NIH Public Access
Author Manuscript
J Clin Psychopharmacol. Author manuscript; available in PMC 2014 September 27.

Published in final edited form as:
J Clin Psychopharmacol. 2009 August ; 29(4): 396–398. doi:10.1097/JCP.0b013e3181accfd9.

The Effects of Risperidone on the Cognitive Performance of Individuals With Schizotypal Personality Disorder

Margaret M. McClure, PhD,
VA VISN3 Mental Illness Research Education and Clinical Center Veterans Affairs Medical Center Bronx, NY and Mt. Sinai School of Medicine New York, NY

Harold W. Koenigsberg, MD,
VA VISN3 Mental Illness Research Education and Clinical Center Veterans Affairs Medical Center Bronx, NY and Mt. Sinai School of Medicine New York, NY

Diedre Reynolds, MD,
The Bristol Hospital Counseling Center Bristol, CT

Marianne Goodman, MD,
VA VISN3 Mental Illness Research Education and Clinical Center Veterans Affairs Medical Center Bronx, NY and Mt. Sinai School of Medicine New York, NY

Antonia New, MD,
VA VISN3 Mental Illness Research Education and Clinical Center Veterans Affairs Medical Center Bronx, NY and Mt. Sinai School of Medicine New York, NY

Robert Trestman, MD, PhD,
University of Connecticut Health Center Farmington, CT

Jeremy Silverman, PhD,
Mt. Sinai School of Medicine New York, NY

Philip D. Harvey, PhD, and
Emory University School of Medicine Atlanta, GA

Larry J. Siever, MD
VA VISN3 Mental Illness Research Education and Clinical Center Veterans Affairs Medical Center Bronx, NY and Mt. Sinai School of Medicine New York, NY

Margaret M. McClure: Margaret.McNamara@mssm.edu

To the Editors

Cognitive dysfunction is a core feature of schizophrenia and is present in most patients with the illness, frequently preceding the onset of other symptoms and persisting even after other symptoms have been effectively treated.[1] These abnormalities, which are the best predictor

AUTHOR DISCLOSURE INFORMATION
In the last 3 years, Dr Harvey has served as a consultant for Eli Lilly and Company; Johnson and Johnson, Inc; Pfizer, Inc; Solvay-Wyeth; The Sanofi-Aventis group; Neurogen, Inc; Daimippon Sumitomo America. Dr Harvey also has grant support from AstraZeneca Pharmaceuticals. Dr Trestman has received investigator-initiated support from Eli Lily. The rest of the authors have no disclosures to report.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

of impairments in various aspects of functional outcome in schizophrenia,[2,3] predict poorer treatment adherence[4,5] and increased tendency for relapse in first episode patients.[6]

Several of the cognitive deficits found in patients with schizophrenia are also present in individuals with other schizophrenia spectrum disorders, such as schizotypal personality disorder (SPD).[7–10] We have previously demonstrated that the cognitive impairments of individuals with SPD are amenable to treatment with pharmacological agents, in particular those that modulate catecholamine functioning. In particular, 4 weeks of treatment with guanfacine, significantly improved the context processing abilities of SPD participants compared with those treated with placebo.[11] In addition, treatment of SPD patients with a low dose of risperidone resulted in a significant reduction in negative and general symptoms over 3 weeks.[12]

There is some evidence that second generation, or atypical antipsychotics, improve the cognitive performance of individuals with schizophrenia.[13,14] Based on these results, we sought to evaluate the impact of risperidone on the cognitive functioning of individuals with SPD. We hypothesized that risperidone would result in improvements in the cognitive performance of SPD participants, in that guanfacine was more effective at reducing cognitive impairments in people with SPD than in schizophrenia.[11,15]

We recruited male or female participants between the ages of 18 and 60 years from the outpatient clinics at the Mount Sinai Medical Center (New York, NY) and the Bronx Veterans Affairs Medical Center (Bronx, NY). Participants were required to meet *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* criteria for SPD. When there was comorbidity with other personality disorders, SPD was judged by to be the primary diagnosis. All patients received a urine toxicology screen. See our previous publications for the full diagnostic assessment. The study was approved by the institutional review boards at the 2 institutions, and all participants signed a written informed consent statement. Data were collected from 1995 to 2001.

