Reviewer's report

Title: Antipsychotic medications and cognitive functioning in bipolar disorder: moderating effects of COMT Val108/158 Met genotype

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Reviewer: Sandra Dittmann

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The manuscript by Arts et al. entitled “Antipsychotic medications and cognitive functioning in bipolar disorder: moderating effects of COMT Val108/158 Met genotype” presents very interesting data regarding the association of cognition and treatment with antipsychotics in bipolar patients. The investigators concluded that patients with bipolar disorder displayed a negative moderating dose-response effect of the COMT Val allele load on the effects of antipsychotics on two-year cognitive functioning.

This paper is of high interest because only few manuscripts deal with a possible association between cognitive functioning and treatment in bipolar disorder. In addition, it might have an impact on treatment selection, because in recent years, polypharmacy and treatment with antipsychotics have been widely used. Furthermore antipsychotics are increasingly used as mood stabilizers. Due to the fact that cognitive impairment seems to be negatively related to functional and clinical recovery and psychosocial functioning, it is important to identify possible causes for neuropsychological deficits.

However, there are some concerns that need to be addressed:

Major Compulsory Revisions:

Much of the methodology section is not clear:

1. The authors do not describe with which statistical methods they have analysed the cognitive data as well as the demographic data. Even though they mention that there have been no differences between the three genetic groups concerning these data they should mention which analyses they have done. This is especially important, because of the small sample size.

2. The authors have analysed the interaction of the COMT Val/Met polymorphism and antipsychotics using regression analyses. However some details have to be clarified.

First of all, the authors have analysed the data on cognitive functioning over the period of two years. In the regression analyses they have included the time factor as a random effect. However, if subjects repeat cognitive tests several times the
training effect is quite significant. Therefore the time effect in these analyses should not be a random but a fixed factor.

3.
The authors claim that they have used parallel tests to account for the training effect. But they have tested the patients every two months for a period of two years. Did they really use 12 different parallel tests to avoid those training effects?

4.
In addition the authors should describe more in detail how they have classified the patients as far as the use of antipsychotics is concerned. The patients were examined over a time period of 2 years. The authors have written, that the use of antipsychotics was classified with dummy variables of 0 and 1. However it remains unclear whether patients who were taking antipsychotics used them for the whole time period or if some started or stopped the use during the study period.

If the patients started or stopped antipsychotic medication during the study period how was this accounted for?

If every single visit of the patient was classified differently, the authors should have used a different statistical method (e.g. Marginal Structural Models).

5.
Furthermore the authors should describe how the use of antipsychotics is distributed within the three genetic groups.

6.
The authors do not describe the affective state the patients were in. Were the patients euthymic over the whole time period? Have the authors used rating scales for depressive and manic symptomatology? If so, the authors should state the mean scores of the rating scales in Table 1.

If the patients had recurrences or subsyndromal symptomatology the authors should account for the symptomatology in the regression analyses.

7.
Table 2 should be described in more detail. It is not clear whether table 2 only shows the interaction between antipsychotic medication and the genetic allele load. If this is the case, the two main effects (medication and genetic allele load) should also be presented. In addition psychopathology and time should also be accounted for as fixed factors and should be presented.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.
Declaration of competing interests:

I declare that I have no competing interests