Evaluation and Management of Breakthrough Depressive Episodes

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Clinicians are faced with a diagnostic challenge when a bipolar patient reports breakthrough depressive symptomatology. Breakthrough depressive symptoms during treatment for a bipolar depressive episode may be a manifestation of recurrent bipolar depression or the emergence of a mixed episode. Treatment of recurrent bipolar depression and mixed episodes differs considerably, and antidepressant therapy during a mixed episode can worsen the episode and initiate or exacerbate rapid cycling. Therefore, accurate diagnosis and appropriate treatment are imperative to achieving a positive outcome. Research indicates that optimizing the current mood stabilizer therapy or adding another mood stabilizer may be the best treatment options for patients with a history of rapid cycling—in patients without a history of rapid cycling, adding an antidepressant to a mood stabilizer may be less risky and therefore a reasonable choice. Combination therapy with a mood stabilizer and an atypical antipsychotic may also be effective in managing bipolar depressive episodes.

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Clinicians face a diagnostic challenge when a patient reports depressive symptomatology. Distinguishing depressive symptoms as a manifestation of either major depressive disorder or a bipolar depressive episode can be difficult. Studies[1] indicate that a considerable number of patients with bipolar disorder (particularly bipolar II) are initially misdiagnosed as having major depressive disorder.[2] For example, Ghaemi et al.[2] found that 37% of patients who sought treatment with a mental health clinician following their first manic or hypomanic episode were misdiagnosed with unipolar depression. Additionally, more than 50% of patients with bipolar disorder experience a depressive episode as their first mood episode.[3]

Accurately distinguishing between unipolar depression or bipolar depression is not the only challenge associated with the presentation of depressive symptomatology. The appearance of depressive symptoms in patients who have been diagnosed with bipolar disorder may signal recurrent bipolar depression or the emergence of a mixed episode. This diagnostic distinction is crucial because treatment of recurrent bipolar depression and mixed episodes differs considerably—antidepressant pharmacotherapy during a mixed episode can worsen the episode and initiate or exacerbate rapid cycling. To date, there is a paucity of research regarding how to identify and manage breakthrough depressive episodes in bipolar disorder; however, recognizing prodromal symptoms may help in thwarting an emerging depressive episode, and optimizing treatment can aid in preventing additional breakthrough episodes. Bipolar spectrum disorders are a common global health problem[4,5] that is highly correlated with difficulties in workplace performance and social and family life, as well as criminal behavior and jail time.[6] Therefore, accurate diagnosis and appropriate treatment are imperative to achieving positive outcomes that affect patients, their families, employers, and society at large.

ANALYZING MOOD STATE PRIOR TO ONSET OF DEPRESSION

Mood state prior to onset of depression has been identified as an indicator for treatment choice and a predictor of treatment outcome in patients with bipolar disorder who experience breakthrough depressive episodes. MacQueen et al.[7] examined the role of prior mood state and the likelihood of treatment response in a cohort of patients with bipolar depression who were treated with antidepressants and mood stabilizers in a naturalistic treatment setting. Detailed life-charting data from 42 patients with 67 depressive episodes among them were reviewed, and patients were categorized on the basis of preceding mood state and type of drug received for depression (antidepressant or mood stabilizer). Response rates and rates of switch into mania were then compared. They found that

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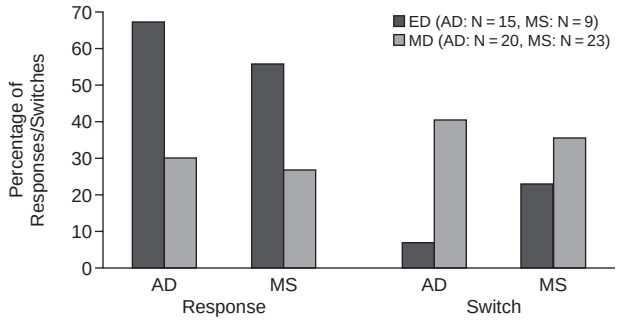
Figure 1. Percentage of Patients Who Responded or Switched Into Mania or Hypomania After Treatment With Either Antidepressant or Mood Stabilizer Medication[a]