Patients were randomly assigned in a 1:1 ratio to receive risperidone or placebo in identical tablets. All patients received a single-blind 2-week placebo lead-in followed by a double-blind 10-week medication trial. The dosage of risperidone was titrated upward in a stepwise design, beginning with 0.25 mg/d for the first week, 0.5 mg/d for weeks 2 and 3, 1.0 mg/d for weeks 4 and 5, 1.5 mg/d for weeks 6 and 7, and 2.0 mg/d for the remaining weeks. Cognitive performance was assessed at baseline, as well as at weeks 6 and 12. The cognitive assessment battery consisted of measures of a range of neuropsychological functions, including spatial and verbal working memory, vigilance, spatial memory, and word list learning (for a more complete description of these assessments, please see our previous work[7]). For all the dependent variables, we computed change scores from baseline to 6 and 12 weeks. We then conducted a series of univariate analyses of variance comparing the change scores of individuals in our risperidone group to those in our placebo group.

Thirty-one participants entered into the study, 19 of whom were randomized to risperidone and 12 to placebo. Several participants in both groups dropped out of the study for various reasons, such as boredom or fatigue, ostensibly not related to group assignment. Two

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

participants in the risperidone group were withdrawn, 1 because of an increase in suicidal ideation and 1 because of galactorrhea. In total, 9 participants in the placebo group and 11 participants in the risperidone group completed all 12 weeks of the trial and were included in the analysis. The groups did not differ significantly in the number of participants who terminated prematurely (Fisher exact test, $P = 0.452$, NS). The groups were also comparable in terms of age, education, sex, vocabulary scores, or block design performance (all Ps = NS). Clinical response to risperidone was previously reported[12] in a sample that included 23 of the 31 participants in the current study; raw scores on the symptom assessment of the current sample are presented in Table 1.

Raw scores for the cognitive assessments at baseline, week 6 and week 12, are presented in Table 1. There were no significant differences between the risperidone group and the placebo group in change from baseline on any of the cognitive variables following either 6 weeks, all Fs < 2.5, all Ps > 0.15, or 12 weeks, all Fs < 1.2, all Ps > 0.28, of treatment.

DISCUSSION

We hypothesized that individuals with SPD, who frequently demonstrate a similar profile of cognitive impairment to individuals with schizophrenia, would benefit from treatment with risperidone, as they had previously been shown to benefit from other cognitive enhancement therapies. The results of the current study did not support this hypothesis and are not as large as those seen in the generally negative Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial looking at schizophrenia patients and atypical antipsychotics.[16] These data suggest that although antipsychotic medications may reduce clinical symptoms in SPD, they may not have a substantial benefit for cognitive functioning.

There are several possible explanations for our failure to find statistically significant results. The small sample size and high number of drop-outs led to modest power. Furthermore, examination of baseline performance in both groups suggests that the SPD patients were less impaired on cognitive measures than cohorts in our previous studies. Although we failed to find statistically significant differences between individuals with SPD treated with risperidone and those treated with placebo on our cognitive assessments, more severe cognitive impairment in SPD might have responded to risperidone. Future research on other treatments targeting these deficits in SPD is warranted, especially in those individuals who demonstrate cognitive abnormalities that are closer to the severity of what is seen in schizophrenia.

Acknowledgments

This work was supported by a grant from Janssen Pharmaceuticals to Drs Koenigsberg and Siever as an investigator-initiated study and was supported in part by grant 5 M01 RR00071 for the Mount Sinai General Clinical Research Center from the National Center for Research Resources, National Institute of Health, Bethesda, MD, and by the VA VISN3 MIRECC.

References

1. Reichenberg A, Weiser M, Caspi A, et al. Premorbid intellectual functioning and risk of schizophrenia and spectrum disorders. J Clin Exp Neuropsychol. 2006; 28(2):193–207. [PubMed: 16484093]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

