What Constitutes Evidence-Based Pharmacotherapy for Bipolar Disorder? Part 1: First-Line Treatments

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Ever since the term *evidence-based medicine* (EBM) entered the medical lexicon in 1992,[1] there has been much furor among clinicians both in and out of academic circles about what practices do and do not fall within its domain. Randomized controlled trials still provide the greatest level of rigor for determining whether or not an intervention is efficacious. This is largely because the process of randomization, if successful, accounts for confounding biases that might otherwise influence treatment decisions, such as an unwitting tendency to favor (or avoid) certain treatments in patients with particular characteristics. Active comparator studies also provide useful information, after efficacy has already been established, particularly if they have been adequately powered (e.g., for noninferiority, if not for superiority). Open or nonrandomized studies carry risks for misattributing improvement (or worsening) to a treatment when, in reality, it may be impossible to differentiate drug effects from the natural course of illness.

Yet, most controlled studies in bipolar disorder exclude patients with unstable medical illnesses, comorbid psychiatric or substance use disorders, atypical or complex forms of illness, or poor treatment adherence—that is, the vast majority of individuals treated for bipolar disorder within community settings. Rather than impose EBM findings literally and generically upon any and all patients, it is more useful to consider general evidence-based principles that can inform individualized treatments. Some examples of these principles are highlighted in the following paragraphs.

Formulate as clear an impression as possible about the disease phenomenology and clinical state for which a treatment is being devised. Treatment responses may well differ from those reported in controlled efficacy studies, based on the presence or absence of features such as bipolar I versus II subtype, psychosis, rapid cycling, degree of treatment resistance, past medication response, and mixed versus pure manifestations of mania or depression, as well as the presence of comorbid medical, psychiatric, or substance use disorders. Candidacy for lithium, for example, is much more compelling in an uncomplicated first-episode euphoric manic patient than a multi-episode patient with untreated alcohol dependence and mixed affective features who has already not responded to olanzapine and divalproex.

Distinguish comorbid disorders from differential diagnoses. Truly comorbid conditions may require separate or sequential treatments. For example, in pediatric bipolar disorder with comorbid attention-deficit/hyperactivity disorder (ADHD), randomized trial data indicate that when mood stabilizers such as divalproex fail to improve ADHD symptoms during mania, adjunctive stimulants appear efficacious and safe.[2]

Avoid treatments that visibly worsen either phase of the illness. There are no data to support the use of antidepressants during mania, yet many manic inpatients inexplicably receive antidepressants. While depressive episodes often follow acute manias, there is no evidence that retaining (or starting) antidepressants during mania helps forestall subsequent depressive episodes; neither do antidepressants "selectively" treat depressive symptoms accompanying mania.[3]

Assure adequate medication trials have occurred before determining that a treatment lacks efficacy. Failure to use a medication (or electroconvulsive therapy, ECT) at an adequate dose for an adequate duration represents a common source of purported lack of efficacy in patients thought to be "treatment resistant." "Nonresponse" to ECT is difficult to ascertain if seizure threshold has not been reached or duration is suboptimal. What constitutes an adequate pharmacotherapy trial for mania? No empirically derived definition exists. In the 2004 Expert Consensus Guideline Series for the Treatment of Bipolar Disorder,[4] nearly three quarters of respondents felt that no signs of response after 1 week warranted a change of medications, but no consensus emerged about reasonable timeframes for medication changes after partial responses.

Adjunctive antidepressants have shown no greater efficacy than mood stabilizers alone for bipolar depression. The field has long been concerned that antidepressants incur risks for mood destabilization in bipolar depression, taking for granted their presumed efficacy by extrapolation from unipolar depression. In fact, randomized trials reveal that overall, adjunctive antidepressants neither hasten recovery nor induce mania for most bipolar patients.[5,6] Even nonrandomized data suggest that only about 1 in 10 depressed bipolar patients will respond acutely and long-term (up to 1 year) with adjunctive antidepressants.[7] Risk for antidepressant-induced mania or hypomania may be higher in certain at-risk subgroups, such as those with prior antidepressant-induced mania, concurrent manic and depressive symptoms, recent mania, bipolar I subdiagnoses, and comorbid substance abuse.[8] Hence, the utility and safety of antidepressants for bipolar depression appear best determined on a case-by-case basis, informed by patient-specific characteristics.

Know which medications have or have not been studied in bipolar disorder. Whether or not one elects to use a pharmacotherapy "off label" from its U.S. Food and Drug Administration indication, a separate matter lies in whether or not evidence exists for (or against) efficacy for a particular purpose. It would be disingenuous to favor using anticonvulsants with no data (or negative controlled data) over those with demonstrated efficacy. Similarly, while the general utility of antidepressants in bipolar disorder remains a matter of debate, it becomes risky to use antidepressants that have not been studied in a controlled fashion for bipolar depression (such as escitalopram, duloxetine, or mirtazapine) over ones that have. Bipolar depression differs fundamentally from unipolar depression; one must therefore recognize the uncertainties of prescribing a medication that has never been well-studied for a specific disease state over other medications that have (e.g., bupropion or sertraline).[9] One also might be inclined not to prescribe adjunctive antidepressants that have failed to show superiority to mood stabilizers alone, such as paroxetine.[5,6] Moreover, since prior studies demonstrate that noradrenergic agents (e.g., tricyclics) or mixed agonists (i.e., venlafaxine) carry an elevated risk for inducing mania or hypomania,[9] one might exercise caution if using other noradrenergic agents that lack data in bipolar depression (e.g., duloxetine or atomoxetine).

