Potential control of risperidone-related cognitive deficits by adjunctive aripiprazole treatment

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Abstract
We have read with great interest Uchida and colleagues’ paper in your journal (2009; 29: 571–576), which reported that a high dosage of risperidone had a negative impact on cognition in older patients with schizophrenia. This finding is consistent with that of a previous study of a younger patient group showing that schizophrenia patients under high antipsychotic dosage have poor cognitive function performance....

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Key words: Aripiprazole, risperidone, dopamine D2 receptor, cognitive function
Editors,

We have read with great interest Uchida and colleagues’ paper in your journal (2009; 29: 571–576), which reported that a high dosage of risperidone had a negative impact on cognition in older patients with schizophrenia. This finding is consistent with that of a previous study of a younger patient group showing that schizophrenia patients under high antipsychotic dosage have poor cognitive function performance. One key issue is how to control risperidone related attention deficit. Uchida and colleagues suggested minimizing the adverse effects of risperidone on cognitive function by identifying/using the lowest effective dose of antipsychotics in schizophrenia patients. Although very valuable, a low dosage of risperidone may also cause adverse effects on cognitive function, which could be particularly problematic in aged patients due to age-related pharmacodynamic and pharmacokinetic changes. It is very important that Uchida and colleagues identified that attention deficits induced by risperidone negatively correlated with dopamine D2 receptor blockade. We propose that an adjunctive aripiprazole administration with risperidone could be an effective method to control risperidone related attention deficits (and other cognitive deficits) through improving D2 receptor activity.

Aripiprazole is a newly introduced antipsychotic drug that has a favourable safety and tolerability profile, particularly in the elderly patients. Aripiprazole was developed as a potent D2 partial-agonist, 5-HT1A partial-agonist, and also 5-HT2A antagonist, however, recent studies have suggested that aripiprazole is not a simple
partial-agonist, but a functionally selective drug that can act as a D2 agonist or D2 antagonist depending on different brain regions\textsuperscript{6,7}. It is possible that aripiprazole could be used to control risperidone related attention deficits (caused by dopamine D2 receptor blockage) through its D2 agonistic effect. In fact, aripiprazole can preferentially increase dopamine release in the medial prefrontal cortex and hippocampus\textsuperscript{8} and dopamine synthesis in the nucleus accumbens\textsuperscript{6}. A recent study has shown that typical antipsychotic treatment resulted in hypoactivation in the dorsal anterior cingulated cortex, which could be improved after switching to aripiprazole and is correlated with improved performance of working memory\textsuperscript{9}. Findling et al.\textsuperscript{10} examined the effectiveness and cognitive effects of aripiprazole in children with a primary diagnosis of attention-deficit/hyperactivity disorder (ADHD), and showed that aripiprazole led to clinical benefit in reducing ADHD symptoms and improving cognition functioning. Moreover, adjunctive aripiprazole treatment has been trialled in risperidone related hyperprolactinemia\textsuperscript{11,12} and olanzapine/clozapine-induced obesity\textsuperscript{13,14}. These studies showed that adjunctive treatment using aripiprazole with other antipsychotics (such as risperidone and olanzapine) was generally safe and well tolerated, and is effective even without reducing the original doses of other antipsychotics\textsuperscript{4,11,13,14}. Therefore, co-administration of aripiprazole and risperidone will result in multiple pharmacological actions and improve the adverse effects beyond the attention deficits (such as weight gain\textsuperscript{15}). Of course, further animal studies and clinical trials are necessary for testing adjunctive aripiprazole/risperidone
treatment, especially in elderly patients that are at increased risk from drug–drug interactions.
References


