Update on Diagnosis and Treatment of Bipolar Disorder

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Terence A. Ketter, MD, Stanford University School of Medicine, Stanford, California, USA, discussed anticonvulsants in the treatment of bipolar disorder. Of the available anticonvulsants, 3 are mood stabilizers that are approved for use in bipolar disorder by the United States Food and Drug Administration (FDA)—namely, carbamazepine, valproate, and lamotrigine. Evidence is accumulating for a fourth drug, oxcarbazepine, which is not yet FDA approved. Anticonvulsants for conditions that are comorbid in bipolar disorder (eg, anxiety) include diazepam, lorazepam, clonazepam, gabapentin, pregabalin, topiramate, and zonisamide.

Carbamazepine, valproate, and lamotrigine all have safety concerns (Table 1).

Table 1. Safety and Tolerability Concerns of Bipolar Anticonvulsants

	Valproate	Carbamazepine	Lamotrigine
Gastrointestinal	√	√	√
Weight gain	√		
Rash		√	√
Tremor	√		
Neurotoxicity		√	
Hepatotoxicity	√	√	
Headache			√
Dizziness			√
Thrombocytopenia	√		
Thyroid changes		√	
Pruritus			√
Hair loss	√		
Blood dyscrasias		√	
Dream abnormality			√
Pancreatitis	√		
Cardiac toxicity		√	
Hyponatremia		√	
Polycystic ovarian syndrome	√		
Teratogen	√	√	√
Suicidality	√	√	√

Bold outline indicates United States Food and Drug Administration boxed warning in prescribing information.

Source: Ketter TA (ed). *Clinical Manual of Bipolar Disorder*. American Psychiatric Publishing, Inc.; Washington DC, In press.

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Table 2. Characteristics of LiTMUS Participants (n=283)

Require change in treatment (entry in any mood state except recovered)
Clinical Global Impression–Bipolar Severity Scale ≥3 (mild)
Not currently receiving lithium
Could have received lithium in the past
Willingness to be randomly assigned

LiTMUS=Lithium Treatment Moderate-Dose Use Study.

Valproate formulations include valproic acid, divalproex, and valpromide. The pivotal randomized controlled trial (RCT) data for the approval of divalproex are decades old from 2 studies involving 36 patients and 179 patients. Carbamazepine pivotal data for approval are about a decade old, and the RCTs of immediate and extended-release capsules involved 204 patients [Weisler RH et al. *J Clin Psychiatry* 2004] and 239 patients [Weisler RH et al. *J Clin Psychiatry* 2005], respectively. A modified version of carbamazepine (oxcarbazepine) was formulated with the aim of reducing toxicity without compromising efficacy. However, a 7-week double-blind RCT addressing acute pediatric mania involving 116 subjects did not reveal a significant effect when compared with placebo in the total population, although significance was evident in children 7 to 12 years old who were treated with oxcarbazepine (n=37) relative to placebo (n=36; p<0.04) [Wagner KD et al. *Am J Psychiatry* 2006]. Racemic licarbazepine (a derivative of oxcarbazepine) and a licarbazepine prodrug (eslicarbazepine acetate) have been studied. Although the studies were completed more than 5 years ago, no publications have emerged, which does not bode well for the potential of these drugs.

Other drugs that have been studied but not yet proven effective in mania include gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, and zonisamide.

Michael J. Ostacher, MD, Stanford University School of Medicine, Stanford, California, USA, discussed 2 trials of lithium for bipolar disorder: the Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation (BALANCE) and the Lithium Treatment Moderate-Dose Use Study (LiTMUS). Lithium is one of the old guard for treatment of bipolar disorder, having received FDA approval in 1970. Its first-line use in the United States is declining, although it is firmly established as a maintenance treatment.

Nonetheless, the patients encountered in a clinician's daily practice may bear little resemblance to the patients in the studies on which drug approval is based. This has to do with efficacy and effectiveness. Efficacy trials—such as those on which FDA approval of lithium was based—are good at pinpointing the effect of a drug on the specific target. In doing so, generalizability is sacrificed, since other subjects can be excluded from the analyses. Effectiveness trials generally tend to be directed at a larger patient population, with internal validation sacrificed. Data from effectiveness trials are important in real-world treatment, since they can reveal risks that preclude the use of the drug.

The LiTMUS randomized comparative trial evaluated the effectiveness of optimized personalized treatment of bipolar disorder patients with and without lithium [Nierenberg AA et al. *Am J Psychiatry* 2013]. The BALANCE randomized open-label trial evaluated lithium + valproate combination therapy versus monotherapy with either drug for relapse prevention in bipolar I disorder [Geddes JR et al. *Lancet* 2010].

LiTMUS compared optimized treatment with or without lithium (which managed comorbid conditions and symptoms of anxiety and insomnia). The 6-month primary outcomes of LiTMUS were Clinical Global Impression–Bipolar Severity Scale score over the study period and necessary clinical adjustments. Treatment was open and consisted of an initial low dose, with an increase to 600 mg for 8 weeks and adjustment as needed thereafter; the assessments were blinded. Secondary outcomes included mood metrics, quality of life, and suicidality. Subject characteristics are summarized in Table 2.

