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Bipolar II Disorder: Current and Future Treatment Options

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Background. *Bipolar II (BPII) disorder is a significant public health problem in the United States, and there is a dearth of studies of effective treatment modalities to deal with the recurrent major depressive episodes that accompany the disorder. This review attempts to summarize available data on agents useful in treating patients with the disease.*
Methods. *English language controlled clinical trials involving BPII patients obtained from an extensive Medline search were critically reviewed.*
Results. *Agents that have potential utility in the treatment of BPII are profiled, based on their efficacy in bipolar I (BPI) or unipolar depression.*
Conclusions. *The most efficacious agents are likely those with bimodal stabilizing properties, such as lithium, carbamazepine, and quetiapine. In fact, on the strength of favorable efficacy data obtained in patients with major depressive symptoms accompanying bipolar disorder, quetiapine recently became the first agent to be indicated by the FDA for monotherapeutic use in the treatment of bipolar depression, including BPII depression. Aside from the aforementioned agents, lamotrigine also shows promise in the treatment of BPII.*

Keywords Bipolar II, Mania, Mixed, Depression, Mood stabilizers

INTRODUCTION

A significant amount of literature exists on the treatment of bipolar- and unipolar-related depression (1,2). However, there remains a paucity of data on successful pharmacotherapy for the symptomatically divergent bipolar type II (BPII) disorder. There is also significant controversy regarding the disorder, from the criteria used to diagnose it, to the treatment strategies used to manage it successfully. Consequently, there are a limited number of proven treatment modalities for patients with BPII.

This review summarizes BPII, discusses data published to date concerning treatment of patients, and focuses on the therapies with the best chance of success in ameliorating disease symptoms.

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Characterization of BPII

Identified in 1976 by Dunner and colleagues (3,4), BPII was originally characterized by severe depressive episodes that required hospitalization together with mild hypomanic episodes that did not. Hospitalization has been seen by many as an artificial criterion, and this definition has since changed,

though the disorder has become no less troublesome. While long recognized by many researchers and diagnosed by many clinicians, BPII did not become incorporated into the American Psychiatric Association's *Diagnostic and Statistical Manual* until the fourth edition in 1994 (*DSM-IV*) (5). This delayed official recognition has contributed to the dearth of controlled studies for this condition.

The classification of BPII as an autonomous entity distinct from bipolar I (BPI) disorder is supported by data from several familial studies, which show that BPII is more prevalent in the relatives of those with previous diagnoses of the disease (4,6,7,8). These studies suggested a genetic link not only in BPII, but in BPI as well. Accordingly, a careful analysis of BPI and BPII proband families by Simpson and associates indicated that BPII was the most common affective disorder in both (9). Though BPII clearly affects a large number of people (a recent study by Hirschfeld and colleagues found a lifetime prevalence of nearly 4% for BPI/BPII (10), more research is required before this result can be extrapolated to the whole of the bipolar population. This estimate of the lifetime prevalence of BPI and BPII disorders is probably conservative as it does not take into account subsyndromal individuals who fall just below the threshold in terms of meeting fully the criteria for BPI and BPII disorders. As reported by Judd and Akiskal (11), a more broadly defined bipolar spectrum disorder to include those with subthreshold bipolarity yields a lifetime prevalence rate of 6.4% of "bipolarity." These patients may indicate a high prevalence of subthreshold cases.

There is evidence that BPII can be misdiagnosed as major depressive disorder (12). Recent data suggest that young adults with early onset-major depressive disorder may be at high risk for progression to bipolar disorder (13). Preliminary results indicate that antidepressant-induced hypomania and high hypomanic symptom counts, regardless of the duration, may help identify those who are likely to have a bipolar spectrum illness, but do not meet *DSM-IV* criteria for bipolar disorder. A recent prospective longitudinal study of the natural history of BPII reveals a clinical course that includes the full severity range of depressive and hypomanic symptoms but is dominated by depressive symptoms of minor and subsyndromal severity (14). These data lead some to conclude that BPII is most likely subthreshold bipolar disorder. There is some question as to whether BPII is in fact the predominant and truest form of bipolar disorder or is a possible intermediate disorder, halfway between unipolar depression and full-blown BPI.

