this late delayed diagnosis. Firstly, both patients and clinicians may fail to recognize hypomania reliably. The difficulty for clinicians to diagnose hypomania may be related to one of its essential defining criteria in the DSM-IV that the change in mood state, unlike mania, is not severe enough to cause marked impairment in social or occupational functioning (psychotic symptoms and hospitalization must also be absent).[9,12] Clearly, drawing diagnostic lines accordingly may be too subjective. In addition, although the DSM-IV-TR requires a 4-day duration of symptoms to diagnose hypomania, hypomanic swing is often very brief and just lasts 1-3 days.[13] Furthermore, patients and their family members often do not recognize hypomania as a pathological state, and they frequently do not volunteer a history of hypomanic symptoms. Secondly, there is a tendency to overlook the close relationship between recurrent depression and BP II, and thus the failure to probe patients and their families for features of mood swing to the other side.[9-11] Indeed, several authors have reported significantly increased rates of BP II, somewhere in the order of 30-50%, when depressed outpatients are systematically interviewed for a history of hypomania.[13-16] In a study of 168 outpatients presenting with a major depressive episode, 61% were diagnosed with BP II when they were systematically probed for past symptoms and behaviours suggestive of hypomania, even when screening questions for past hypomanic mood were initially negative.[17] It was also shown that BP II could be reliably diagnosed when experienced psychiatrists use semistructured interviews.[18] The rate of diagnosis can also be improved by the use of screening instruments such as mood disorder questionnaire (MDQ) and hypomania checklist 32 (HCL-32). MDQ has good sensitivity (0.73) and very good specificity (0.90)[19] whereas HCL-32 has a sensitivity 0.8 and specificity 0.51 for both BP I and BP II disorders.[20] Both MDQ and HCL-32 have been translated and validated in versions in different languages.

The increased awareness of the prevalence of BP II, coupled with a growing appreciation of the disability and suffering it inflicts, makes finding effective treatment strategies a task or considerable importance. There is substantial evidence to suggest that the rates of psychosocial impairment and use of mental health services are comparable between BP I and II patients,[21,22] as are rates of suicide. Some authors also report a greater tendency of suicide for the BP II subtype. In addition, BP II patients have been described as having higher rates of rapid cycling (Baldessarini 2000), and significant comorbidity.[16,21] The National Comorbidity Survey Replication[5] also found that the clinical severity and role impairment due to major depressive episode was more common in BP II than for BP I cases. Other studies have also found that BP II is associated with rates of disability that are comparable to Bipolar disorder I.[23] The notion that BP II is a milder form of BP I is no longer tenable.[21,24] In fact BP II disorder is sufficiently different from BP I to deserve particular attention.[25,26]

The uncertainty surrounding the diagnosis of BP II extends to decisions about its treatment. How best to treat patients with BP II remains controversial. There are limited data on the pharmacological treatment of the BP II disorder, in spite of the growing recognition of this disorder. There are very few large randomized, double-blind, placebo-controlled trials involving only BP II patients. Making recommendations for the treatment of BP II patients basing on evidence derived from studies of BP I patients seems not appropriate.

Making an early and accurate diagnosis of BP II utmost importance. Moreover, it is also a big challenge in choosing the most appropriate and effective therapies. Proper consideration of short-term and long-term treatment strategies allows us to consider many critical issues. There are a few questions that we have to answer: Is there a scientific basis for contemporary pharmacological treatment of BP II? Are mood stabilizers (lithium or anticonvulsants) known as central to the treatment of BP II as they are to BP I? Can antidepressants be used in the treatment of BP II depression? If antidepressant is to be used, can it be used as monotherapy or it must be used in conjunction with mood stabilizers? Is there a role for antidepressants in maintenance treatment to prevent relapse? Can antipsychotics, particularly the newer generation antipsychotics, whether as monotherapy or in combination with mood stabilizers, be used in the management of hypomania? We certainly want to have our therapeutic choices be guided by sound evidence.

