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Bipolar disorder: current clinical research trends

'The database for the pharmacotherapy of bipolar depression has been astonishingly meager for decades.'

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Although meaningful clinical research in bipolar disorder has continuously evolved over the last 50 years, the last few years have witnessed a particularly productive time. During the last 5 years, important new conceptualizations and treatment findings have emerged in four areas:

- Diagnostic boundaries
- Treatment of bipolar depression
- A new class of mood stabilizers
- Refined thinking about measuring and improving the long-term outcome of bipolar patients

This editorial will briefly summarize the current status and delineate the near future trends in these developments.

Bipolar spectrum: an evolving boundary

In the diagnostic realm, the most important current discussion/controversy reflects the uncertain boundaries of bipolar disorder. The Diagnostic and Statistical Manual of Mental Disorders (DSM) – IV defines two subtypes of bipolar disorder, Types I and II, distinguished by the severity of the manic (vs. hypomanic) syndromes. Lifetime prevalence rates of these disorders range between 1 and 2%. Yet, epidemiologic and clinical studies clearly show that a substantial group of patients show bipolar mood swings that would not meet criteria for either of the two DSM-IV subtypes. The term 'bipolar spectrum' has emerged to describe these patients. (In fact, bipolar spectrum is not a new concept at all, but an ancient one re-emerging with new data.) Many, but not all, of the bipolar spectrum variants would be classified in DSM-IV as bipolar disorder not otherwise specified, the 'waste basket' term reserved for bipolar disorders that exhibit high and low mood swings but of insufficient severity or time to meet criteria for bipolar disorder I or II. Subtypes within the bipolar spectrum differ between research groups but include recurrent brief hypomanias (fewer than the 4-day minimum for DSM-IV hypomania), hypomanias characterized by overactivity without mood change, antidepressant-induced hypomanias (currently defined as substance-induced mood disorder in DSM-IV), cyclothymic disorder, and hyperthymic or cyclothymic temperament with recurrent depressions. Epidemiologic data suggest a lifetime prevalence of bipolar spectrum disorders of 6–12% [1,2], yielding a total bipolar prevalence rate up to 15% and unipolar/bipolar prevalence ratio verging towards 1:1. Family history studies show a high familial load for bipolar disorder in these bipolar spectrum patients [3].

'During the last 5 years, important new conceptualizations and treatment findings have emerged...'

However, other observers present legitimate concerns about the expansion of the bipolar boundaries prematurely with the subsequent risk of weakening the core concept of bipolar disorder. Premature acceptance of bipolar spectrum patients as defining a unitary disorder creates the danger of including heterogeneous subjects for biologic, genetic and treatment studies which could manifestly alter the results [4]. These concerns are analogous to similar diluting trends in the past for schizophrenia and depression.

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A further concern reflects the as yet untested assumption that bipolar spectrum patients should be treated pharmacologically identically or similar to that of more classic bipolar patients. Mood stabilizers are not universally benign medications. Their indiscriminate use without data supporting their efficacy in specific populations could create an unwarranted ratio of risks to benefits. Thus, nosology studies must be followed by treatment studies.

Pharmacotherapy of bipolar depression

The database for the pharmacotherapy of bipolar depression has been astonishingly meager for decades. In the absence of a substantial database, recommendations tend to be made on physicians' individual clinical experiences and/or recommendations from expert panels. A disparity has clearly arisen between these two groups. Community clinicians frequently prescribe antidepressants to bipolar patients, both with and without mood stabilizers. In contrast, most Practice Guidelines (including those of the American Psychiatric Association, written predominantly by academic psychiatrists), are exceedingly cautious about the prescription of antidepressants for bipolar depression with the concerns of triggering pharmacologic manias/hypomanias or inducing a period of mood instability/rapid cycling. With the recent data demonstrating that depression is the dominant pole of bipolar disorder, measured by the number of episodes or time spent in mood states [5,6], the issue is of vital clinical importance.