Long-term studies do not support the bipolar continuum theory, however. For example, Coryell and associates have reported that BPII represents a stable condition, with less than a 5% chance of depressed patients progressing to BPI disorder over an 11-year time period (15). Additional support for the concept of BPII as an independent disease can be derived from treatment studies such as the one by Faedda and colleagues that demonstrated that none of the BPII patients in their study experienced a manic episode up to 1 year after lithium discontinuation, while 50% of the BPI patients experienced a manic episode (16).

Criteria for Diagnosis

DSM-IV set forth general criteria for the diagnosis of BPII as an independent entity (5). This definition of the BPII subtype maintains that a patient can be diagnosed with the disorder if he or she has experienced at least 1 hypomanic episode (a minimum of 4 days' duration) and 1 or more major depressive episodes. Furthermore, the *DSM-IV* diagnostic criteria require a lack of prior manic or mixed episodes. The criteria for BPI disorder differ in that diagnosis requires the presence of at least 1 manic or mixed episode, though patients may have experienced hypomanic or depressive episodes as well (5).

Interestingly, the minimum duration requirement of 4 days for diagnosis of a hypomanic episode is the subject of current controversy. Angst and associates have recently suggested that the prevalence of BPII would be increased to 5.3% with a reduced hypomanic episode criterion of 1 to 3 days (17), a finding similar to Judd and Akiskal's prevalence of 6.4% of bipolarity when criteria are loosened (11).

Misdiagnosis of BPII

In contrast to the disruptive manic phase experienced by BPI disorder patients, those with BPII-associated hypomanic episodes seek medical assistance infrequently (18,19). This finding suggests a possible reason that the historically reported prevalence of BPII is so low. Type II bipolar patients almost invariably seek medical attention during the depressive phase of their illness (19). Presentation with major depression together with the difficulty in diagnosing a hypomanic episode by patients' historical report may lead to an incorrect diagnosis of unipolar depression, and it has been estimated that up to 37% of those with bipolar disorder are incorrectly diagnosed with unipolar depression (20).

The potential severity of BPII is exemplified in a study by Kupfer and associates, who found that more than 60% of patients with bipolar disorder had experienced a depressive episode within the last 6 months (21). Furthermore, BPII patients tend to have a higher lifetime rate of attempted suicide compared to both unipolar depression and BPI with 24% of suicides being completed by BPII subjects compared to 17% by BPI subjects, and 12% for unipolar depressed patients (22). Obviously, diagnosing these patients expeditiously and correctly is of primary concern.

Increasing the confidence of a diagnosis of BPII is currently a topic of much interest. Several factors can provide a clearer demarcation line between BPII and unipolar depression. Such factors include but are not limited to age of onset, course of illness, response to treatment, family history, and current signs and symptoms. Bipolar II disorder is typically seen earlier in life than unipolar depression (4). A significant family history is also seen in patients with BPII (4,7,8). Mismanagement of the disorder through inappropriate medication and treatment can be both costly and unproductive. Increasing diagnostic confidence

in BPII could potentially alleviate this predicament. However, the most important factor is increasing the ability of clinicians to recognize the hypomanias that are central to the diagnosis. In this regard, the recent reports of specific mood questionnaires or modifications of existing tools to better diagnose hypomania are of interest (23).

METHODS

A literature review was performed for clinical trials published after January 1994, the time that BPII became an accepted diagnosis in the *DSM* series. References were limited to those analyzing data from BPII patients separately from BPI patients. Randomized controlled trials as well as observational and retrospective trials were included in the review. The following key words were used in a Medline literature search to identify referenced articles: "bipolar disorder" (combined with the terms type II or type 2), "BPII," "bipolar 2," "hypomania," and "bipolar spectrum." Articles included were identified based on relevance to the treatment of BPII. Studies included were also restricted to English-language journals containing data from both adult and child samples. Studies that included fewer than 15 patients were excluded unless they utilized a randomized, double-blind design.

RESULTS

Applying the above criteria to the current literature revealed 14 articles relating specifically to the pharmacotherapy of patients with BPII (24–37). Although large, double-blind, randomized trials are preferable, the majority of the trial information specifically about BPII patients is observational in nature. It is well known that studies of this kind are vulnerable to error. However, as information secondary to treatment of patients with BPII is lacking, a review of these data is nevertheless informative and can serve to provoke further research as well as encourage randomized controlled trials (RCTs).