BP II disorder has become a focus of research interest in the past decade, especially with the emergence of new agents such as Lamotrigine and newer generation antipsychotic drugs in the treatment of bipolar disorder. Unfortunately, this new interest in BP II disorder is not so far reflected in large randomized and placebo-controlled studies. Given the difficulties in reliably diagnosing BP II, and thus identifying and recruiting appropriate research subjects, it is difficult to get sufficiently large subject numbers to provide statistical power in drug trials or studies on treatment strategies. Small number of subjects and thus weak statistical power may lead to false conclusions that two treatments are equally efficacious when a difference in outcome cannot be demonstrated. Apart from the small sample size, most studies investigating the pharmacotherapy of BP II are methodologically limited. Many of these studies are open, observational, or retrospective studies only. Therefore, the findings in clinical studies can only be interpreted with caution. At the end of the day, we must work with what we have available. However, it is important that clinicians treating BP II patients should not draw too strong conclusions about the effectiveness of the various therapeutic agents without taking into consideration of the actual condition of the patient.

Due to the lack of large randomized and placebo-controlled studies to guide the treatment of BP II disorders, most contemporary treatment guidelines on the treatment of BP II are mainly consensus based and follow those for the treatment of BP I. It seems that the CANMAT and world federation of societies of biological psychiatry (WFSBP) are the only guidelines that have separate consideration for BP II/hypomania. In the canadian network for mood and anxiety treatments (CANMAT),[27] there is a section devoted to the recommendations on BP II disorder. In the WFSBP guideline, only recommendation for maintenance treatment of BP II disorder[28] is available. The WFSBP considers hypomania as a milder form of mania. There is only a section on the management of hypomania in the guideline on the treatment of acute mania rather than the management of acute hypomanic state in BP II disorder, both in the initial version[29] and the update version.[30] Other popular clinical guidelines, including the American Psychiatric Association guideline,[31] Australian and New Zealand guideline,[32] National Institute for Health, and Clinical Excellence clinical guideline[33] and the Texas Implementation of Medication Algorithms (known as the Texas Medication Algorithm Project previously) [34] do not include recommendations specific to the treatment of BP II disorder.

Despite belonging to the same spectrum, the natural history and longitudinal course of BP I and II disorder is distinct enough to allow for separation as separate entities.[24] As BP II has been well established as a distinct diagnostic entity, simply extending guidelines for BP I is inadequate or even inappropriate.

In the paper, the discussion in the treatment of BP II is divided into three parts, namely, the treatment of acute hypomania, the treatment of acute depression, and the prevention of relapse of either hypomania or depression or maintenance treatment.

THE MANAGEMENT OF BIPOLAR II ACUTE HYPOMAIA

As stated above, most of the major treatment guidelines do not have separate consideration for the management of BP II mania. Some guidelines (eg, WFSBP) took the view that hypomania may be known to be the prelude to full-blown mania in individual patients, in which case treatment should be as for mania. Actually in the WFSBP guideline for the management of hypomania,[30] it was suggested that hypomania is not a common point for the initiation of new treatment. It is recommended that if no further prophylaxis is planned, short-term treatment with drugs that have a good safety profile, well-tolerated, and a relatively rapid onset of action can be given in order to minimize the danger that hypomania develops into mania within the next days. Either valproate or an atypical antipsychotic may be the best choice.

Although most antipsychotics are effective in mania, there is little evidence on whether they are also effective in hypomania. If the differences between mania and hypomania are quantitative than qualitative, it can be assumed that effective treatments for mania can be readily applied to hypomania. To address this general presumption, Vieta *et al*.[35] conducted a study exclusively exploring the role of a newer generation antipsychotics, namely risperidone, in the treatment of hypomania associated with BP II. Forty-four consecutive BP II patients experiencing a hypomanic episode with YMRS score >7 were enrolled and followed prospectively for 6 months in this open-label, observational study. All patients met DSM-IV criteria for BP II. Outcome measures to determine efficacy included the Spanish version of the YMRS, CGI, and HAM-D; a positive response was defined as a 50% reduction from the patients' baseline YMRS score. Of the 44 subjects, ten subjects dropped out, two of which were lost to follow-up, and a last observation carried forward analysis was employed to account for these losses in determining the positive response rate. At the study endpoint, 73% of patients were considered responders in terms of their YMRS scores ($P<0.0001$);

according to the CGT, 60% of patients were rated asymptomatic, while 78% were considered improved or much improved ($P<0.0001$); and a significant decrease in HAM-D was reported (8.8-2.6, $P<0.0001$). A statistically significant difference was not found when patients receiving monotherapy ($n=14$) were compared with those receiving Risperidone in combination with mood stabilizers ($n=30$). However, because of the small sample size and high dropout, it is not clear how meaningful this outcome was for patients.