[a]Reprinted with permission from MacQueen et al.[7]
Abbreviations: AD = antidepressant, ED = patients who became depressed following a euthymic period, MD = patients who became depressed following a manic or hypomanic episode, MS = mood stabilizer.

patients who became depressed following a period of euthymia were much more likely to respond to either mood stabilizers or antidepressants than those whose mood state had been mania or hypomania immediately prior to depression (Figure 1). In addition, patients who were euthymic before the depressive episode were less likely to switch to a manic episode than patients who had recently been manic or hypomanic, especially with antidepressant treatment rather than mood stabilizers. Thus, in patients with bipolar depression, the mood state they were experiencing prior to a depressive episode breaking through appeared to be relevant to drug response and to rates of switching.

Recognizing Prodromal Symptoms of Breakthrough Depression

The number of bipolar depressive episodes a patient experiences has been identified as a strong indicator of functioning and well-being in patients with bipolar disorder.[8] The number of past depressions appears to be a stronger determinant of outcome than past manias,[8] and rapid intervention is necessary to minimize the number of depressive episodes if patient functioning is to be maintained.

Jackson and colleagues[9] recently published a literature review of affective disorders in which data about prodromal symptoms as harbingers for full-blown depressive recurrence were included. Seventy-three publications of prodromal symptoms in bipolar and unipolar disorders were identified by computer searches of 7 databases (including MEDLINE and PsychLIT) supplemented by hand searches of journals, and of these, 17 studies (total N = 1191) met criteria for inclusion in a systematic review. Included in the 17 studies were 8 that reported prodromal symptoms of bipolar depression. The analyses revealed that as many as 80% of patients with bipolar I disorder were able to identify prodromal symptoms a mean length of 19 days prior to the recurrence of bipolar depression. The most robust early symptom of mania was sleep disturbance (median prevalence of 77%), and the 3 most common prodromal symptoms of bipolar depression were mood change (48%), psychomotor symptoms (41%), and increased anxiety (36%). Jackson and colleagues concluded that early symptoms of relapse in bipolar disorder could usually be identified and that identification of early symptoms could lead to treatment to prevent the relapse.

Keitner et al.[10] conducted a similar study to identify prodromal and residual symptoms of mania and depression reported by patients with bipolar I disorder and their family members. Researchers asked 74 patients and 45 adult family members to report any prodromal symptoms of mania and depression prior to breakthrough, and clinicians classified reported symptoms into 6 broad categories: behavioral, cognitive, mood, neurovegetative, social, and other, categorizing all the symptoms as typical or idiosyncratic. Seventy-eight percent of the patients reported prodromal depressive symptoms, and 87% reported prodromal manic symptoms. Patients and their families reported similarities as well as differences in perception and recognition of symptoms. Cognitive symptoms were the most consistently reported first warning signs of recurrent depression by both patients and family members. Patients described the emergence of poor concentration and indecisiveness, and family members reported distractibility and anxious ruminations as the most common early warning signs of depression.

Although no single symptom occurs in every patient, these studies indicate that fundamentally recognizable signs of emerging bipolar depression are usually present. Understanding what general symptoms to look for could aid patients, their families, and their physicians to make individualized lists of prodromal symptoms that warn of an upcoming depressive episode. In this way, preventive treatments can be implemented.

TREATING BREAKTHROUGH BIPOLAR DEPRESSION

Optimizing Current Therapy

Research concerning pharmacologic treatment for breakthrough bipolar depressive episodes is limited. However, in randomized, controlled trials for bipolar depressive disorder, mood stabilizers continue to be the gold standard.[11] Therefore, one reasonable clinical approach in treating breakthrough depression in acute bipolar depression is to optimize mood stabilizer therapy.

Evidence suggests that in patients being treated with lithium for bipolar disorder, increasing lithium levels to a reasonably high therapeutic range may help ward off

a depressive episode as it emerges. In support of this suggestion, Nemeroff et al.[12] compared lithium plus adjunctive paroxetine, imipramine, or placebo and found that depression improved in patients receiving low concentrations of lithium (< 0.8 mmol/L) plus paroxetine compared with lithium plus placebo. However, patients receiving higher concentrations of lithium achieved no substantial benefit from the addition of either antidepressant to lithium compared with placebo. These findings may suggest that in mid-to-upper therapeutic serum concentrations, lithium monotherapy provides adequate antidepressant benefit that is comparable to augmentation with paroxetine in patients who can not tolerate such lithium concentrations.

