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Wrestling With Antidepressant Use in Bipolar Disorder: The Ongoing Debate

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The Fall 2019 ASCP Psychopharmacology Update in New York included a debate by the authors on the controversial topic of whether, and when, antidepressants are appropriate in bipolar disorder. Our mutual goal was to suggest that the current state of knowledge precludes absolute recommendations for or against the use of traditional monoaminergic antidepressants. Rather, clinicians should have a clear rationale in mind when deciding whether to use or avoid antidepressants in any given patient with bipolar disorder. Herein we recap the concepts we consider of greatest relevance for decision-making on this relentlessly contentious topic, focusing on which patients may fare better or worse with antidepressants.

The controversy surrounding antidepressant use in bipolar disorder arose from initial observations in the 1970s and 1980s, mainly with tricyclic antidepressants, that some depressed bipolar patients may develop a next manic episode sooner than expected following antidepressant exposure and/or incur more frequent subsequent episodes as an iatrogenic phenomenon. Some clinicians refer to adverse outcomes as antidepressant “misadventures”; however, we discourage use of this term because it fosters automatic assumptions that antidepressants expectably cause poor outcomes. Problematic is how to differentiate polarity switches or cycle accelerations that “clearly” result from antidepressant exposure versus mood episodes that simply reflect the natural course of illness. The seminal NIMH Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) failed to identify either an acute benefit or mood destabilization in a large group of depressed

bipolar patients taking a mood stabilizer with versus without an antidepressant¹—failing to discriminate switches due to antidepressants versus natural illness course. Longer-term data on the purported hazard for antidepressants to hasten mania relapse long-term come mainly from older data comparing lithium or imipramine,² with almost no studies exploring longitudinal course with versus without modern antidepressants.

The largest meta-analysis to date examining acute risk of polarity switch in acute bipolar depression (encompassing over 10,000 subjects from 51 trials) reveals a risk ratio of about 12% when considering only randomized data (about 14% with all prospective studies, and as high as 31% with only retrospective trials).³ The 12% switch rate from prospective studies is not much different from the STEP-BD-observed 10.7% risk of switch from depression to mania/hypomania using *only a mood stabilizer*.³ Sidor and MacQueen⁴ identify a very high number needed to harm (NNH) of 200 with respect to antidepressant-associated polarity switch. Their meta-analysis also showed underwhelming antidepressant efficacy in bipolar depression, with a rather high number needed to treat of 29.⁴ From one perspective, the collective database argues that antidepressants are, on average, neither helpful nor harmful—that is, they are most likely a waste of time for the majority of depressed bipolar patients. The fact that clinicians nevertheless tend to favor their use (both short- and long-term) over FDA-approved treatment options (ie, olanzapine-fluoxetine combination, quetiapine, lurasidone, or cariprazine) defies evidence-based medicine.

On a deeper level, though, the sheer presence of a bipolar diagnosis alone may not convey sufficient information for deciding whether to use an antidepressant. Simply “having a bipolar diagnosis” may be tantamount to having a diagnosis of cancer (how is an appropriate antineoplastic drug then chosen?), an upper respiratory infection (is an antibiotic appropriate? Which one? Or an antifungal drug? Or tincture of time?), or a headache (when and how do we decide the appropriateness of nonsteroidal antiinflammatories, steroids, opiates, antimigraine drugs, or a therapeutic lumbar puncture?). Identifiable bipolar subgroups have empirically been shown to fare better with antidepressants, including those with bipolar II (rather than bipolar I) depression, non-rapid cyclers, patients with pure (non-mixed) depressed phase episodes, and those lacking a history of alcohol or substance use disorders, among other characteristics.⁵ Long-term antidepressant use appears to be a wiser proposition mainly (if not only) when it initially produces a marked acute response (rather than an incomplete or nonresponse).⁶

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Table 1. The Arguments for and Against Antidepressant Use in Bipolar Disorder