In a 9-week open trial of olanzapine in 25 subjects with bipolar disorders presenting with depressed or elevated mood reported a 60% response rate (CGI≤2).[36] Though results for the ten BP II patients included in the study were not reported separately, the authors noted that a significant difference across bipolar subtype was not found. Again, because of the small number of subjects, there is doubt on whether the study was adequately powered to detect any difference between the two subtypes if it was in fact present.

In another study in mild to moderate mania, olanzapine was significantly more efficacious than placebo but not valproate at 3 weeks and significantly more efficacious than valproate at 12 weeks.[37] However, it is unclear whether this positive results for olanzapine can be extrapolated to hypomania in BP II disorder.

Lithium and other anticonvulsants are well studied in the treatment of mania in BP I disorder. However, there is no large-scale well-designed RCT study in the treatment of acute hypomania in BP II disorder.

Apart from pharmacotherapy, psychosocial intervention may be considered. In contrast to the more severe manic states, hypomania may be still manageable to some extent by behavioral interventions in combination with pharmacotherapy. These inventions may centre around modifications of daily routines, eg, maintaining a natural sleep wake cycle, stress avoidance, and some elements of cognitive behavioral therapy (CBT).[34,38] Actually in the WFSBP guideline for the management of hypomania,[30] it was suggested that hypomania is not a common point for the initiation of new treatment.

ACUTE MANAGEMENT OF BIPOLAR II DEPRESSION

Despite the fact that hypomania being the hallmark of the disorder, patients spend far more time in and experience greater distress from their depressed states. Therefore, effective treatment for BP II depression is perhaps the most important issue in BP II.

Unfortunately, the majority of patients with BP II depression are inadequately treated. The National Comorbidity Survey Replication (9,282 subjects) has shown that only about 16% of patients with BP II received appropriate medication which was defined as given lithium/valproate, anticonvulsants or antipsychotics, while 60% received no medication.[5] Similarly, data from the Jorvi Bipolar Study[39] found that only 44% of subjects with BP II were treated with an anticonvulsant or lithium. Patients with BP II were significantly more likely to receive treatment with an antidepressant compared to subjects with BP I. Only 31% of patients with BP II were considered to be receiving adequate pharmacotherapy. In a community sample of newly diagnosed patients with BP II ($n=1\ 001$), 55.5% were prescribed an antidepressant (65% of them had antidepressants as monotherapy), compared to 31% who were prescribed lithium, an anticonvulsant, or an antipsychotic.[40]

The best available evidence for the acute treatment of bipolar depression comes from studies on quetiapine. There are now four large RCTs demonstrating the efficacy of quetiapine monotherapy in combined groups of patients with BP I or II depression: BOLDER I[41] and II,[42] and two additional eight-week RCTs, EMBOLDEN I[43] and II.[44] These four trials included substantial numbers of patients with BP II depression: BOLDER I ($n=181$) and II ($n=170$), EMBOLDEN I ($n=303$) and II ($n=262$). In patients with BP II depression in BOLDER I and EMBOLDEN I, improvements in MADRS were numerically but not statistically significant at endpoint (week 8), although they were significant at various weekly visits. In contrast, the BOLDER II and EMBOLDEN II trials showed significant benefits in the patients with BP II. In addition, a post hoc pooled analysis of the patients with BP II depression from both BOLDER trials ($n=351$) found that both doses of quetiapine demonstrated significant benefits as early as week 1, which were sustained throughout the 8 weeks.[45] Two subanalyses of the BOLDER I data showed that among patients with BP II depression, quetiapine was effective in patients with rapid cycling,[46] but anxiety scores (HAM-A) were not significantly improved.[47] However, in the pooled analysis of BOLDER I and II, the changes in HAM-D, HAM-A, and CGI were significantly greater for both quetiapine groups versus placebo, and Quetiapine 600 mg/day was effective in both rapid and nonrapid cycling depression.[26] Based on statistically significant improvements in two RCTs and numerically superior improvements in two additional trials, quetiapine monotherapy can now be recommended as a first-line treatment.

