European Neuropsychopharmacology (2014) **24**, 575–584

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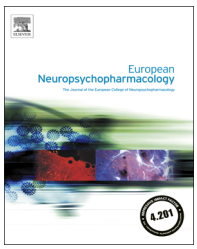

Open, randomized trial of the effects of aripiprazole versus risperidone on social cognition in schizophrenia

Arija Maat[a,*], Wiepke Cahn[a], Harm J. Gijsman[b], Johannes E. Hovens[c], René S. Kahn[a], André Aleman[d]

[a]*Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Huispostnummer A 00.241, Postbus 85500, 3508 GA Utrecht, Utrecht, The Netherlands*
[b]*Pro Persona Mental Health Care, Expertise Center for Psychosis, UMC St Radboud, Huispostnummer 958, Postbus 9101, 6500 HB Nijmegen, Nijmegen, The Netherlands*
[c]*DeltaBouman Psychiatric Teaching Hospital, Poortugaal, Delta Psychiatrisch Centrum, Afdeling Dorpsblik, Postbus 800, 3170 DZ Poortugaal, The Netherlands*
[d]*Department of Neuroscience, University Medical Center Groningen, University of Groningen, Groningen, Faculteit Medische Wetenschappen/UMCG, A Deusinglaan 2, 9718 AW Groningen, The Netherlands*

Received 28 August 2013; received in revised form 3 December 2013; accepted 10 December 2013

KEYWORDS
Aripiprazole;
Neurocognition;
Risperidone;
Schizophrenia;
Social Cognition

Abstract
To date, only few studies have examined the impact of medication on social cognition and none have examined the effects of aripiprazole in this respect. The goal of this 8-week, randomized, multicenter, open-label study was to examine the effects of aripiprazole and risperidone on social cognition and neurocognition in individuals with schizophrenia. Eighty schizophrenia patients (*DSM-IV-TR*) aged 16–50 years were administered multiple computerized measures of social cognition and neurocognition including reaction times at baseline and the end of week 8. Social functioning was mapped with the Social Functioning scale and Quality of Life scale. The study ran from June 2005 to March 2011. Scores on social cognitive and neurocognitive tests improved with both treatments, as did reaction time. There were few differences between the two antipsychotics on (social) cognitive test-scores. The aripiprazole group performed better (more correct items) on symbol substitution ($P=.003$). Aripiprazole was also superior to risperidone on reaction time for emotional working memory and working memory ($P=.006$ and $P=.023$, respectively). Improvements on these tests were correlated with social functioning.

*Corresponding author. Tel.: +31 88 755 6003; fax: +31 88 755 54 66
E-mail address: a.maat@umcutrecht.nl (A. Maat).

0924-977X/$ - see front matter
http://dx.doi.org/10.1016/j.euroneuro.2013.12.009

In conclusion, aripiprazole and risperidone showed a similar impact on social cognitive test-scores. However, aripiprazole treatment produced a greater effect on patients' processing speed compared to risperidone, with these improvements being associated with concurrent improvements in social functioning. Further research on the long-term effects of aripiprazole on cognition is warranted.

1. Introduction

Impairments in social functioning are a core characteristic of schizophrenia, and have been shown to be most pronounced in persons with schizophrenia, compared to other clinical disorders, such as bipolar disorder (Penn et al., 1997; Wiersma et al., 2000). Deficits in social functioning are present throughout the course of the disorder (Addington and Addington, 2008). Indeed, they are even present before the onset of psychosis (Cannon et al., 2002; Davidson et al., 1999) and have been reported in relatives of schizophrenia patients (Hans et al., 2000).

The study of social cognition in schizophrenia examines the processes underlying social dysfunction (Penn et al., 1997; Pinkham et al., 2003). Social cognition has been defined as "a set of related processes applied to the recognition, understanding, accurate processing, and effective use of social cues and information in social situations (Penn et al., 1997)." Investigations of social cognition in schizophrenia, employing affect recognition tasks, social knowledge tasks, and theory-of-mind tasks have shown consistent impairments (Penn et al., 1997). A crucial finding is that performance on social cognition tasks predicts social functioning, and that this association cannot be accounted for by cognitive deficits (Couture et al., 2006; Fett et al., 2011).

