

assumed only after the exclusion of such factors that may lead to apparent treatment failure. However, we would also argue that our staging model simply quantifies the degree of treatment resistance, but does not implicitly specify the cause of such resistance. Apparent resistance to standard treatments for depression may relate to many factors, and the determination of the underlying mechanism is a matter of clinical judgment based on clinical assessment and in-depth structured interviews supplemented by laboratory investigations. We would also argue that it is imperative to search for those factors that can be modified, one of which is undetected bipolarity (above or below threshold) or other diagnostic failures. Our staging model³ will account for this as the number of unsuccessful trials will be higher in those treated suboptimally due to diagnostic failures, but the model also takes into account other predictive features of the illness.

In essence, perhaps Dr Pies is describing 2 possible causes of treatment resistance: iatrogenic treatment resistance in which full bipolar disorder is missed and incorrectly treated, and an inherently more difficult condition to treat in which there is an admixture of depression with subthreshold manic symptoms. Nevertheless, few good clinical trials are available in treatment-resistant depression as a whole, let alone in specific subgroups such as those with subthreshold manic symptoms, and we believe that until the evidence base improves sufficiently to make clearer recommendations as to which patients will respond best to which treatments, an empirical approach such as we have proposed remains the most useful way of staging treatment resistance.

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Drs Fekadu and Cleare Reply

To the Editor: We thank Dr Pies for his comments. We agree with his observation that the presence of bipolar diathesis is an important cause of apparent treatment resistance in depression. As summarized by Dr Pies, a high proportion of cases with treatment-resistant depression, even as high as 50% in some reports, are said to have a bipolar diathesis.¹ This is known to lead to poor treatment response with antidepressants alone. For example, it has been shown that the occurrence of 1 to 3 potentially subthreshold symptoms of hypomania was associated with a history of poor treatment response in recurrent depressive disorder.² Because of its frequent association with treatment-resistant depression and therapeutic implication, due emphasis should be put on the need to detect a bipolar diathesis as suggested by Dr Pies.

Nevertheless, it is also important to consider other potential causes of treatment failure, such as overlooked psychotic symptoms or undetected physical diseases. Perhaps it is also worth noting that, in contrast to the cited study from Parker and colleagues,² in our tertiary care setting such diagnostic failures are not especially common: a recent audit found that in only 15/225 (6%) patients was the subtype of affective disorder modified after detailed assessment. Furthermore, in 6 cases, the diagnosis was changed from bipolar to unipolar, and in only 1 case was the diagnosis changed from unipolar to bipolar. More common was the diagnosis of a nonaffective disorder as the primary disorder, which occurred in just over 15% of cases.

We believe a lack of clarity remains in relation to the terminology of “treatment resistance.” In the strict sense, the factors raised by Dr Pies are diagnostic failures, and, in the presence of these, the depressive disorder should not be considered treatment resistant unless provision of the appropriate treatment fails to resolve the depression. In other words, “true” treatment resistance should be

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