Other atypical antipsychotics have also been studied but no controlled studies are available so far with

antipsychotics in BP II disorder. Olanzapine in combination with fluoxetine was found to be effective in BP I depression,[48] but it is unclear whether it would work in BP II as well. On the other hand, an 8-week open trial of Ziprasidone monotherapy in 20 patients with BP II depression found the drug at a relatively low dose appears to be a rapid, effective, and generally well-tolerated treatment for BP II patients experiencing major depression. There was significant improvement in depression scores within 1-2 weeks, which were sustained to end of treatment.[49] However, larger placebo-controlled trials are needed to confirm these findings.

Evidence from several open studies supports the effectiveness of lithium, lamotrigine, and valproate in the acute treatment of patients with BP II depression. A randomized open study comparing lithium and lamotrigine in BP II acutely depressed patients concluded that both were effective and there were no major treatment response differences between them.[50] A 16-week, open, randomized trial assessed the efficacy of lithium (n=56) or lamotrigine (n=46) monotherapy in patients with acute BP II depression.[45] Mean MADRS scores significantly decreased from baseline in both groups (Lamotrigine from 28.9 to 12.5 and lithium from 29.9 to 15.2), and there was no differences between the two treatments. There were no differences in response between patients with rapid cycling (72% of patients) or without, although there was a high dropout rate in the rapid cycling group (42% of patients).

Valproate is bot only used as monotherapy, but also as augmentation. A 12-week open trial of valproate sodium monotherapy in 19 BP II depressed outpatients showed a statistically significant response rate (P<0.001) of 63%.[51] It was also shown to be effective in a 7-week, open trial in 28 patients with BP II depression.[52] Response was statistically similar with monotherapy (45%, n=21) and adjunctive therapy (71%, n=7). Although these data are suggestive, the sample size was too small and the results require confirmation from well-designed RCTs with larger number of subjects.

Much controversy surrounds the use of antidepressants in BP II depression.[9,53,54] In BP II patients it is very important to control depressive episodes. The challenges for clinicians in managing patients with BP II is to treat acute episodes of depression without causing switches into hypomania. There may be situation that antidepressant treatment may be useful.[55] Unfortunately the treatment of BP II disorder with antidepressants is still an understudied area. Most recommendations for the treatment of BP II depression are derived from findings of studies that have included both BP II and BP I patients. Like in the treatment with antidepressant (especially tricyclic antidepressant) in BP I patients, the risk of switching from depressive to hypomanic states when treated with antidepressants is also a concern in the use of antidepressant in BP II patients. However, the risk-benefit ratio for antidepressant use in BP II is still an unresolved issue. Whether the same risks and pitfalls associated with treating depression in BP I readily apply to BP II has not been conclusively demonstrated. Furthermore, the risk of hypomanic switch or cycle acceleration with antidepressants in patients with BP II is less than in those with BP I is still controversial. The risk of antidepressant-induced cycle acceleration has been reported by some authors to be more likely in BP II patients than their BP I counterparts.[53] However in this study, the cases were taking the older generation (heterocyclic) antidepressants. In more recent studies in which patients were taking the newer generation antidepressants (eg, SSRI, venlafaxine, and buproprion), BP II patients have a lower switch rate compared to BP I patients.[56,57]

There is some evidence for antidepressant monotherapy including fluoxetine,[58,59] venlafaxine[60,61], and citalopram.[62] In a small, 9-month, randomized, crossover trial involving ten treatment-naive patients with BP II, patients received SSRI treatment had a significant reduction in depression severity, percentage of days depressed or high, and percentage of days impaired, without illness destabilization, when compared with placebo.[62] Furthermore, a post hoc analysis of a placebo-controlled RCT of antidepressant monotherapy in 248 unipolar and 62 BP II patients found that both groups benefited comparably from active treatment, with no switch noted in the BP II patients.[63]

Amsterdam and his colleagues have specifically addressed the use of antidepressants in BP II patients in three studies.[58,60,61] The largest of these studies[58] compared acute and continuation phase treatment with fluoxetine monotherapy in 89 BP II patients with age and gender matched, and 661 unmatched, unipolar (UP) patients. Although all subjects met criteria for a major depressive episode according to semistructured clinical interviews based on the structured clinical interview for DSM III-R, BP II patients were identified by retrospective chart review, presumably based on DSM-IV criteria. Subjects were part of a larger study, comprised of a 12-week, open label, treatment phase and a 50-week, double blind, placebo-substitution, relapse-prevention phase, designed to test the efficacy and safety of fluoxetine in the prevention of depressive relapse. Outcome measures were based on HAM-DI7 scores, with response defined as 50% reduction. Fluoxetine was effective in both short-term treatment of the depressive episode and