Pharmacotherapy of Patients with BPII: Current Results

Articles published after 1994 were chosen for this review, following the publication of the current definition of BPII in the *DSM-IV* (5). Several studies were published prior to 1994 containing data from patients with BPII illness, though those studies classify BPII as a disorder not otherwise specified (NOS) or an atypical bipolar disorder. There are also several publications that contain data on patients with BPII, but they do not analyze the data separately from patients with BPI, unipolar depression, bipolar NOS, or related conditions. To be succinct in the summary of data pertaining to specific treatment modalities for BPII, these studies were excluded.

There is also a wealth of information describing chemotherapeutic treatment of bipolar depression that does not specify BPI or BPII illness (38–41). Due to the increased time spent in the depressive phase of the illness, these studies may ultimately have a bearing on the treatment of patients with BPII. However, for the purposes of this review, these studies were also excluded.

Lithium

Most literature related to the treatment of patients with BPII involves the use of lithium. Lithium is a well-known chemotherapeutic agent for BPI disorder (42–45), though its efficacy in BPII is not yet well accepted. A study by Tondo and associates (30) analyzed the clinical research records of a relatively large group of BPII patients (N = 129) before and after starting maintenance lithium treatment. Mean lithium maintenance treatment time was 6.4 years, and the data showed not only that lithium was efficacious in reducing both manic and depressive symptoms, but that this improvement in bipolar symptomology was greater in BPII patients than in 188 type I patients also studied (30). Another long-term maintenance study of BPII patients in Sardinia utilizing lithium was published in 2001 (31). This observational study followed 142 patients with BPII for 6 years after initiation of lithium monotherapy for maintenance. The study examined morbidity before and during lithium maintenance and found significant decreases in time spent ill and in depressive symptoms during lithium therapy. Another observational study tested the hypothesis that the resumption of lithium treatment is less effective after its previous discontinuation in bipolar disorders (29). The data showed no difference in treatment improvement with lithium before or after its previous discontinuation, and both BPI and BPII patients benefited from restarting treatment in this naturalist study.

Anticonvulsants

Although observational and prospective studies detailing the use of anticonvulsants in BPII have been performed, limited RCT data exist. A double-blind, placebo-controlled, 6-month maintenance trial by Calabrese and colleagues studying the use of lamotrigine in rapid-cycling BPII patients has provided interesting data (27). Patients with BPII on lamotrigine in this study (n = 52) were significantly less likely to experience a relapse for the 6 months after initiation of monotherapy compared to those on placebo (18% vs. 46%, respectively; $P = .05$). However, the BPI population on lamotrigine did not show a significant separation from placebo-treated patients in this study, indicating that lamotrigine was more effective in the treatment of depressive episodes than in manic episodes. This result is consistent with previously published literature in patients with BPI disorder regarding lamotrigine showing clear depressive prophylaxis and weak manic prophylaxis (42,43,46,47). Open trials have also been performed in a BPII patient population with both divalproex and gabapentin

(28,36). In both cases, patients who were mood stabilizer-naïve have better responses to drug than patients who were not. This finding is likely due to the presence of hard-to-treat patients who had previously failed other treatment regimens in the non–mood stabilizer-naïve population. The response to the two drugs was very different; divalproex substantially benefited 63% of patients (n = 19), but gabapentin was effective in only 30% of patients (n = 50), a very low number for an open study. The negative findings of gabapetin use are consistent with those from a controlled, double-blind trial of gabapentin monotherapy in refractory BPI and BPII patients (n = 25) (48) in which the response rate did not vary significantly between gabapentin and placebo-treated patients (20% gabapentin vs. 32% placebo). A more recent trial by Vieta and associates looked at the adjunctive use of topiramate in patients with BPII (35). In this study, topiramate was shown to be effective in the treatment of both hypomanic and mixed symptoms associated with BPII, as significant improvements in both the Hamilton Depression Rating Scale (HDRS) and the Young Mania Rating Scale were seen. However, the concomitant treatment of these patients with other mood stabilizers (carbamazepine, lithium, and valproate) clouds these findings. Together with the significant weight loss seen in patients on topiramate in this trial, these results prompted further investigation of topiramate as monotherapy in BPI patients. Despite the efficacy shown in the open-label trial, pooled data from 4 randomized, double-blind, placebo-controlled studies showed no improvement with topiratmate monotherapy (n = 427) compared with placebo (n = 433) in the treatment of acute mania in adults (49).