Brain circuits underlying social cognition include the ventral striatum, the amygdala, the medial prefrontal and orbitofrontal cortex, the anterior cingulate, and the insula (Adolphs et al., 1998; Chemerinski et al., 2002; Hulshoff Pol et al., 2001; Phan et al., 2002). The importance of dopamine pathways in neural processing in these circuits is well established (Grace, 2000). Numerous investigations have revealed evidence that dopamine is involved in cognitive function such as attention, planning and working memory (Cools and Robbins, 2004; Veselinovic et al., 2013). Clinical studies in schizophrenia have suggested a negative correlation between neurocognitive performance and D2 receptor blockade (Sakurai et al., 2013; Uchida et al., 2009). So far, antipsychotics have not been able to reverse the social deficits associated with schizophrenia (Mishara and Goldberg, 2004; Woodward et al., 2007), which might be due to their general antagonist activity at dopamine D2 receptors. We hypothesized that treatment with aripiprazole, because of the unique action of this drug as a partial dopamine agonist in brain circuits underlying social cognition (Burris et al., 2002), will lead to a significant improvement in social cognitive processing compared to other antipsychotics. To test this hypothesis we compared the effects of aripiprazole and the frequently prescribed atypical antipsychotic agent risperidone. Computerized behavioral tasks were used to measure social cognition and neurocognition and questionnaires were used to map social functioning.

2. Experimental procedures

2.1. Sample

Eligible patients were 16–50 years of age with a clinical diagnosis of schizophrenia (DSM-IV-TR criteria) and an adequate understanding of Dutch. Diagnosis was based on clinical interview, observational documentation and case note information. To improve the study's generalizability, patients with drug misuse were not excluded and there were no stability criteria. Exclusion criteria were: pregnancy, lactation, mental retardation and a history of severe cerebral injury. The study was conducted between June 2005 and March 2011 at three Dutch clinical sites. Institutional review boards of each of these sites approved the study, and all patients or their legal guardians provided written informed consent. The study was registered at Eudra-CT (identifier: 2008-003345-86).

The patients were randomly assigned in a 1:1 ratio to receive either aripiprazole or risperidone. A flexible dosage was used in the first week (i.e., start with 1 or 2 mg for risperidone and 7.5 or 15 mg for aripiprazole), and the dosage could be increased thereafter to a maximum of 6 mg for risperidone and 30 mg for aripiprazole, according to the treating physician's judgment. Overlap in the administration of the antipsychotic agents that patients received before study entry was permitted for the first two weeks after randomization to allow gradual transition to study medication. Concomitant medication other than antipsychotics was permitted throughout the trial; the dosage was restricted to a maximum of 30 mg diazepam or equivalent, 120 mg propranolol, and 12 mg biperden or equivalent. Before they entered the trial, information on previous drug use was obtained with the Composite International Diagnostic Interview (CIDI) (Cottler et al., 1989). Symptom ratings were done at baseline and after 8 weeks of treatment with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

Computerized assessments of social cognitive and neurocognitive performance were conducted at baseline and after 8 weeks of treatment. Measures of social functioning were performed at baseline and endpoint. All measures used in the trial, were selected on the basis of established relevance and sensitivity to schizophrenia, as well as on their feasibility for use in a multisite study. As lengthy testing is not always acceptable to patients, the social cognitive and neurocognitive tests selected represent a compromise between the comprehensiveness of the tests and the desire to reduce the amount of missing data.

2.2. Social cognitive assessment

Facial affect recognition (van 't Wout et al., 2004): In this task 40 trials were presented, consisting of ten face presentations in each of four conditions: angry, fearful, happy or neutral. The faces had been passed through a filter that reduced visual contrast by 30% in order to increase the difficulty of the task. Subjects were asked to indicate the expression of each face.

Emotional working memory: In this task, a face of a man or a woman was shown on a computer screen, expressing a certain affective facial emotion, e.g. "fear". After two seconds the face was replaced with a word (e.g. "deer"). Subjects were asked to indicate whether the facial emotion presented before rhymed with