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More recently, even within academic circles, two camps have emerged. On one side, exemplified by Goodwin and Ghaemi, are those who champion the academic position that has dominated thinking in this area for at least 20 years [7]. Their core concerns are:

- Antidepressants induce hypomania/mania and mood cycling at high rates
- Antidepressants have not been shown to decrease suicide rates in treated patients, whereas lithium (specifically and alone among the mood stabilizers) has
- Mood stabilizers (including lithium and some of the anticonvulsants) are equivalently effective to antidepressants in treating acute bipolar depression
- Mood stabilizers are more effective than antidepressants in preventing bipolar depression

In contrast, others have focused on what is perceived to be the excessive concern about the negative effects and insufficient appreciation of the positive effects of antidepressants in treating bipolar depression [8]. In this viewpoint, the concerns about antidepressant-induced pharmacologic manias and rapid cycling are dominated by data on tricyclic and monamine oxidase inhibiter antidepressants – two classes of agents that are rarely used first line any more. More recent studies examining the newer antidepressants (e.g., selective serotonin reuptake inhibitors, venlafaxaine and bupropion) consistently find much lower switch rates. The findings of a recent systematic review and meta-analysis on antidepressants for bipolar depression support the more liberal use of antidepressants [9]. Examining all randomized, controlled trials in the area, the authors concluded that antidepressants were more effective than placebo in treating acute bipolar depression and that switch rates were relatively low, with the new antidepressants demonstrating lower switch rates than the tricyclic antidepressants. However, relatively few studies in this area have been published and there are insufficient data to compare acute antidepressant efficacy of antidepressants with that of mood stabilizers in bipolar depression.

Adding to the controversy are two recent case-controlled studies that showed that a subgroup of bipolar patients appear to do best on a combination of mood stabilizers plus antidepressants with fewer depressive relapses and, in one study, fewer manic relapses [10,11]. It is important to note that this occurred only in a relatively small subgroup of bipolar depressed patients and should not be generalized to all bipolar patients.

Thus, the battlelines on the relative merits and demerits of antidepressants versus mood stabilizers in the acute and preventive treatment of bipolar depression have been drawn. Lamotrigine's efficacy as both an acute bipolar antidepressant and preventive treatment for bipolar depression helps support the Goodwin/Ghaemi position. In contrast, the studies demonstrating relatively low switch rates with the newer antidepressants are in favor of Grunze/Moller's ideas. For now, with insufficient data, each clinician practices in a manner that fits individual biases and clinical experience with the literature supporting both viewpoints. Further data on the treatment of bipolar depression from the Stanley Foundation [12] and the Systemic Treatment Enhancement Program for Bipolar Disorder study will hopefully illuminate this controversy.

Second-generation antipsychotics as primary treatments of bipolar disorder

By a large margin, most double-blind studies over the last 5 years evaluating the efficacy of medications for bipolar disorder have studied antipsychotics. At this point (late 2004), all five second-generation antipsychotics (SGA; I am excluding clozapine in this discussion because its unique negative properties preclude its use as a first-line agent) – olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole – have received indications from the US Food and Drug Administration (FDA) for acute mania as solo or add-on treatments. The observation that antipsychotics are effective treatments for acute mania should shock no one. For many decades, typical antipsychotics have been prescribed to treat acute mania. The difference is that we have so much more data supporting the use of SGAs. What is interesting and surprising is the emerging database on the use of SGAs for both depression and as maintenance treatments in bipolar disorder.