In a randomized, multicenter long-term study in which bipolar subjects were randomly assigned to either lithium or carbamazepine and followed for 2.5 years, carbamazepine was found to be equivalent to lithium in preventing future episodes in type II patients (50). When risk of patient hospitalization was considered, lithium proved superior to carbamazepine in patients with bipolar I disorder. Interestingly, in "nonclassical" patients (BPII patients and not otherwise specified) carbamazepine was found to be superior to lithium (51). These data strengthened the belief that carbamazepine may have a wider spectrum of efficacy than lithium. Recent randomized, placebo-controlled data suggest the efficacy of carbamazepine in bipolar I disorder (52,53) and indicate the need for further study of this compound in BPII.

Atypical Antipsychotics

The therapeutic utility of quetiapine, at doses of 300 mg/d and 600 mg/d, in BPII disorder was examined in a large, 8-week, randomized, multicenter, placebo-controlled trial involving patients with BPI disorder and patients with BPII disorder who were experiencing a major depressive episode (32,33). An analysis of the overall study cohort in that trial showed that both quetiapine 300 mg/d and quetiapine 600 mg/d were statistically superior to placebo in reducing symptoms of depression and anxiety, while exploratory analyses in which patients were stratified by bipolar subtype showed that both quetiapine doses under study had statistical superiority over placebo in reducing depressive symptoms in patients with BPI depression and numeric superiority over placebo in reducing depressive symptoms in patients with BPII depression (32). Additional secondary analyses were conducted in which anxiety data from trial participants with a given bipolar subtype who received quetiapine at either dose were pooled together and compared against anxiety data from trial participants with the same bipolar subtype who received placebo. Those analyses found that quetiapine was statistically superior to placebo in reducing symptoms of anxiety both in patients with BPI depression and in patients with BPII depression (33).

Important findings regarding the efficacy of quetiapine in BPII disorder were also made in an unpublished (but publicly presented) a priori subanalysis in which data from patients with BPII disorder in the aforementioned quetiapine trial were pooled together with data from patients with BPII disorder from a second placebo-controlled, 8-week quetiapine bipolar depression trial (54). That subanalysis (total: N = 351 [quetiapine 300 mg/d: n = 107; quetiapine 600 mg/d: n = 106; placebo: n = 108) revealed significant benefit for quetiapine-treated patients versus placebo-treated patients in terms of scores on the Montgomery Asberg Depression Rating Scale (MADRS) beginning as early as 1 week from baseline and persisting through week 8 (300 mg/d vs. placebo: $P = .005$; 600 mg/day vs. placebo: $P = .001$), with similar treatment-related benefits being seen in terms of scores on the HDRS and the Clinical Global Impressions Severity of Illness scale. Furthermore, the same subanalysis found that at end point, patients receiving quetiapine 300 mg/d were significantly more likely to be in MADRS remission (defined by a MADRS score ≤ 12) when compared with patients receiving placebo (49.5% vs. 35.2%, respectively; $P<.05$). The difference between patients receiving quetiapine 600 mg/d and patients receiving placebo in terms of MADRS remission rates at end point did not reach statistical significance (47.2% vs. 35.2%, respectively; P = NS). Similarly, rates of MADRS response (defined as a $\geq 50\%$ improvement in MADRS score between baseline and end point) were numerically, but not statistically superior, for both quetiapine treatment groups relative to the placebo treatment group (300 mg/d: 54.2%; 600 mg/d: 51.9%; placebo: 43.5%; P = NS for quetiapine 300 mg/d and quetiapine 600 mg/d vs. placebo). Effect size calculations performed using data from the subanalysis indicated that the treatment effect of quetiapine (as measured using MADRS scores) in patients with BPII depression was moderate in magnitude (effect sizes: 300 mg/d, 0.45; 600 mg/d, 0.54). The treatment effect of quetiapine was larger in magnitude for the 694 BPI patients participating in the same two studies (effect sizes: 300 mg/d, 0.78; 600 mg/d, 0.80) (55).