in relapse prevention for patients in remission over a 1-year follow-up period. Short-term treatment was shown to be similarly efficacious for BP II and UP patients; a nonsignificant trend toward earlier reduction in HAM-D17 scores was observed in the BP II group. Likewise, survival analyses at 26, 50, and 62 weeks, demonstrated similar relapse rates between the two groups. It is worth highlighting that, by the 26th, 50th, and 62nd weeks the BP II patients numbered 28, 19, and 8, respectively (with comparable figures in the matched unipolar group). Manic switch episodes, ascertained retrospectively, were reported for 3.8% (three of 80) BP II patients, no matched UP patients and two of 661 unmatched UP patients during short-term treatment, and 3.6% (one of 28) BP II and 0.8% (two of 241) unmatched UP patients during the relapse-prevention phase. None of the manic switch episodes apparently met DSM criteria for mania. However, it should be noted that this retrospective evaluation may not have detected all cases of antidepressant-induced hypomania. Furthermore, the dropout rate was high. By the end of the relapse-prevention phase (62nd week) the sample size had dropped to only eight patients, a number far too small on which to base strong conclusions that UP and BP II responded similarly, both in terms of relapse rates and the induction of hypomania.

Venlafaxine has also been evaluated. In a small, 6-week, prospective trial,[60] 30 UP and 16 BP II depressed patients were randomly assigned to receive once or twice daily venlafaxine monotherapy following a 1-week placebo lead in. A semistructured SCID interview was used to diagnose major depressive episodes; at entry, and after the first week, subjects had baseline HAM-D21 scores of 20. It is not clear how the diagnosis of BP II was established. Outcome measures were based on the HAM-D, Montgomery-Asberg depression rating scale (MADRS) and CGI, completed weekly for the first month and then again at 6 weeks. Although similar overall efficacy between the two groups was shown, BP II patients who completed the trial demonstrated a statistically significant more rapid reduction in their HAM-D ($P<0.03$) and MADRS ($P<0.02$) scores. However, when patients who did not complete the study (nine unipolar and two BP II) are accounted for by a last observation carried forward analysis; a nonsignificant trend is observed instead. No episodes of venlafaxine-induced switching were observed. Another 12-week, open, randomized trial in 83 patients with BP II depression found that there were higher response and remission rates with venlafaxine compared to lithium.[64] Discontinuation rates were significantly lower with venlafaxine compared to lithium, and there was no evidence of hypomanic switch in either group.

On the other hand, bupropion does not have positive result as in the case of fluoxetine and vanlafaxine. In a 16-week RCT of adjunctive Bupropion in 20 patients with BP II depression who had an inadequate response to 8 weeks of Lamotrigine found no differences between bupropion and placebo on either depression or mania scores.[65] However, the number of subjects was too small to make any definite conclusion on the effectiveness of the drug.

All these studies have shown that there is a low rate of treatment emerge hypomanic switch with antidepressant monotherapy in BP II patients. Actually, the overall lower propensity to develop hypomanic symptoms of BP II to I patients has also been shown.[66] According to a meta-analysis of available data for antidepressant treatment in BP II patients, the rate of treatment emerge hypomanic switch during acute treatment may be intermediate between BP I and unipolar depression.[67]

The STEP-BP study,[68] comparing adjunctive antidepressants (bupropion or paroxetine) plus lithium or valproate and lithium or valproate alone, for up to 26 weeks, included 114 patients with BP II. In the combined sample (BP I and BP II) as well as between BP I and BP II patients, rates of durable recovery (8 consecutive weeks of euthymia) were comparable for adjunctive antidepressants and lithium or valproate alone. Although the antidepressants did not increase the risk of manic switch, it did not have any added benefit when the patient is already receiving a mood stabilizer. Hence, antidepressant treatment may not be useful for every patient and perhaps should be reserved for those patients who have inadequate response to other mood stabilizers such as lithium, anticonvulsant, and newer generation antipsychotic medication.