No SGA has received an FDA indication for acute bipolar depression. Olanzapine/fluoxetine combination (OFC; marketed as Symbyax®), however, has demonstrated sufficient efficacy in treating bipolar depression to receive an FDA indication. Of note, in the pivotal study, both olanzapine alone as well as OFC were more effective than placebo (remission rates 33 vs. 49 vs. 25%; $p < 0.001$ for comparisons of both active drugs vs. placebo) [13]. It is difficult interpreting the efficacy of the OFC combination without a fluoxetine alone cell in the study; the OFC data could simply reflect fluoxetine's antidepressant effect with olanzapine simply preventing bipolar switching. The lesser but still observable efficacy of the olanzapine alone group is worthy of note. More recently, in support of this, quetiapine demonstrated a double-blind efficacy in acute bipolar depression at doses of either 300 or 600 mg daily compared with placebo with remission rates of 53% for both active treatments versus 28% for placebo ($p < 0.001$) [14]. Studies evaluating the antidepressant efficacy of other SGAs are ongoing.

'The dominance of data for olanzapine among the SGAs in mood effects is apparent.'

In evaluating the long-term preventive efficacy of SGAs in bipolar disorder, olanzapine has been shown to be more effective than placebo in preventing both manias and depression, earning it an FDA indication as a maintenance treatment [15]. Olanzapine has also demonstrated a somewhat greater preventive efficacy compared with lithium in a 1-year study, and comparable efficacy to valproate in another study [16,17]. A relatively small, unpublished study showed the preventive mood stabilizing efficacy of aripiprazole compared with placebo over 6 months [UNPUBLISHED DATA].

The dominance of data for olanzapine among the SGAs in mood effects is apparent. However, it is as yet unclear whether this reflects greater efficacy. Eli Lilly & Co., olanzapine's manufacturer, was clearly farsighted enough to evaluate the efficacy of it's product well before its competitors did, resulting in far more data available for its product compared with the other SGAs. Within the next few years, data regarding the antidepressant and preventive efficacy of the other SGAs will be available and meaningful comparisons will be available.

Despite these intriguing data, many experienced clinicians (including myself) do not routinely use SGAs as solo maintenance treatments or as antidepressants in treating bipolar depression. As the field accumulates more experience, this is likely to change. Most exciting, however, is the clear observation that we now have three distinct first-line pharmacotherapeutic classes – lithium, anticonvulsants and SGAs – prescribed either singly or in combination for treating bipolar patients.

Syndromal versus functional outcome in bipolar disorder

Ultimately, the goal of all treatments is to minimize the effect of psychiatric disorders on the quality of patients' lives. Unfortunately, we have spent too much time and effort evaluating syndromal outcome in bipolar disorder by counting symptoms or episodes (e.g., time to relapse or numbers of relapses per unit time). These latter variables are vital in establishing both the natural history of the disorder and in examining the potential efficacy of preventive treatments. Nonetheless, patients and their families are less interested in episode counting than in measures of life quality and function: Can the patient work? Have consistent long-term relationships? Keep up with age-matched peers? Only belatedly have we begun to observe the functional outcome of bipolar patients and to understand the predictors and correlates of these outcomes. Without doubt, syndromal and functional outcome are correlated: those with more mood episodes have a greater functional impairment. Yet, the relationship between these two domains is more complex than that. At the core, although syndromal and functional outcomes are related, the relationship is probably circular (i.e., poor symptomatic outcome leads to poor function, and poor function [and stressful lives] leads to a greater number of symptoms and episodes) [18].

Additionally, even those bipolar patients who appear not to have recent syndromal relapses show diminished function in occupational and social realms. The question at this point is: Why do many bipolar patients show poor psychosocial outcome even if symptomatically stable? Why are lives so much harder to heal than symptoms? The answer to this critical question is still unclear but a number of possibilities are worthy of exploration. They are:

- The differential effect of manias versus depressions
- The potentially functionally disruptive effect of subsyndromal symptoms, especially depression
- Comorbid disorders, such as drug and alcohol abuse
- The effect of personality factors on traits such as resilience and demoralization
- Neurocognitive deficits that have been demonstrated in bipolar patients when they are not in acute episodes and may diminish work and school performance [19]

With increasing evidence of the poor functional outcome in bipolar disorder, it is incumbent upon us to understand this phenomenon better and then, hopefully, to construct more effective strategies to enhance our patients' lives while we simultaneously prevent mood episodes.

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