Homocysteine may cause neuronal insult by several mechanisms, including vascular lesions, increased NMDA activation, DNA lesions and apoptosis induction (1, 6). In view of recently published data and the coexistence of WMH and hyperhomocysteinemia in our patient, particularly in the absence of other risk factors, we have raised some important questions: (i) Is there a link between the WMH observed in bipolar patients and increased serum homocysteine? (ii) Could the administration of folate and vitamin B12 improve outcome? To the best of our knowledge, there is no data on the association between WMH and homocysteine in bipolar disorder and this has initiated a new direction for our research into the association between WMH, hyperhomocysteinemia and outcome in bipolar I patients.

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Key words: bipolar disorder – homocysteine – white matter hyperintensities

Letter to the Editor: Agomelatine adjunctive therapy for acute bipolar depression: preliminary open data

To the Editor:

Calabrese et al. (1) conclude that agomelatine, when added to lithium or valpromide, may have 'good efficacy and safety' in the treatment of depressed patients with bipolar I disorder. Based on their study, they further add that this efficacy may be sustained over the long term. Similar conclusions have been reached in studies and meta-analyses of established antidepressants (2), but it is debatable whether or not these conclusions logically follow from the data presented. Nineteen patients out of the original 21 in this study continued treatment beyond six weeks. The authors state that 16 of these 19 patients were responders at the end of the study period (1, p. 631), but in the same paragraph they report that only 11 out of 19 continued treatment for one year. Therefore, based on intent-to-treat, the maximum number of possible responders is 52.3% (11 out of 21), not the 84.2% that the authors claim. In Figure 2 it appears that only 10 patients out of the original 21 remained responders at 52 weeks, which is 47.6%. The highest rate of response occurred at

Week 12 – 14 out of 21 (67%) – and declines thereafter. Acute response to antidepressants within the first 12 weeks is consistent with Gijsman et al.'s meta-analysis (2), but again, this does not establish long-term benefit.

In addition, Calabrese et al. report that there were three cases of mania or hypomania and two cases of agitation. The nature of the agitation is not described but could potentially indicate a mixed state or subthreshold hypomania. This is a rate of mood switches between 14.3% and 24% and, again, is likely to increase with time.

Long-term outcome in bipolar disorder is poor, yet long-term stability is the ultimate goal of treatment in order to reduce the high rates of disability and mortality from this illness. From the patients' point of view, an antidepressant response during the first 12 weeks is of limited benefit if not sustained over the long term. In bipolar patients treated with adjunctive antidepressants, rates of mood switches and relapse increase as a function of study length (3). The goal for the patient is long-term stability, not acute antidepressant response. It appears from this albeit preliminary open study that agomelatine, like established antidepressants, is unlikely to contribute to long-term stability and sustained improvement for many patients with bipolar disorder.

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Key words: antidepressants – bipolar – depression

Reply to Dr. Eppel regarding 'Letter to the Editor: Agomelatine adjunctive therapy for acute bipolar depression: preliminary open data'

To the Editor:

We agree with the caution that Dr. Eppel has recommended regarding the interpretation of these open agomelatine data (1). In addition, it is worth noting that compounds that do not cause sedation, increased appetite, and weight gain, such as is the case with agomelatine, tend to have difficulty separating from placebo. 'Clean' drugs, compounds with fewer side effects, seem to be more difficult to develop because our rating scales tend to count side effects (increased appetite, sedation, etc.) as evidence of efficacy. Accordingly, we agree that such preliminary data should only be viewed as 'hypothesis-seeking', and never confirmatory. That being said, the community of mental health providers and the patients we serve are in desperate need of new treatments for bipolar depression.

The design of this pilot study included two different phases, which were used as endpoints for the estimates of efficacy: (i) acute efficacy after six weeks of adjunctive agomelatine, and (ii) longer-term efficacy with ongoing open-label treatment up to one year.