The overall Clinical Global Impression–Bipolar Severity Scale score was nearly identical between the study arms. Necessary clinical adjustments were also not significantly different. However, use of lithium was associated with reduced use of atypical antipsychotic medications (lithium + optimized treatment, 48.3%; optimized treatment, 62.5%; p=0.028).

The BALANCE study featured an active run-in phase with 459 patients (permitting screening for adherence, clinical response, and tolerability) before randomization of 330 patients to treatment for up to 8 weeks with lithium

(0.4 to 1.0 mmol; n=110), valproate (n=110), or lithium + divalproex (n=110). Males and females in each group were equal. The mean age of participants was 43 years, with 75% having a long-term history of drug therapy. During the 2-year follow-up, the primary outcome was time to first intervention for mood episode. Secondary outcomes were times to hospitalization, first use of new medication, first episode of depression, first episode of mania, and switch from allocated treatment. Mood or severity was not measured. Combination therapy with lithium + divalproex was more likely to prevent relapse than valproate monotherapy (HR, 0.59; p=0.0023), and lithium alone was more effective than valproate alone (HR, 0.71; p=0.0472) for up to 2 years.

The bottom line from LiTMUS and BALANCE is that while lithium had benefit in reduced use of other medications, it was not compelling enough to inspire general changes in clinical practice for bipolar disorder. But for patients who need maintenance therapy, lithium may be the best course of action.

S. Nassir Ghaemi, MD, MPH, Tufts University School of Medicine, Boston, Massachusetts, USA, presented an update on antidepressants in bipolar depression. Antidepressants constitute about 62% of the drugs prescribed for psychiatric conditions in general and bipolar disorder in particular. Yet, contends Dr. Ghaemi, antidepressants should not be used for bipolar disorder. More than a dozen meta-analyses of RCTs involving ~3000 patients have revealed the near absence of any benefit of antidepressants, with any benefit coming disproportionally from the smallest RCTs [Sidor MM, Macqueen GM. *J Clin Psychiatry* 2011]. As well, Dr. Ghaemi presented as-yet unpublished data from a study that he was part of, in which 119 patients were randomly assigned to receive citalopram (n=60) or placebo (n=59) for 6 weeks, followed by a 1-year maintenance dose. That study failed to show any drug benefit.

Discontinuation of antidepressants may be beneficial. Dr. Ghaemi and colleagues randomly assigned 80 patients with acute bipolar depression who had responded to a mood stabilizer and an antidepressant, either to 1 year of continued therapy with both drugs (n=40) or to just the mood stabilizer (n=40). Discontinuation of antidepressant led to moderate improvement in subsyndromal depressive symptoms at 1 year and longer time to first depressive episode [Ghaemi SN et al. *J Clin Psychiatry* 2010].

An important issue in the disconnect between the negative data concerning antidepressants for bipolar disorder and the popularity of the drugs may be the tendency of randomized trials to evaluate patients who have already responded—that is, with analyses of the other, confounding patients excluded. The use of antidepressants for bipolar disorder can be further questioned on the basis of findings of a meta-analysis of 6 RCTs involving 370 patients, which showed a causative association of tricyclics and mania [Gisman HJ et al. *Am J Psychiatry* 2004]. This mood destabilization could counteract the benefits of mood-stabilizing drugs.

Roger S. McIntyre, MD, University of Toronto, Toronto, Ontario, Canada, discussed defined mixed features in bipolar depression. The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* supplanted "mixed states" of bipolar depression with "mixed specifier," recognizing the real-world reality of patients and the high rate of misdiagnosis. Bipolar depression is more likely if 5 or more of the following criteria are met:

- Symptomology
  - Hypersomnia
  - Hyperphagia
  - Psychomotor retardation
  - Other "atypical" symptoms
  - Psychosis and/or pathological guilt
  - Mood lability or manic symptoms
- Onset and course
  - Earlier onset (<25 years of age)
  - Multiple depressions (^{3}5 episodes)
- Family history of bipolar disorder

About 20% to 55% of cases of major depressive disorder are characterized by lifetime symptoms of some degree of subthreshold hypomania. Compared with those who have "pure" depression, those who have lifetime subthreshold hypomanic symptoms may have more complex illness and less favorable courses and outcomes.

Obesity is detrimental in both major depressive disorder and bipolar disorder. In the latter, obese people are more likely to have depressive symptoms, more severe symptoms that elevate the risk of suicide, and poor cognitive performance. Overweight bipolar people can also have elevations in levels of kynurenine and neopterin, indicative of proinflammation [Reininghaus EZ et al. *Bipolar Dis* 2013], and can display depressed cognitive function [Yim CY et al. *Eur Psychiatry* 2012].