To the Editor: Fekadu et al. are to be commended for their article on quantifying treatment-resistant depression (TRD). But while the authors note the importance of "paradigm failures" in producing apparent TRD—for example, the failure to discern the type of depression showing "resistance"—I believe greater emphasis should be given to diagnosing what I call pseudoresistant bipolar depression (PBD). Parker et al. found that more than 30% of apparent TRD patients had undiagnosed and inappropriately managed bipolar disorder. In my own tertiary-level psychopharmacology consultation practice, I found that well over half of patients referred for TRD were actually bipolar spectrum patients. With the collaboration of Ghaemi and colleagues, my findings led to the development of a screening instrument, the Bipolar Spectrum Diagnostic Scale, for the detection of bipolar II and other "softer" variants of bipolar spectrum disorder.

In general, I found that what referring doctors had called treatment resistance was actually a characteristic dysphoric response during multiple antidepressant trials. This was not the frequently reported "switch" into hypomania or mania; rather, patients almost always described feeling "antsy," "wired," irritable, aggressive, or insomniac while taking antidepressants. This is similar to what Phelps called "agitated dysphoria," in a patient with apparent unipolar mood disorder who experienced this syndrome after...
late-onset loss of antidepressant response. Similarly, Akiskal et al⁵ have argued that “agitated, activated, or otherwise excited depressions (which we consider as depressive mixed states) overlap considerably with the so-called antidepressant ‘activation syndrome’.”

Clinicians faced with apparent TRD should carefully assess the patient for covert bipolar spectrum disease, PBD, and antidepressant-induced agitated dysphoria.

**References**


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