Prophylactic lithium use has been reported to alter thyroid function, possibly leading to hypothyroidism and triggering mood instability and a recurrence of depressive symptoms. Frye et al.[13] conducted a post hoc analysis of a 3-year study comparing maintenance treatment with lithium or carbamazepine monotherapies or the combination of both agents in patients with bipolar depressive disorder to examine the relationship between changes in thyroid indices and mood stability. For the first 2 years of the original study, 30 patients with bipolar depressive disorder were randomly assigned to receive either 1 year of treatment with lithium and then 1 year of treatment with carbamazepine, or 1 year of treatment with carbamazepine and then 1 year of treatment with lithium. In the third year, both patient groups were treated with lithium plus carbamazepine. Researchers used a stepwise regression analysis to evaluate the degree and timing of lithium- and carbamazepine-induced thyroid changes and to determine their subsequent relationship to long-term mood stability. Results indicated that a lower mean level of serum free thyroxine (T_4) was associated with more affective episodes and a greater severity of depression during monotherapy treatment with either lithium or carbamazepine. Overall, the lower the free T_4 level, the greater the instability of mood regardless of mood stabilizer treatment. Therefore, clinical monitoring of free T_4 levels is warranted to help prevent a breakthrough episode.

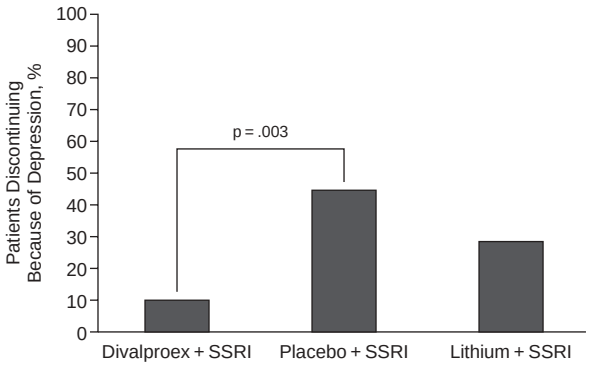
In addition to the clinical management of free T_4 levels, physicians can help stave off a breakthrough depressive episode by monitoring serum thyrotropin levels. Cole et al.[14] found that patients with bipolar disorder who had lower-than-median values of free thyroxine index (FTI) and higher-than-median levels of thyrotropin experienced slower response to antidepressant therapy than other patients. In fact, patients with levels of FTI below the median and thyrotropin above the median experienced an average time-to-remission of depressive symptoms that was 4 months longer than patients with levels on the opposite sides of those median levels. It is important to note that all patients except 1 had FTI and thyrotropin values within the normal range. Therefore, checking thyroid hormone levels may be a useful intervention, not just in patients receiving lithium, but for all patients with bipolar depressive disorder experiencing breakthrough depressive episodes.

Adjunctive Therapy

Besides optimizing the current mood stabilizer, other treatment options for patients with breakthrough depression in bipolar disorder include adding either a second mood stabilizer or an atypical antipsychotic or supplementing the current mood stabilizer with an antidepressant or lamotrigine. Young et al.[15] compared the addition of an antidepressant versus a second mood stabilizer for 27 inpatients being treated for bipolar depression. The patients, who were receiving either lithium or divalproex and had experienced breakthrough depressive symptoms, were randomly assigned to groups that received double-blind treatment with paroxetine or the alternative mood stabilizer (lithium or divalproex) for 6 weeks. Both treatment groups showed substantial improvement in depressive symptoms during the 6-week trial; however, fewer patients taking paroxetine withdrew from the study than those taking a second mood stabilizer, suggesting that the addition of an antidepressant may have greater clinical utility in the treatment of bipolar depression than the addition of a second mood stabilizer. In fact, the only patient who switched into mania during the course of the study was a patient receiving combination mood stabilizer therapy. However, the findings were somewhat limited by the small sample size.

