Reviewer's report

Title: Identification of early changes in specific symptoms that predict longer-term response to atypical antipsychotics in the treatment of patients with schizophrenia

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Reviewer: Ofer Agid

Reviewer's report:

This is a well written manuscript that used data from six randomized, double-blind clinical trials of atypical antipsychotic medications for treatment of moderately to severely ill patients with chronic schizophrenia to develop a simple decision tree employing early symptom improvement to predict longer-term response to treatment.

This study deals with an important issue that has some clinical implications. I agree with the authors that their findings could serve as a foundation for development of a clinically relevant evaluation tool for guiding treatment decisions early in the course of atypical antipsychotic drug therapy. Moreover, the practicality of using a tool consisting of only six questions rather than administering the entire 30-question PANSS cannot be overemphasized.

Some minor issues:

1. The authors state that for consistency, all analyses were limited to data through 8 weeks of treatment, the duration of the shortest study. I wonder if it would be possible to use this method for (available) longer studies – with a smaller sample size – would the results be the same?

2. The author mentioned the references for the original studies ("Detailed descriptions are available in their respective published reports [2,16-22]") however, I wonder if there were some major differences in between those studies, in terms of: washout period, reason for switching medications (acute exacerbation/ stable patients), and other differences that can influence response to treatment.

3. Re: the CART. The CART has been around for more than 25 years. The performance of the model depends critically on choices of cut-points (eg. using 2 point drop, 2 of the 5 selected PANSS positive items) which can be VERY unstable since there are so many combinations of these choices. CART is another way to fit a logistic regression for dichotomous outcomes (responder y/n), replacing continuous predictors (eg. PANSS positive subscale or change score) by dichotomous variables ( y/n for at least 2 point on 2 of the 5 positive items), linear/nonlinear functions by step functions etc.

I think that the authors should explain the reason of using CART. I am not sure I
understand the reason to apply CART in a basically single predictor model (PANSS positive). The proposed model ignored the study drug effects, center (in which the subjects were recruited) effects, baseline severity, and other study effects which were main drivers of variations in these pooled studies. In addition, there is also only limited validity using PPV and NPV for evaluating predictive test performance and thus it is not surprising that Week 2 PANSS positive predicts Week 8 PANSS total score within subject.

I think that the authors should clarify this point.

**Level of interest:** An article of importance 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