As far as the switch into mania with antidepressant use is concerned, all the larger studies suggest that this risk is quite modest, at least when combined with a mood-stabilizing medication, and seem to be generally lower in BP II than in BP I patients. However, data on the long-term effect of use of antidepressant in BP II is scarce. Therefore, the appropriate role for antidepressants in the acute and long-term treatment of BP II disorder will need to be defined by future well-controlled studies.

MAINTENANCE THERAPY FOR BIPOLAR II DISORDER

Studies in treated samples demonstrate that BP II patients spend approximately half of their lives with depressive symptoms.[24,7] The focus of long-term therapy for patients with BP II is prevention of depressive episodes.

Concerning the maintenance treatment of bipolar disorders, lithium is the best-studied agent. The effectiveness of lithium maintenance treatment in BP I is firmly established and well recognized.[69-71] The case for BP II, however, has not been clearly clarified. Due to a lack of evidence, it has been suggested that lithium may not be as effective in BP II as it is in BP I. However some large-scale naturalistic studies had already showed the effect of lithium in the prevention of depressive episodes in BP II patients.[72,73,21] Tondo studied the lithium maintenance treatment in BP I and II patients and showed that lithium had superior benefits in BP II patients. There was significantly greater reduction of episodes per year and of the percentage of time ill. Reduction of depressive morbidity was similarly strong in both BP I and II diagnoses. Tondo in another study a few years later[74] found similar results and concluded that long-term lithium maintenance treatment in compliant patients without comorbid substance use disorder remained effective, even in subgroups of supposedly poor prognosis, such as patients with mixed episodes, psychotic episodes, or rapid cycling. However, only about a quarter of the patients in this study experienced complete remission during maintenance treatment, suggesting that full protection was not commonly achieved with lithium or with alternative treatments. Some clinical factors found early in the course of illness (age at illness onset and a longer interval between first and second lifetime episodes) or early in treatment with lithium (rapidity of recovery from the index episode at the start of lithium treatment, and a longer interval to the first subsequent recurrence) were significantly associated with a better long-term treatment response as indicated by the overall proportion of the time of illness during treatment. Although the evidence for the use of lithium in long-term therapy is largely based on observational studies, the many years of close follow-up, comparatively larger subject numbers, and "harder" clinically meaningful outcomes measures (eg, hospitalization), enhance our confidence in its role in treating BP II patients.

Lamotrigine is a newly emerged anticonvulsant drug in the treatment of bipolar disorders. In the late 1990's, some open case series with smaller number of BP II patients[75-77] gave supportive evidence to the use of lamotrigine as a maintenance agent. Lamotrigine is the only anticonvulsant agent with demonstrated efficacy as monotherapy in BP II cases in double-blind RCT. With a sample of rapid-cycling bipolar patients, Calabrese *et a1*.[78] studied the safety and efficacy of lamotrigine in a double-blind, placebo-controlled study. The results suggested that lamotrigine might be a well-tolerated and effective mood stabilizer with prophylactic properties when used as monotherapy in some patients with rapid cycling. Secondary analysis of the study showed that differences favoring lamotrigine were consistently greater for BP II than BP I patients and suggested that it may be of special value in BP II patients.[79] For the 52 patients with BP II disorder, median time to intervention was significantly greater in those receiving lamotrigine (17 weeks for lamotrigine versus 7 weeks for placebo). However, the positive effect of lamotrigine in BP II was a post hoc finding and related to reduction of depression only. Also, because its positive effect was only shown in a subgroup analysis of 54 rapid-cycling BP II patients, the generalizabilty of these results cannot be established. Subsequently, two retrospective, naturalistic studies including a total of 61 patients with BP II reported clinical improvements with lamotrigine, primarily used in combination with antidepressants or lithium/valproate, for an average of 20 months.[80,81] These data provide additional support for the use of adjunctive Lamotrigine in patients with BP.

