What Constitutes Evidence-Based Pharmacotherapy for Bipolar Disorder? Part 2: Complex Presentations and Clinical Context

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Part 1 of this ASCP Corner examined general principles of evidence-based medicine (EBM) regarding first-line pharmacotherapies across illness phases of bipolar disorder.[1] We shall now consider evidence-based pharmacotherapy for clinical presentations that fall outside the usual and customary realm—for example, due to atypical (e.g., "not otherwise specified" [NOS]) or mixed affective features, course specifiers (e.g., rapid cycling), true comorbidities, or frank treatment resistance. Since many patients with bipolar disorder are neither usual nor customary, those with "non-prototypical" features may well comprise the majority of treatment-seeking patients.

EBM discourages sweeping overgeneralizations (e.g., "Aminoglycosides are good antibiotics"), instead linking drug utility with *context* (e.g., "Aminoglycosides are good antibiotics for gram-negative infections in renally intact patients"); hence, distinct clinical contexts (e.g., "Quetiapine treats depression in bipolar II patients with rapid cycling") may offer more useful ways of thinking than unspecified clinical contexts (e.g., "Is quetiapine useful for bipolar disorder?"). We will generously assume that working diagnoses, and terms such as *treatment resistant, rapid cycling, mixed episode,* and *comorbid,* have been arrived at with due rigor and that prior medication "nonresponse" is not simply the result of wrong or underdosed treatments for inaccurate diagnoses.

"NOS" Diagnoses

"Not otherwise specified" subdiagnoses hold value for identifying non-unipolar mood disorders that fall short of DSM-IV criteria for mania or hypomania. As such, they should prompt formulations broader than DSM-IV categories (e.g., disorders of impulse control, affective dysregulation, or chronobiological disturbances) rather than force-fit a diagnosis in an attempt to oversimplify complex problems. Findings from trials in bipolar I or II disorder must be extrapolated cautiously to "NOS" patients. Indeed, it may be impossible to conduct randomized controlled trials (RCTs) when symptom heterogeneity prevents first establishing valid, reliable diagnostic categories. Moreover, specific ways in which medications for bipolar I or II disorder may benefit "NOS" patients have yet to be demonstrated empirically.

Mixed Episodes

Antidepressants do not hasten recovery when bipolar depression coincides with even subsyndromal mania.[2] Depression during mania may portend a better response to divalproex than lithium.[3] Most atypical antipsychotics, divalproex, and extended-release carbamazepine are U.S. Food and Drug Administration (FDA) approved in mixed episodes.

Rapid Cycling

Originally defined based on lithium nonresponsivity, the term *rapid cycling* is sometimes used imprecisely to mean "mood lability" (a separate phenomenon for which no psychotropic, ironically, has been formally studied). DSM-IV rapid cycling shows comparable prophylaxis rates (~50%) with lithium or divalproex.[4] Antidepressants have never been shown to improve rapid cycling, with the possible exception of low-dose monoamine oxidase inhibitors.[5] Retrospective intramural data from the National Institute of Mental Health (NIMH) suggest that antidepressants may accelerate cycling frequency in a minority (about one fourth) of bipolar patients.[6] Substituting placebo for antidepressants eliminated rapid cycling in 17 of 51 (33%) NIMH bipolar subjects, supporting the view that antidepressant cessation alone constitutes an evidence-based treatment for rapid cycling.[5] Elsewhere, secondary analyses of some controlled studies with atypical antipsychotics, notably, olanzapine[7] and quetiapine,[8] demonstrate acute antimanic or antidepressant efficacy, respectively, despite prior rapid cycling. No medication has prospectively shown longer-term "anti–rapid cycling" effects (i.e., the ability to prevent multiple episodes for up to 1 year). Perhaps coming closest to this benchmark is lamotrigine; one RCT showed longer time to dropout with lamotrigine than placebo over 6 months in bipolar II rapid cyclers,[9] and increased weekly achievement of euthymia,[10] but the primary outcome of time until intervention for relapse in that study was negative. Case-control data suggest nimodipine may be of some value,[11] although replications or robust controlled data with other calcium-channel blockers (e.g., verapamil) are lacking. Suprametabolic thyroid augmentation, if not contraindicated by osteopenia or arrhythmias, is sometimes advocated based mainly on 1 small study (N = 11) that involved single- or double-blind within-subject placebo substitution,[12] although no long-term studies exist.

