See article by Maccariello et al

Are (Some) Antipsychotics Depressogenic in Bipolar Disorder?

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In this issue of the *Journal*, Maccariello and colleagues[1] present one of the first studies dedicated to examining the phenomenon of mood destabilization from mania to depression in bipolar disorder patients and the possible risk for depressive switches associated with first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). That the authors have simply framed the issue of treatment-emergent affective switch (TEAS) to depression instead of mania is itself a major contribution given that attention to this topic has historically focused more on the question of iatrogenic polarity switches from depression to mania. Within the context of the broader literature, however, readers will wonder whether and when antipsychotics treat or cause bipolar depression, whether antipsychotic use could sometimes simply be a proxy for other factors that might predispose to depressive episodes, and whether or not all antipsychotics are created equal with respect to their antidepressant versus prodepressant properties. Let us consider each of these points, starting with the last.

Knowing whether psychotropic class effects exist for certain drugs has long been a point of fascination and debate within psychopharmacology. Among anticonvulsants, for example, only 3 (of many more that have been studied) have unequivocally been shown to possess mood-stabilizing properties (ie, carbamazepine, divalproex, and lamotrigine, with only the latter having more robust antidepressant than antimanic properties). Among antipsychotics, some SGAs are demonstrably better than placebo for treating acute bipolar depression, accompanied by large effect sizes (namely, quetiapine, lurasidone, cariprazine, and olanzapine [with or without fluoxetine]); others have failed to do so across multiple adequately powered randomized trials (notably, aripiprazole[2] and ziprasidone[3]), while still others remain unstudied in randomized trials (eg, brexpiprazole, clozapine, paliperidone).

The TEAS phenomenon in bipolar disorder has traditionally focused more on concerns about drugs that might catalyze switches from depression to mania—particularly (and controversially) antidepressants. From that much-debated literature, we now recognize that randomized, placebo-controlled trials are the sole means by which one can confidently know when to blame depression-to-mania switch events on an antidepressant versus on the natural course of the disorder. Moreover, the field has learned that attributions of drug effects cannot be considered without appreciating and accounting for predisposing factors to a switch event. In the case of antidepressant-associated mania, such outcome moderators include bipolar I subtype, mixed features, rapid cycling, and differential risks with specific antidepressants (eg, tricyclics), among other factors.[4]

Far less attention and empirical study have addressed the risk of TEAS from mania to depression. Depressogenic drug effects, in general, are well-recognized from older studies of monoamine depletion (with, eg, reserpine, tetrabenazine), glucocorticoids (eg, prednisone), and interferon-α (through varied hypothesized mechanisms involving hormonal, proinflammatory, and most likely other cellular effects). In bipolar disorder patients, whose susceptibilities to drug-induced mood changes may differ from those of psychiatrically healthy subjects, risk for mood destabilization (to either mania or depression) following psychotropic drug exposure, with control for confounding variables, remains understudied.

Among antipsychotics, a handful of controlled trials suggest that some (but not all) SGAs possess antidepressant effects, while at least some FGAs could be prodepressant. Notably, olanzapine and haloperidol demonstrate comparable acute antimanic efficacy, but haloperidol has shown a nearly 2-fold higher risk for depression arising within 12 weeks of initiation.[5] Similarly, depressive switches after mania were significantly more likely among bipolar patients taking a mood stabilizer plus the FGA perphenazine than among those taking a mood stabilizer plus placebo.[6] Consistent with those observations, Maccariello et al[1] found that depressive switch events were more frequent among manic patients who received FGAs than among those who received SGAs. Other randomized trials have shown no advantage over placebo to prevent depressive episodes with certain SGAs, notably, ziprasidone,[7] risperidone long-acting injectable (LAI),[8] or aripiprazole (either oral[9] or LAI[10])—though, in fairness, these latter study designs involved index manic and/or mixed episodes and were therefore enriched for relapse to mania rather than depression and thus more accurately demonstrated no increased risk for inducing depression with these agents.

The findings by Maccariello et al[1] linking antipsychotics with depression TEAS events are provisional because theirs was not a randomized trial. Nevertheless, the authors

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wisely (and elegantly) controlled statistically for important moderators of depressive recurrences, including polarity proneness—an underappreciated yet key construct when treating bipolar disorder, first described over 30 years ago by Quitkin et al.[11] That Maccariello et al also successfully controlled for histories of rapid cycling (which was no different in frequency between subjects who did or did not have depressive switches) lends further elegance and rigor to their naturalistic findings.

Importantly, in past SGA studies, depression-predominant polarity has been a moderator of poorer acute antidepressant response even with otherwise efficacious bipolar depression treatments such as olanzapine-fluoxetine combination.[12] In their regression model, Maccariello et al showed that both depression-predominant polarity and FGA or SGA use each strongly predicted post-manic depression, raising very interesting questions about the extent to which depression-proneness simply begets more depressions unameliorated by overall antipsychotic use or whether an interaction could exist between depression-proneness and TEAS events with certain antipsychotics. Notably, Maccariello et al also found that depressive switch events were more common among antidepressant recipients—posing the vexing question of whether, here again, medication (antidepressant) use was depressogenic or, more likely, simply a proxy for depression-proneness. On the basis of randomized placebo-controlled relapse-prevention trials, we might speculate that perhaps some antipsychotics predispose to switches to depression (eg, perphenazine,[6] ziprasidone,[7] aripiprazole,[9] or risperidone LAI[8]) while others might be preventive (eg, quetiapine,[13] asenapine,[14] olanzapine[15]) depending on a given patient's polarity proneness, alongside other patient-specific moderators of outcome. Imagine the potential impact on clinical outcomes if clinician-readers of this article began to routinely assess polarity predominance in bipolar patients before choosing from among antimanic treatment options.

The present nonrandomized study, underpowered to explore hypotheses about specific antipsychotics even provisionally, begs for future randomized trials to test the critical distinction between their putative antidepressant and depressogenic effects, and differential effects as a function of mania- versus depression-polarity proneness, when comparing drugs that we collectively call "antipsychotics." Only then will followers of this literature gain better insight into factors that drive the natural course of illness versus treatment effects that are detrimental, beneficial, or spurious.

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