Do not presume psychotropic "class effect" generalizations. Among anticonvulsants, only divalproex, carbamazepine, and lamotrigine have demonstrated efficacy over placebo in large clinical trials for any phase of bipolar illness, whereas negative placebo-controlled findings have been

published in mania with oxcarbazepine, topiramate, and gabapentin.[10] Despite the theoretical appeal of linking mood stabilization with anticonvulsant GABAergic and antiglutamatergic drug mechanisms, clinical trials have not borne out such broad generalizations. It would empirically be a misnomer to construe all anticonvulsants as having mood-stabilizing properties. Similarly, among atypical antipsychotics, some have demonstrated efficacy for acute bipolar depression (e.g., quetiapine or olanzapine-fluoxetine combination), while others either have not demonstrated efficacy or have not been studied for that purpose.

Differentiate psychotropic effects other than mood stabilization for anticonvulsants and other psychoactive agents. Anticonvulsants that fail to treat mania or depression may, nevertheless, exert benefits for other types of symptoms in patients with bipolar disorder. Gabapentin may have utility for anxiety disorders (e.g., panic disorder or social phobia—common comorbidities in bipolar disorder) entirely separate from its debated thymoleptic value. Similarly, despite topiramate's lack of antimanic efficacy in multiple placebo-controlled trials, controlled studies do support its efficacy for migraine, binge-eating disorder, and alcohol dependence—all common comorbidities with bipolar disorder.[10] Mood stabilization with quetiapine or olanzapine-fluoxetine combination also appears to be linked to anxiolytic effects in the context of treating bipolar depression, potentially obviating the need to accrue additional (potentially unnecessary) anxiolytic medications.

Favor pharmacologic parsimony when feasible. Pharmacologic craftsmanship often involves combining agents that exert complementary pharmacodynamic effects. Examples include pairing the antiimpulsivity effects of lithium or divalproex with the more prominent antidepressant efficacy of adjunctive lamotrigine; or using anxiolytic anticonvulsants (e.g., gabapentin) in conjunction with thymoleptic anticonvulsants (e.g., divalproex) when relevant; or adding the psychostimulant modafinil "off label" to quetiapine or lamotrigine for anergic bipolar depression, counteracting iatrogenic sedation if present, and capitalizing on potential antidepressant synergy, since these medications have nonredundant mechanisms and each has at least one published positive randomized controlled trial for acute bipolar depression.

Certain psychotropic agents may exert targeted benefits for specific symptoms or psychopathology dimensions, regardless of efficacy for affective syndromes. Lithium, for example, may diminish the risk for suicide attempts in mood disorder patients independent of its thymoleptic efficacy and, as such, deserves consideration in the regimen of mood disorder patients with high suicide risk independent of antimanic or antidepressant efficacy.[10] Similarly, divalproex may hold value for alcohol abuse symptoms in dual-diagnosis bipolar patients regardless of its efficacy for mood symptoms.[10]

Use antipsychotic medications at appropriate dosages to treat psychosis. Psychosis sometimes can be misidentified as anxiety, leading to subtherapeutic doses of antipsychotic drugs and presumed lack of efficacy.

Consider the extent to which mood stabilizing agents exert relative antimanic versus antidepressant effects. Lithium prevents both manias and depressions in bipolar disorder but exerts a more robust effect against manias than depressions,[11] while lamotrigine appears to do the opposite.[12] Therefore, it may be more pragmatic to discuss the extent to which a mood stabilizing agent exerts its effects by virtue of its relative antimanic or antidepressant properties, rather than in absolute terms of bimodal efficacy.

Exercise caution when combining potentially redundant medications or medications that may exert undesirable pharmacokinetic or pharmacodynamic interactions. By example, the use of multiple atypical antipsychotics is common—sometimes deliberate, sometimes by happenstance, and always in the absence of controlled data. Using 2 or more atypical antipsychotics at subtherapeutic doses without first optimizing one poses an increased risk for cumulative adverse drug effects without a priori reason to expect better efficacy. Moreover, combining agents with tight binding affinities for the D_2 dopamine receptor (e.g., risperidone, aripiprazole) may serve merely to increase extrapyramidal or tuberoinfundibular effects. Dopamine-blocking agents that bind tightly to the D_2 receptor, such as these, would also be more likely to displace the binding of other dopamine-blocking agents that bind with lower affinity to the D_2 receptor (e.g., quetiapine) and may altogether defeat the purpose of combining such drugs, other than speculative complementary activity at other receptor sites.

The principles of evidence-based medicine, far from stipulating dogma, involve the judicious application (rather than sheer recapitulation) of findings from the literature as a means to inform clinical decision-making—a skill that depends on the ability of individual practitioners to integrate knowledge of empirical studies with their own observations and experiences. Logical pharmacotherapies result when clinicians critically evaluate and weigh the strength of evidence for or against therapeutic agents and devise interventions based on cogent rationales and strategies.

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