The first randomized, multicenter, double-blind study[16] to compare divalproex, lithium, and placebo as prophylactic therapy for depression comprised 2 trial periods (a 90-day open-label phase and 52-week randomized maintenance phase). Patients with bipolar I disorder who may have been treated with open-label lithium or divalproex and who met recovery criteria within 3 months of the onset of a manic episode (N = 372) were randomly assigned to receive maintenance treatment with divalproex, lithium, or placebo in a 2:1:1 ratio. Over the first 2 weeks of maintenance treatment, open-label divalproex or lithium was tapered off, and all other psychotropic medications were discontinued. The primary outcome measure was time to recurrence of any mood episode, and secondary measures were time to a manic episode, time to a depressive episode, average change from baseline in Schedule for Affective Disorders and Schizophrenia-Change Version subscale scores for depression and mania, and Global Assessment of Functioning scores. The initial analysis showed that the active treatments were equally effective at preventing a mood episode and that divalproex was slightly more effective than lithium on some secondary outcome measures. Those who experienced breakthrough depression were allowed adjunctive therapy with a selective serotonin reuptake inhibitor (SSRI), sertraline or paroxetine. An analysis of these patients indicated that the combination of dival-

Figure 2. Early Discontinuation Due to Depression in Patients Taking a Mood Stabilizer Plus a Selective Serotonin Reuptake Inhibitor (SSRI)[a]



[a]Reprinted with permission from Gyulai et al.[17]

proex with an SSRI was a more effective treatment for breakthrough depression than the combination of lithium and an SSRI, although this difference was not significant. Treatment with divalproex plus an SSRI was significantly more effective than placebo plus an SSRI, whereas lithium plus an SSRI was not.

Gyulai et al.[17] recently published a report describing in further detail the above study[16] of divalproex, lithium, and placebo as prophylactic therapy for depression in order to elucidate the effect of divalproex on multiple dimensions of depressive morbidity in bipolar disorder. They found that patients who were previously hospitalized for affective episodes or who had taken divalproex in the open period of the study had a longer time to relapse with divalproex than those patients who received lithium during the maintenance period. Divalproex improved several dimensions of depressive morbidity and reduced the probability of depressive relapse in bipolar disorder, especially in patients who had responded to divalproex during a manic episode and among patients with a more severe course of illness. Those taking divalproex plus an SSRI discontinued treatment due to depression at a lower rate than those taking lithium plus an SSRI and at a significantly lower rate than the placebo plus SSRI group (Figure 2).

Augmenting a mood stabilizer with an atypical antipsychotic, such as olanzapine, is another treatment option for patients with bipolar disorder with breakthrough depressive episodes. Due to the lower potential for neurotoxicity and preliminary evidence that suggests improved efficacy in bipolar disorder over typical antipsychotics,[18] atypical antipsychotics are increasingly having a more prominent role in the pharmacologic management of bipolar disorder. Double-blind controlled studies with atypical antipsychotics in managing breakthrough depressive episodes and in providing long-term treatment of bipolar disorder are still largely unavailable; however, recent uncontrolled studies have suggested that olanzapine may have beneficial effects in depressed bipolar patients.[18] However, until there are systematic data from long-term, controlled follow-up studies on the comparative efficacy of these agents with mood stabilizers, atypical antipsychotics should be used with caution, preferably only in combination with a mood stabilizer during the maintenance phase of treatment.

SUMMARY

Further randomized controlled trials of patients with bipolar disorder and breakthrough depressive symptoms need to be conducted. Available research indicates that, after optimizing current mood stabilizer therapy, the best clinical option for treating breakthrough depressive episodes in patients with a history of rapid cycling may be adding a second mood stabilizer. In patients without a history of rapid cycling, adding an antidepressant to the mood stabilizer may be less risky and therefore the better choice. Combination therapy with a mood stabilizer and an atypical antipsychotic may also be effective; however, more long-term controlled follow-up studies are needed on the comparative efficacy of these agents with mood stabilizers.

Drug names: carbamazepine (Epitol, Tegretol, and others), divalproex (Depakote), imipramine (Tofranil and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), paroxetine (Paxil and others), risperidone (Risperdal), sertraline (Zoloft).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, carbamazepine is not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder; and sertraline, divalproex, imipramine, lamotrigine, paroxetine, and risperidone are not approved for the treatment of bipolar depression.

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