On the basis of the findings made in the two quetiapine trials discussed here, quetiapine recently became the first agent to be approved by the US Food and Drug Administration (FDA) for monotherapeutic use in the acute treatment of bipolar depression. This FDA indication includes acute depression

associated with BPII disorder, as well as acute depression associated with BPI disorder. Nonetheless, it should be remembered that despite the approval of quetiapine for treatment of acute bipolar depression, there are no controlled trials that have demonstrated the long-term safety and efficacy of quetiapine. Such data are required to ensure appropriate chronic treatment of BPII patients.

Aside from quetiapine, risperidone is the only other atypical antipsychotic to have been investigated for efficacy in BPII disorder in a published clinical trial meeting the criteria for this review. The trial, by Vieta and colleagues, examines the role of risperidone in the treatment of BPII patients (34). As with other atypical antipsychotics, risperidone is frequently used in the treatment of bipolar disorder. In this study, 20 of 34 patients who completed the trial were taking other medications, most commonly lithium, valproate, and carbamazepine. Although concomitant medications and the lack of a placebo arm in this study make analysis of the data difficult, there were significant reductions in both manic and depressive symptoms in patients taking part in the study. Further research into the possible role of risperidone and other atypical antipsychotics in the pharmacotherapy of BPII is warranted.

Antidepressants

Although antidepressants (tricyclics, selective serotonin reuptake inhibitors) are commonly used and generally effective in the treatment of unipolar depression, their use in bipolar disorder has been the topic of much scrutiny (56–58) (for a review, see Thase, Bhargava, and Sachs (59)). Their perceived tendency to induce a switch from depressed to manic states has caused some to avoid their use in bipolar patients. Those who do prescribe an antidepressant for patients with bipolar disorder will generally combine it with a mood stabilizer to avoid a switch in mood (57,59). Three studies analyzing the use of antidepressants specifically in patients with BPII meet the criteria of this review; two analyzed venlafaxine (24,26), and one fluoxetine (25). In the first study with venlafaxine, 42 patients with a major depressive episode completed the 6-week trial. Patients with BPII (n = 16) were found to respond similarly to those with unipolar depression (n = 26), as gauged by both the Montgomery-Asberg Depression Rating Scale (MADRS) and the HDRS (24). Similar findings were reported in a second 6-week study of venlafaxine in women experiencing a major depressive episode (BPII, n = 15; unipolar depression, n = 17) (26). Importantly, there were no episodes of hypomanic switch in these short-term studies. The prospective study using fluoxetine therapy for up to 12 weeks demonstrated that patients with BPII (n = 80) experienced an improvement in their depressive symptoms similar to that of patients with unipolar depression (n = 79) (25). However, 3.8% of BPII patients and no unipolar patients experienced a hypomanic switch during the short-term treatment with fluoxetine. This result highlights the concerns of some clinicians and the need for more properly controlled trials. Furthermore, the consequences of long-term antidepressant treatment have not been adequately studied.

Dopamine Agonists

In a double-blind, randomized, placebo-controlled study by Zarate and associates, the potential utility of adjunctive pramipexole was investigated (37). Twenty-one patients taking either lithium or valproate were assigned to treatment with either pramipexole or placebo. Efficacy, as assessed by the MADRS, showed that 60% of treatment patients versus 9% of placebo patients experienced a treatment effect (>50% decrease in MADRS score). Although one subject taking pramipexole experienced a manic switch, the results are intriguing, and provide insight into the potential for dopamine agonist therapy in mood disorders.

Other Treatment Modalities

While BPI and BPII patients are rarely analyzed separately, there are reports of nonpharmacologic therapies for bipolar disorder, namely, electroconvulsive therapy (for reviews see Berk and colleagues (60)) and vagus nerve stimulation (61). However, there are other nonpharmacologic therapies for the bipolar population, including light-box therapy (62) and psychoeducation (63). These therapies have shown varying efficacy, and specific study of bipolar II patients is needed before recommendations for their use can be given.