Comorbid Substance Abuse

Divalproex is the sole medication shown to reduce alcohol use better than usual treatment, independent of mood effects, in adult dual-diagnosis bipolar disorder with alcoholism (and intact hepatic function).[13] Pediatric dual-diagnosis patients function better and have less drug use with lithium than placebo[14]—in contrast to poorer retrospectively observed responses to lithium among adults with bipolar mania and substance abuse.[15] Small open trials with other medications for bipolar disorder with alcohol or drug abuse have yielded varying results (e.g., reduced craving and improved mood but no change in toxicology screens with quetiapine [N = 30][16]; improved mood and reduced alcohol use with lamotrigine [N = 21][17]). Other agents are relatively unstudied. As noted in part 1, large-scale RCTs support the off-label use of topiramate for craving and alcohol symptoms in primary alcohol dependence, but not for mood symptoms in bipolar disorder.

Comorbid Anxiety

In the absence of prospective controlled trials for bipolar-anxiety dual disorders, inferences must be drawn from anxiolytic effects shown during treatment for bipolar depression with olanzapine-fluoxetine combination, quetiapine, or divalproex. Certain anticonvulsants (e.g., gabapentin,[18,19] pregabalin[20]) with negative RCT data for mood symptoms have positive RCT data for generalized anxiety disorder or social phobia (e.g., gabapentin, pregabalin) and may reasonably extrapolate *specifically as anxiolytics* among bipolar patients. Serotonergic antidepressants may be helpful, but their anxiolytic efficacy and safety in bipolar disorder are unstudied and therefore, technically, experimental. Adjunctive cognitive-behavioral therapies are most likely underutilized.

Treatment-Resistant Bipolar Depression

A small (i.e., underpowered) but randomized trial[21] found modest, comparable response rates with lamotrigine (N = 21, 25%), inositol (N = 23, 16%), and risperidone (N = 22, 4%)—the latter finding suggesting that not all atypical antipsychotics possess antidepressant properties. The anti–Parkinson's disease drug pramipexole outperformed placebo in 1 small (N = 22) controlled trial.[22] Interest in possible antiglutamatergic mechanisms has led to favorable preliminary, open-label data (N = 14) with riluzole added to antimanic agents.[23] Adjunctive monoamine oxidase inhibitors are sometimes viewed as useful in anergic bipolar depression, based mainly on a high response rate (81%) found in 1 RCT studying 56 non–treatment-resistant patients.[24] Olanzapine-fluoxetine combination carries FDA approval for acute bipolar depression and shows efficacy in unipolar depression unresponsive to 2 prior antidepressants,[25] suggesting an evidence-based extrapolation for treatment-resistant bipolar depression. No other traditional antidepressant has shown superiority to placebo for bipolar depression, treatment-resistant or otherwise. Electroconvulsive therapy also may be underutilized, although modern trials are scarce. Novel forms of brain stimulation, such as vagal nerve stimulation or repetitive transcranial magnetic stimulation remain experimental and not well established.

Metabolic Risk Ratios

No formula exists for perhaps the most difficult of EBM decisions: determining when the potential for weight gain or glycemic or lipid dysregulation outweighs, or is outweighed by, illness severity. Constructs such as "number needed to treat" (the lower the better) versus "number needed to harm" (the higher the better) offer a useful metric for gauging relative benefits versus risks. In principle, agents with the fewest adverse effects yield safer and more satisfactory outcomes provided that they are efficacious. Floridly ill, treatment-resistant patients may have disastrous psychiatric outcomes if clinicians shun proven treatments (e.g., lithium, olanzapine, or divalproex) based solely on concerns about tolerability. On the other hand, it is possible that patients with simpler illness presentations could benefit sufficiently from medications with fewer adverse effects, even if the medications are less well studied in complex disease states.

Internet search engines such as PubMed and MEDLINE give clinicians ready access to primary source literature, allowing practitioners to determine for themselves what treatments have or have not been studied (and at what level of rigor) for clinical states that arise in particular contexts. So equipped, clinicians can easily integrate EBM with personal expertise and observation to solidify rationales behind treatment decisions in virtually any clinical context.

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