There is little data on the efficacy of valproate compared to lithium and lamotrigine. Some evidence of usefulness of valproate comes from the trial by Calabrese and Delucchi.[82] Thirty of the 55 individuals with rapid cycling had a BP II disorder. Interestingly, responsiveness to valproate appeared to be slightly better in those BP II patients compared to BP I. Furthermore, valproate has marked antimanic and mixed state efficacy but the antidepressant properties less impressive. In another small open trial over 3 years, valproate was effective in reducing mood episodes in patients with BP II disorder and rapid cycling.[83]

There was a suggestion for a higher prophylactic efficacy of carbamazepine versus lithium in BP II patients compared to BP I.[84] BP I patients without mood-incongruent delusions and without comorbidity had a lower rehospitalization rate with lithium than with carbamazepine prophylaxis (P=0.005). For other subjects (including BP II/not otherwise specified, mood-incongruent delusions, comorbidity), a trend in favor of carbamazepine was found. Lithium group also had a positive association between hospitalization rate in this latter group of patients while this association was negative for carbamazepine. The author concluded that lithium seemed to be superior to carbamazepine in treating BP I cases. Other patients (which included BP II) might profit more from prophylaxis with carbamazepine, which seems to have a broader spectrum of activity. However one randomized trial versus carbamazepine[84,85] showed equality of lithium prophylaxis against carbamazepine.

Although Quetiapine is recommended as a first-line option for the acute treatment of BP II depression, long-term data are not yet available. The pooled analyses from EMBOLDEN I and EMBOLDEN II trials for

maintenance treatment of BP II depression may give more data on its effect on long term treatment.

The use of tricyclics in maintenance treatment is discouraged due to their probable propensity to induce rapid cycling.[53] However, long-term treatment with modern antidepressants should not be ruled out, although the evidence is still preliminary.[86] As mentioned earlier, the switch rates into mania for BP II patients treated with modern antidepressants are still a subject of controversy,[87] but if switches occur they are more likely of moderate severity.[88] Therefore, if antidepressant drugs has to be given for any particular reasons, the patient should be monitored closely.

Apart from the morbidity associated with severe depressive episodes,[89,21] BP II disorder is also characterized by with more interepisodic.[90] Furthermore, it also has a high degree of suicidality.[91-93] There is no clear evidence that a specific mood stabilizer is superior to others in BP II disorder. Thus, in the choice of mood stabilizers, those which show preventive effects mainly on depression in BP I disorder, such as lamotrigine or suicidality, such as lithium,[94] may be the agents of choice. However, other clinical factors have also to be considered in the choice of drugs. Furthermore, it is reasonable to continue the mood stabilizer that was effective in acute treatment. For those patients receiving a mood stabilizer for the first time, general illness features may also guide the selection of a treatment.

CONCLUSION

Making an early and accurate diagnosis of BP II utmost importance in the management of BP II disorder. The clinician should have this diagnosis in mind when he is facing a patient presenting with mood problems, particularly unipolar depression. The patient and family members should be probed about hypomanic symptoms. It is worthwhile to use screening instruments such as MDQ or HCL-32 which is relatively easy to administer and not time consuming.

Overall, broad recommendations based on the studies conducted so far cannot be easily made because there is a lack of large-scale well-designed controlled studies in this area. However, some provisional conclusions can be drawn about both the short-term and long-term treatment of BP II disorder. Quetiapine and lamotrigine are the only agents with demonstrated efficacy in double-blind RCT. However, in the case of lamotrigine, because its positive effect was shown in a subgroup analysis of 54 rapid-cycling BP II patients, the generalizabilty of these results is not established. Although the evidence for the use of lithium in long-term therapy is largely based on observational studies, the many years of close follow-up, comparatively larger subject numbers, and 'harder' clinically meaningful with bipolar disorder outcomes measures (eg, hospitalization), enhance our confidence in its role in treating BP II. With respect to short-term treatment, there is some limited support for the use of risperidone and olanzepine in hypomania and for fluoxetine, venlafaxine and valproate in treating depression. Whether these agents can be effectively and safely used in long-term treatment remains to be seen.[95,96]

The current clinical debate over whether one should use antidepressants as monotherapy or in combination with a mood stabilizer when treating BP II depression is not yet settled. If antidepressants are prescribed, the patients and family members ought to be both educated about the risks of mood destabilization and close monitoring is needed. The clinicians must remain alert for signs of antidepressant-induced mood instability. Certainly, more placebo controlled, double blind, randomized trials with large number of subjects should be conducted.

Applying the efficacy data on BP I or from unipolar depression to the management of BP II disorder is inadequate or even inappropriate. There is a need for large, well-designed RCTs to cast more definitive light on how best to manage patients with BP II disorder. Also, the studies should specifically recruit adequate numbers of patients with BP II instead of a mixed sample with BP I and other disorders in the spectrum. It is with great interest that we await the results of better quality research and drug trials to guide our choice of drugs.[96]

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