Who Gets Worse on an Antidepressant? Six Patients to Watch For

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RESEARCH UPDATE

I suspect that a selection bias is changing the types of patients we see in psychiatric practice. Primary care providers now prescribe 80% of antidepressants in the US,[1] so psychiatrists can expect to see more patients who don’t recover on these agents while the ones who do are absorbed by primary care clinics. Among these are patients with treatment-resistant depression and others whose depression worsened on an antidepressant.[2] It’s helpful to understand these reactions, as an adverse response is often more informative than a non-response.
Six types of patients at risk

The following slides will detail 6 types of patients who are at risk for adverse neuropsychiatric events on antidepressants. I’ve listed them in approximate order of risk, but bear in mind that none of these risks are absolute or even close to 100%; there are many patients in each group who respond very well to antidepressants.
In patients with bipolar disorder, antidepressants are more likely to cause a mixed state than to flip a depression into euphoric mania. Patients tend to experience this as a worsening of their depression rather than a new episode. Koukopoulos’s original description of depressive mixed states sheds helpful light on that experience: “The patient complains of anxiety, inner tension, irritability, anger, despair, suicidal impulses, crowded and/or racing thoughts, rumination, and insomnia.”[3]

This risk varies among the antidepressants: lower with bupropion, SSRIs, and MAOIs; midlevel with the SNRIs; and highest with the tricyclics.[4] The risk is greater for patients with bipolar I than II, and for those with recent (meaning ≤ 6 months) manic symptoms or rapid cycling.[4] A minority of bipolar patients improve on antidepressants (approximately 1:29 to 1:46), but, for bipolar patients as a whole, the risks of antidepressants outweigh their benefits.[5]
2. MAJOR DEPRESSION WITH MIXED FEATURES

Around 25% of patients with unipolar depression have 3 or more manic symptoms during their depression,[6] and this condition is recognized as Major Depression with Mixed Features in DSM-5. Although not fully bipolar, these patients share many features with bipolar patients, such as family history, course of illness, and . . . worsening on antidepressants.[7] A new treatment guideline warns against antidepressant monotherapy in these unipolar patients and emphasizes atypical antipsychotics and mood stabilizers instead.[8]
3. DEPRESSION WITH SHORT-DURATION HYPOMANIA

A significant minority of depressed patients cycle in and out of brief hypomanias that fall below the 4-day threshold required for a bipolar diagnosis. DSM-5 includes this syndrome under “conditions for further study,” and new research suggests they too are at risk for worsening on antidepressants. In the large, international BRIDGE study, the risk of antidepressant-induced manic symptoms rose with the duration of hypomania (see above).[9] The lesson from this and similar studies is that the more intense, numerous, frequent, or recent the manic symptoms, the greater the risk of worsening on antidepressants.

More research is needed in this “condition for further study,” but a recent study suggests that lamotrigine confers similar benefits in patients with short hypomanias as it does for those with full bipolar II.[10]
Patients with borderline personality disorder (BPD) are probably a heterogeneous group, at least in terms of their pharmacologic responses. Antidepressants—particularly the SSRIs—are supported by small controlled trials in BPD, but other research suggests that BPD is a risk factor for worsening on antidepressants (even in non-bipolar patients).[11] A hint of this was seen in the early investigations of tricyclic antidepressants in BPD. While some patients benefited, others became more irritable, assaultive, disinhibited, paranoid, and suicidal on the tricyclics.[12,13]
5. CHILDREN, ADOLESCENTS, AND YOUNG ADULTS

Patients under age 25 are at increased risk for suicidality with antidepressants. In adults, the risk is neutral, and it’s not until age 65 and over that a protective effect against suicide is detectable with antidepressants.[14] That was the conclusion of several large meta-analyses a few years back, and recent studies have upheld those results, with one reporting that antidepressants double the risk of suicidality and aggression in children and teens.[15]

It’s tempting to conclude that undetected bipolar disorder is the cause of this association, as the peak onset of that illness is age 15 to 25. However, studies examining that hypothesis have yielded conflicting results.[4]
6. GENETICS: SHORT ARMS AND SLOW METABOLIZERS

Genetic testing may provide clues to adverse effects on antidepressants. The short arm of the serotonin transport gene (ie, the 5-HTTLPR S/S polymorphism on SLC6A4) is the best-studied example. Patients with this gene are less likely to respond to SSRIs and more likely to experience manic symptoms on antidepressants.[16] Studies have also examined whether this gene is associated with agitation, akathisia, or suicidality on SSRIs, but those results are inconclusive.[17]

Patients who metabolize antidepressants slowly may reach high serum levels at normal doses, causing a broad spectrum of adverse effects including anxiety, insomnia, and agitation. Genetic testing of hepatic enzymes, particularly CYP2D6, can identify those cases.
Some of the adverse reactions to antidepressants I’ve described are rare (eg, suicidality), and others more common (eg, mania and mixed states). When society pays too much attention to rare events, it can be a public health disaster: the rate of suicide actually increased among youth in the US after the FDA placed a black-box warning about suicidality on antidepressants in 2004. Psychiatrists, however, can’t afford to ignore that reaction as the patients who have it are more likely to find their way to our offices.
These patients require careful thought when they call in despair after starting a new antidepressant. Telling them to “soldier on” may not be the right advice.
References