Does atypical antipsychotic medication improve executive function in schizophrenia?

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In the April 2006 edition of this journal, Bender and colleagues (2006) describe an improvement in executive functioning in patients with schizophrenia following treatment with atypical antipsychotic medication. This study examined changes in performance on three commonly used neuropsychological tests of executive function in 54 patients randomly assigned to receive 24 wk treatment with clozapine (n = 24) or olanzapine (n = 30). Cognitive assessments were conducted at baseline (T0) and after 4 wk (T1) and 24 wk (T2) treatment. Measures of psychopathology and extrapyramidal side-effects (EPS) were taken at the same time-points, and a number of analyses were undertaken to determine the relative sensitivity of the two medications, the influence of psychopathology and EPS on executive function and changes in executive function throughout the course of treatment. The authors conclude that their results provide evidence that the improvement in executive function observed following treatment was a primary drug effect, as it was not related to the concurrent improvement in EPS or positive symptoms. They further claim that their results suggest both short-term and long-term treatment-related improvements in executive function. Finally, the authors conclude that there was little difference in the effects of olanzapine and clozapine, and therefore that olanzapine is an appropriate alternative treatment to the ‘gold standard’ clozapine.

We have a number of concerns regarding the study design and selection of cognitive tests in this study. These concerns directly impact the authors’ conclusions and the inferences that may be drawn from this study. Our concerns are detailed below.

Many cognitive tests of executive function, including those used in this study, have large and well-described practice, or learning, effects (Basso et al., 1999). Practice effects act to enhance test performance as a consequence of repeated exposure to the testing materials and procedures. Tests that require use of strategy to aid performance, or that have very few alternate forms, typically display greater practice effects than tests measuring more simple cognitive functions or with a larger number of alternate forms (Collie et al., 2003). For example, Basso and colleagues (1999) describe large practice effects on the Winconsin Card Sorting Test (WCST) and other commonly used measures of executive function. The tests used in the study by Bender and colleagues (2006) were the WCST, the Stroop and a computerized Tower of London (ToL) task. It is well known that these tests have large practice effects and very limited alternate forms (for test-specific data see McCaffrey et al., 2000). Therefore, one should expect a certain level of improvement on these tests when they are administered repeatedly.

The challenge when using such tests in clinical trials is to devise methodological and statistical strategies to differentiate practice effects from treatment effects. There are numerous such strategies that may be used, including: (a) the inclusion of a placebo control group to measure the ‘true’ level of practice effect; (b) choosing tests of executive function that have alternate forms and are thus likely to have smaller practice effects; and (c) requiring subjects to complete a practice test before completing the pre-dose baseline assessment. Unfortunately, Bender and colleagues (2006) did not appear to implement any such strategies. The most striking limitation of this study was the failure to include a placebo control group. It is, therefore, not possible to determine whether the improvements in executive function observed at 4 wk and 24 wk were caused by the antipsychotic medication, by practice effects, or by a combination of these factors. The authors’ conclusion that clozapine and olanzapine exert primary effects on executive function, and that both drugs exert short-term and long-term improvement in executive function, are therefore not supported by the data presented.

Clearly, any future studies of executive function following pharmacological treatment require the inclusion of a placebo control group. Active control groups are inadequate as they may also confound treatment and practice effects. Such studies should also seek to use tests of executive function that have
many alternate forms and display minimal practice effects when used in clinical trial settings. There are a number of such tests available that have been utilized in trials of atypical antipsychotic medication in schizophrenia, including the n-back test (Smith and Jonides, 1999), the Groton Maze Learning Task (Snyder et al., 2005) as well as categorical and letter verbal fluency tasks (Harvey et al., 2006).

Scientists designing longitudinal treatment trials examining cognition, and particularly executive function, should be aware of the limitations of many executive function tasks, and should be particularly wary of the issues that arise from the large practice effects often observed on these tasks. There are appropriate strategies for managing these practice effects, as outlined above, and wherever possible such strategies should be incorporated in the study design.

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Statement of Interest

Dr Collie and Dr Maruff are employees of CogState Ltd, who own the GMLT task described in this letter. Dr Snyder is the inventor of the GMLT task.

References


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