The Pro Argument	The Con Argument	The Dilemmas in Trying to Reconcile
Few specific antidepressants have been formally studied in bipolar depression; it would be scientifically disingenuous to “prohibit” the entirety of a drug class based on only a handful of negative trials within that class.	No antidepressant has shown superiority to placebo for treating acute bipolar I depression (with the idiosyncratic exception of fluoxetine plus either olanzapine or lithium), making it hard to justify their widespread use.	Absence of evidence is not evidence of absence; no antidepressant developed after 1999 (including all serotonin-norepinephrine reuptake inhibitors [SNRIs] and newer novel agents such as vortioxetine or vilazodone) has been studied in placebo-controlled trials for bipolar depression.
Risk for treatment-emergent affective switch attributable to antidepressants is much lower than was once thought.	Tricyclics, and possibly SNRIs such as venlafaxine, have consistently shown higher switch rates than other antidepressant classes.	Some antidepressants may be safer and more effective than others. Existing studies that attribute greater hazard to specific antidepressant subclasses do not systematically account for other patient-specific factors that influence outcomes.
Sertraline and fluoxetine both outperform placebo or lithium for bipolar II depression, both acutely and prophylactically. ⁵	Preliminary pilot studies have not been replicated. Is bipolar II disorder such a nosologically distinct construct from bipolar I disorder?	The lack of replication studies plagues efforts to form definitive conclusions.
Stopping an antidepressant after an initial robust response may increase the chance of depression relapse.	Antidepressants could destabilize mood during long-term use, and that risk may not be apparent until it occurs.	There are very few long-term, adequately powered relapse prevention studies with antidepressants in bipolar disorder.
Alternatives to antidepressants are not benign. Specific antipsychotic drugs used to treat bipolar depression carry risks for motor, metabolic, endocrine (prolactin), and other adverse effects (sedation, falls from orthostatic hypotension).	There are currently 4 FDA-approved treatments for bipolar depression, making it hard to justify experimenting with unproven “traditional antidepressants.”	There are no positive long-term continuation/maintenance trials of lurasidone, cariprazine, and olanzapine-fluoxetine combination specifically following a bipolar depressive episode, precluding knowledge of their prophylactic value and safety.

Table 1 presents the core challenges one must consider when deciding on the wisdom or lack thereof in using antidepressants for a given patient with bipolar disorder.

Perhaps the most solemn “takeaway” from this debate was the sense of frustration felt by many clinicians who want clear and simple guidance on “what to do” for bipolar depression, when no such simplicity exists. Having a rationale first requires appreciating that (a) lack of efficacy, more than risk for acute mood destabilization, appears to be the greatest challenge when using antidepressants, but (b) the paucity of large, replicated empirical trials (particularly with more modern agents) makes it hard to form generalizations about whether antidepressants as a class are helpful, harmful, or neither. Devising a strategy—whether that involves a monoaminergic antidepressant, one of the 4 FDA-approved antidepressant antipsychotic preparations, or a novel intervention (such as ketamine, lamotrigine ± lithium or quetiapine, or pramipexole, among others)—depends on the unique clinical profile of a given patient.

Every patient is an “N of 1” experiment, making someone’s personal history of response to a specific drug the most influential datapoint to guide that one patient’s further care. Absent such a personal history, one might weigh pros and cons of specific antidepressants based on the patient’s unique characteristics. Antidepressants appear inappropriate when current manic or hypomanic symptoms exist, and they should be prescribed once lack of efficacy has been judged. Newer antidepressants lack data altogether, and, if chosen, their status as “unstudied entities” should be disclosed to patients. Perhaps most important of all is systematic and careful symptom monitoring, including recognition of manic symptoms in all depressed patients, when using any intervention for a condition as dynamic as bipolar depression; whether circumstances improve or worsen, resulting either from or despite an intervention, clinicians should be astute

to the protean nature of bipolar disorder and be prepared to modify a treatment plan as dictated by changing symptoms and the observable consequences of any treatment, good or bad, antidepressant or otherwise.

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