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LETTER TO THE EDITOR

Two generations of mood stabilizers

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Cousin and Young (2007) have recently made an excellent review of the drug armamentarium for bipolar disorder in which they used the term 'mood stabilizer' only for lithium and valproate. However, given the data obtained in the recent decade, this term, if applied in an appropriate way, should be extended to a number of other drugs.

The 'mood-stabilizing' property of a drug denotes its therapeutic and prophylactic action against both psychopathological poles of the disorder. Such properties have been convincingly demonstrated for the lithium ion, which is a prototype for such drugs (Bauer and Mitchner, 2004). The broader definition of a mood-stabilizing drug as formulated by Bowden (2002) would include a drug that: (1) benefits at least one primary aspect of bipolar illness (mania, depression, cycling frequency, number of episodes or subthreshold symptoms), (2) is effective in both the acute and maintenance phases of treatment, and (3) does not worsen any aspect of the illness. A proposed modification of the definition of mood stabilizer would be: 'A drug that if used as monotherapy: (1) act therapeutically in mania or/and in depression; (2) acts prophylactically against manic or/and depressive episodes as demonstrated in a trial of at least one year's duration and (3) does not worsen any therapeutic or prophylactic aspect of the illness outlined above.'

Traditionally, the term 'mood stabilizer' has been reserved in current literature for lithium, valproate and, especially in Europe, carbamazepine. Recently, lamotrigine has also been mentioned as a 'mood stabilizer from below'. Although compelling evidence for the mood-stabilizing activity of some atypical antipsychotic drugs has been accumulated in recent years, none of these drugs has been directly named a 'mood stabilizer'.

The period of the introduction into the psychiatric armamentarium of individual mood stabilizers fulfilling the criteria mentioned above occurred more that a quarter of century ago. The mood-stabilizing property of lithium was first suggested in the early 1960s (Hartigan, 1963), that for valproates at the turn of the 1960/1970s (Lambert et al., 1971), and for carbamazepine in the early 1970s (Okuma et al., 1973). The first suggestion that the atypical antipsychotic drug, clozapine, had a mood-stabilizing action was advanced in the mid-1990s (Zarate, 1995), and a similar suggestion was made for lamotrigine in the early 2000s (Ketter and Calabrese, 2002). I therefore propose to name lithium, carbamazepine and valproate first-generation mood stabilizers, and atypical neuroleptics and lamotrigine second-generation mood stabilizers.

The anti-manic and long-tem prophylactic effects of valproate and carbamazepine has been sufficiently documented (Bourin et al., 2005; Vieta and Rosa, 2007). No evidence exists for a distinct antidepressant effect of valproate, or for any augmentation of antidepressants in treatment-resistant depression. However, Gyulai et al. (2003) found that divalproex-treated patients had less worsening of depressive symptoms than lithium-treated patients during 1-year maintenance, particularly those who had previously experienced an anti-manic response and those with a more severe course of the illness. The acute antidepressant efficacy of carbamazepine during affective episodes has been reported in the 1980s (Post et al., 1986) as well as an augmentation activity of the drug for antidepressants in treatment-resistant depression (Rybakowski et al., 1999).

Lamotrigine has already been given a special category among mood-stabilizers as a 'mood-stabilizer from below', since it has greater antidepressant than anti-manic properties (Ketter and Calabrese, 2002). In bipolar patients, lamotrigine showed greater long-term efficacy for prolonging the time to a depressive episode compared with lithium (Bowden et al., 2003). The acute antidepressant efficacy of lamotrigine has been observed in bipolar depression (Brown et al., 2006) as well as in brief recurrent depression believed to belong to the bipolar spectrum (Ravindran and Ravindran, 2007). An effective augmentation by lamotrigine of antidepressant drugs in treatment-resistant depression with an efficacy comparable to that of lithium has also been reported (Rybakowski and Tuszewska, 2006).

Conventional antipsychotic drugs, although efficacious in the treatment of mania, are not useful in depression and in the maintenance treatment of bipolar disorder, due to a tendency to induce depressive symptoms and depressive recurrences in this group of patients. Second-generation antipsychotics are devoid

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of pro-depressant activity and some may even exert an antidepressant effect. On the basis of trials performed in recent years, the criteria for a mood stabilizer could probably be fulfilled by clozapine, olanzapine and quetiapine.

The usefulness of clozapine in the treatment and prophylaxis of bipolar illness has long been recognized. However, due to safety restrictions, this drug has mainly been used in treatment-resistant cases. It seems that although results of controlled studies with clozapine are lacking, there is no doubt that the drug is highly effective in mania and in the prophylaxis of bipolar illness, also in refractory cases (Calabrese et al., 1996; Ciapparelli et al., 2003). Distinct antidepressant properties of clozapine and the use of the drug as augmentation therapy for depression have not been reported.

Olanzapine is an atypical antipsychotic that has been thoroughly examined in the treatment and prophylaxis of bipolar disorder using double-blind, randomized controlled trials, with a variety of designs. The anti-manic and long-term prophylactic efficacy of olanzapine has been well documented (Perlis et al., 2006; Vieta and Rosa, 2007). In a study of bipolar depression where olanzapine, olanzapine plus fluoxetine, or a placebo were compared, it was found that although the combination had the best antidepressant efficacy, olanzapine alone also exerted some antidepressant action (Tohen et al., 2003).

The efficacy of quetiapine in mania and in the long-term prevention of manic and depressive recurrences has been demonstrated in open and controlled trials (Perlis et al., 2006; Vieta and Rosa, 2007). Furthermore, the clear-cut acute antidepressant efficacy of the drug in bipolar depression has been confirmed (Calabrese et al., 2005). On the basis of this, quetiapine may deserve to be named a 'second-generation mood stabilizer' in the first place, as well as an 'atypical antipsychotic drug'.

Therapeutic efficacy in mania has been reported for risperidone, ziprasidone and aripiprazole (Perlis et al., 2006). Promising results have been obtained for the antidepressant efficacy of aripiprazole (McElroy et al., 2007), and for augmentation of antidepressants by risperidone or aripiprazole (Ketter et al., 2006; Rapaport et al., 2006). However, no long-term trials in bipolar patients lasting 1 year or more have been reported for these drugs. The results of further controlled studies will be necessary to resolve the issue whether these or other atypical antipsychotic drugs will meet the full criteria for 'second-generation mood stabilizers' or, whether any other substances could be incorporated in that family.

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Statement of Interest

None.

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