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Editorial

Antidepressants and rapid-cycling bipolar II disorder: dogma, definitions and deconstructing discrepant data†

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Summary
It is suggested that a finding that apparently challenges current practice guidelines, namely that patients with a rapid-cycling pattern of bipolar disorder can take antidepressant monotherapy for months without increasing risk of cycling, may be parsimoniously understood by the way that the investigators defined rapid cycling and by their use of acute-phase fluoxetine monotherapy prior to randomisation to continutaion-phase therapy with fluoxetine, lithium or placebo.

Declaration of interest
During the past 3 years, M.E.T. has been an advisor/consultant to Alkermes, Allergan, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Johnson and Johnson (including Janssen Pharmaceuticals), Lundbeck, MedAvante, Merck (including Schering-Plough), Mylan (including Dey), Neuronetics, Otsuka, Pamlab, PharmaNeuroboost, Pfizer, Rexahn, Roche, Shire, Sunovion, Supernus, Takeda, and Teva, and to the US Food and Drug Administration and the National Institute of Mental Health. He has received honoraria for educational talks supported by AstraZeneca, Lundbeck, Mylan, Otsuka, and Pfizer, and research grants from Alkermes, AstraZeneca, Eli Lilly, Forest, NeoSync, Otsuka, PharmaNeuroboost, and Roche, as well as from the National Institute of Mental Health and the Agency for Healthcare Research and Quality.

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Current practice

There are relatively few absolute truths in psychiatric therapeutics. Nevertheless, one of the most widely endorsed recommendations in practice guidelines is that patients with a rapid-cycling course of bipolar affective disorder should not receive antidepressants, particularly as a monotherapy, that is, without concomitant therapy with a mood stabiliser.[1–4] The findings of Amsterdam and colleagues[5] in this issue of the *Journal* are thus of great interest because they appear to challenge the current dogma.

Amsterdam and colleagues' findings

Amsterdam *et al*[5] report that not only did patients with a history of rapid-cycling bipolar II disorder show no increased risk of treatment-emergent affective switches across 50 weeks of fluoxetine monotherapy, but they actually had a nominally better outcome than the patients who were randomly assigned to be switched from fluoxetine to lithium. Do these provocative findings indicate that our current practice guidelines need to be rethought or does a careful reading of this study reveal alternative explanations for such discrepant data?

Perhaps the most important methodological detail of this study concerns the way that Amsterdam and colleagues classified 'rapid cycling'.[5] Specifically, unlike the DSM-IV-TR criteria[6] for a rapid-cycling pattern, which specify that the individual must have experienced four or more distinct episodes during the past year, the patients in the current study were classified as 'rapid cycling' if they had an average of four or more affective episodes per year during the course of their illness. There is no doubt that this definition identified patients with a large number of lifetime episodes: their 'rapid-cycling' group had experienced more than three times the number of lifetime depressive episodes (22.8 *v.* 6.6) and five times more lifetime hypomanic episodes (45.0 *v.* 9.0) than the 'non-rapid-cycling' group. But, this definition did not ensure that the 'rapid-cycling' group actually met the DSM-IV-TR criteria for the past year, nor did it ensure that the 'non-rapid-cycling' group actually did not meet the DSM-IV-TR criteria. We do not know how many of the participants in Amsterdam *et al*'s study would have met the DSM-IV-TR criteria for a rapid-cycling pattern. But we do know that the average length of the index depressive episode of their rapid-cycling group was reported to be of 13.3 months' duration, which essentially precludes the possibility that many of the patients in this group were actually in a rapid-cycling pattern of illness at the time they entered this study. Moreover, as the average index depressive episode of the non-rapid-cycling group was reported as only 4.0 months, their rapid-cycling-group was paradoxically more chronically and persistently depressed than the non-rapid-cycling group at study entry.

A second important methodological detail pertains to the design of the larger study from which these data were drawn[7]: all of the patients included in this report had all been first treated with up to 80 mg/day of fluoxetine for 12 weeks before entering the 50-week, randomised, placebo- controlled discontinuation/substitution phase of this study. Moreover, only those patients who stably remitted on fluoxetine therapy, as defined by a Hamilton Rating Scale for Depression (HRSD) score of eight or less at week 12, entered the next phase of the study. As such, the longer-term study examined a patient group that was 'enriched' not only for response to fluoxetine, but also for the absence of treatment-emergent affective shifts during fluoxetine monotherapy.

The most parsimonious explanation of the results of Amsterdam *et al*[5] is that there is a subset of patients who meet criteria for bipolar II depression who not only can remit on fluoxetine monotherapy but can also continue on this therapy for up to 1 year without an increased risk of treatment-emergent

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affective shifts. Further, their findings suggest that these patients can do well on fluoxetine monotherapy whether or not they have a past history of many past depressive or hypomanic episodes. As such, these results do not inform treatment decisions for patients who have experienced four or more episodes during the year before their decision to seek treatment.

Despite growing recognition that bipolar II disorder may be more prevalent than bipolar I disorder, there are few controlled studies of bipolar II depression and no definitive, placebo controlled studies of antidepressants (see, for example, Swartz & Thase[8]). The current study provides additional information about the utility of antidepressant monotherapy for at least some patients with bipolar II depression. In this respect, the results are fully consistent with a series of earlier reports by this research group,[9] including prior studies of fluoxetine[10–13] and venlafaxine.[14–17] As other investigators have observed venlafaxine to be associated with a high risk of treatment-emergent affective shifts in patients with bipolar depression taking concomitant mood stabilisers,[18,19] there is further reason to suspect that Amsterdam and colleagues have sampled into a group of patients with bipolar II disorder with a relatively low risk of treatment-emergent affective shifts. Nevertheless, the weight of the series of studies of Amsterdam and colleagues does suggest that there is little reason to systematically avoid the use of antidepressants for patients with bipolar II depression who have no prior history of antidepressant treatment or who have been treated successfully with antidepressants in the past.

Conclusions

With the future in mind, the findings of the current study remind us of the importance of clarifying the past treatment history of individuals presenting with a history of a rapid-cycling pattern, whether defined by the DSM-IV-TR criteria or those used by Amsterdam and colleagues. Specifically, it seems likely that injunctions against using antidepressants are most relevant for those who have experienced treatment-emergent affective shifts while taking antidepressants and may not even apply to those who either have never taken an antidepressant or who have previously taken antidepressants without experiencing treatment-emergent affective shifts. Indeed, in the Systematic Treatment Evaluation Program for Bipolar Disorder (STEP-BD) project, the prospective risk of treatment-emergent affective shifts was strongly related to a past history of switching on antidepressants.[20] Of particular relevance, Truman and colleagues[20] also found that patients at increased risk for switching had index depressive episodes of relatively short durations and more extensive histories of past antidepressant treatment. With these findings in mind, it would be worthwhile to carefully examine the past treatment history of the patients of Amsterdam *et al*.[5] It may be that their findings are neither discrepant nor paradigm shifting, but rather reflect important differences in definitions and the vulnerability of their patient population.

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