DISCUSSION

Agents with demonstrated efficacy in both phases of the bipolar spectrum (mania and depression) may be the best option for treatment of BPII disorder. Based on the available data, however, it is clear that there is a relative scarcity of well-controlled, randomized trials conducted to identify agents that possess bimodal mood stabilizing efficacy specifically in patients with BPII. (Available data can be grouped and analyzed in hierarchical order as is summarized in Table 1.) Nonetheless, sufficient data have been obtained to enable quetiapine to gain FDA approval for use in the treatment of bipolar depression, including BPII depression. This recent approval

Table 1 Data Weighting for Treatment of Bipolar II Disorder

Hierarchical order	Source of data
Heavily weighted	Meta-analyses in BPII
	Well-powered RCTs in BPII
	Prospective trials in BPII
	Well-powered RCTs in BPI
	Well-powered RCTs in unipolar depression
Lightly weighted	Retrospective reviews

BPII = bipolar II disorder; BPI = bipolar I disorder; RCTs = randomized controlled trials.

complements an existing FDA indication of quetiapine therapy for acute BPI mania.

Aside from quetiapine, the agents whose utility in BPII disorder have been most extensively investigated in heavily weighted studies have been agents that may not possess bimodal mood stabilizing efficacy. Of those agents, venlaxfaxine, fluoxetine, and the dopamine agonist pramipexole have all shown efficacy in RCT with BPII patients.

What other information is available in patients with BPII lends itself to few conclusions due to the methodological limitations of the observational or retrospective trial designs that have been published. Several such trials suggest that lithium is effective in the long-term treatment of both hypomanic and depressive symptoms associated with BPII. These data, combined with the wealth of knowledge built up over the years from the use of lithium in BPI disorder (64–66) provide additional support for the use of this agent to treat BPII-associated symptoms. One small prospective long-term study found carbamazepine to be equivalent to lithium in BPII subjects (50). Lamotrigine may be an effective treatment for BPII patients, predominantly for associated depression. Risperidone has also been shown in a prospective study to be an effective agent for the treatment of hypomanic and depressive symptoms associated with BPII (34). However, drawing conclusions from these data is complicated by the lack of a placebo comparator and the suggestion that risperidone is more active against hypomanic episodes than depressive episodes. Other prospective studies have been published that suggest efficacy for topiramate (35) and divalproex (36).

Due to the limited data available from studies involving patients with BPII, clinicians frequently seek evidence from other disorders to identify bimodal mood stabilizers that may provide benefit in the treatment of BPII. Often, this evidence is obtained from trials involving patients with BPI disorder or unipolar depression. A vast array of literature is available on the pharmacotherapy of BPI disorder beyond the scope of this review. However, it is clear that based on their efficacy in BPI disorder and unipolar depression, certain agents may be successful in the treatment of BPII. One such drug is lithium. Another agent fitting the mold is carbamazepine. Two recent identical RCTs by Weisler and colleagues utilizing extended-release carbamazepine capsules have shown efficacy against mania in patients with BPI disorder (52,53). Subsequent reanalysis of pooled data from these two trials has demonstrated a significant decrease in HDRS scores in those patients on carbamazepine, as opposed to placebo (67). The failure of divalproex in the treatment of BPI depression in a small (N = 43), placebo-controlled study places this agent lower in the hierarchy of preferred medicinal agents.

CONCLUSION

Going forward, it is likely that agents with bimodal mood-stabilizing properties may be the best choices as chemotherapeutic options in BPII. One such agent is quetiapine, which, in addition to being approved by the FDA for use in the treatment of acute BPI mania, recently gained FDA approval for use in the treatment of bipolar depression, including BPII depression. Aside from quetiapine, drugs such as lithium, lamotrigine, and carbamazepine are also promising therapies for BPII, as they have been shown in clinical trials to be effective against both acute depression and mania, or prevention of these states associated with bipolar disorder. These agents have the additional advantage of controlled data demonstrating their long-term safety and efficacy. In contrast, despite the recent FDA approval for quetiapine, there are no controlled data documenting that quetiapine exhibits long-term efficacy and safety.

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