2. Heinrichs RW. The primacy of cognition in schizophrenia. Am Psychol. 2005; 60(3):229–242. [PubMed: 15796677]
3. Milev P, Ho BC, Arndt S, et al. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. Am J Psychiatry. 2005; 162(3):495–506. [PubMed: 15741466]
4. Bilder RM, Goldman RS, Volavka J, et al. Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry. 2002; 159(6):1018–1028. [PubMed: 12042192]
5. Kraepelin, E. Dementia praecox. In: Cutting, J.; Shepherd, M., editors. The Clinical Roots of the Schizophrenia Concept: Translations of Seminal European Contributions on Schizophrenia. New York (NY): Cambridge University Press; 1987. p. 13-24.
6. Burton SC. Strategies for improving adherence to second-generation antipsychotics in patients with schizophrenia by increasing ease of use. J Psychiatr Prac. 2005; 11(6):369–378.
7. Mitropoulou V, Harvey PD, Zegarelli G, et al. Neuropsychological performance in schizotypal personality disorder: importance of working memory. Am J Psychiatry. 2005; 162:1986–1903.
8. Roitman SE, Mitropoulou V, Keefe RS, et al. Visuospatial working memory in schizotypal personality disorder patients. Schizophr Res. 2000; 41:447–455. [PubMed: 10728721]
9. Bergman AJ, Harvey PD, Mitropoulou V, et al. The factor structure of schizotypal symptoms in a clinical population. Schizophr Bull. 1996; 22:501–509. [PubMed: 8873300]
10. Roitman SEL, Cornblatt BA, Bergman A, et al. Attentional functioning in schizotypal personality disorder. Am J Psychiatry. 1997; 154:655–660. [PubMed: 9137121]
11. McClure MM, Barch DM, Romero MJ, et al. The effects of guanfacine on context processing abnormalities in schizotypal personality disorder. Biol Psychiatry. 2007; 61:1157–1160. [PubMed: 16950221]
12. Koenigsberg HW, Reynolds D, et al. Risperidone in the treatment of schizotypal personality disorder. J Clin Psychiatry. 2003; 64:628–634. [PubMed: 12823075]
13. Woodward ND, Purdon SE, Meltzer HY, et al. A meta-analysis of cognitive change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. Int J Neuropsychopharmacology. 2005; 8(3):457–472.
14. Harvey PD, Keefe RS. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. Am J Psychiatry. 2001; 158:176–184. [PubMed: 11156796]
15. Friedman JL, Adler DN, Temporini HD, et al. Guanfacine treatment of cognitive impairment in schizophrenia. Neuropsychopharmacology. 2001; 25:402–409. [PubMed: 11522468]
16. Keefe RS, Bilder RM, Davis SM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch Gen Psychiatry. 2007; 64:633–647. [PubMed: 17548746]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

TABLE 1

Results of Cognitive Assessments at Baseline, Week 6 and Week 12

	Risperidone Group			Placebo Group		
	Baseline	Week 6	Week 12	Baseline	Week 6	Week 12
	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
PANSS positive	11.9 (4.7)	10.4 (2.8)	9.4 (2.5)	13.1 (5.6)	12.2 (3.5)	12.3 (4.3)
PANSS negative	13.9 (4.7)	12.2 (5.8)	12.1 (5.2)	16.8 (7.8)	16.9 (7.5)	16.0 (6.2)
PANSS general	26.9 (7.7)	23.9 (6.2)	22.1 (5.2)	31.9 (10.6)	32.1 (9.6)	28.9 (9.9)
WMS-VR	33.1 (5.1)	34.00 (5.9)	34.9 (7.1)	32.3 (5.0)	37.5 (0.6)	34.2 (4.1)
WMS-VR LD	29.1 (8.4)	31.6 (7.0)	36.8 (13.5)	29.9 (6.8)	36.5 (1.0)	34.4 (3.9)
WLL trail 5	12.8 (5.3)	14.2 (5.1)	15.7 (5.3)	14.8 (4.9)	16.0 (4.9)	19.5 (3.5)
WLL LD	10.9 (4.2)	12.7 (4.9)	15.7 (6.6)	13.0 (5.4)	14.0 (6.4)	16.8 (5.0)
CPT *d′*	0.9 (0.5)	1.5 (0.8)	1.3 (0.83)	2.0 (1.3)	2.3 (1.1)	2.3 (1.0)
PASAT	31.0 (5.9)	34.6 (14.3)	36.7 (13.5)	34.6 (11.5)	41.4 (7.3)	44.8 (5.2)
DOT 30 s delay	1.2 (1.4)	1.6 (1.6)	0.91 (0.61)	1.4 (1.3)	1.9 (1.0)	1.4 (1.6)

PANSS indicates Positive and Negative Syndrome Scale; WMS-VR, Wechsler Memory Scale Visual Reproduction Test raw score; WMS-VR LD, Wechsler Memory Scale Visual Reproduction Test 30-minute delay interval raw score; WLL Trial 5, Word List Learning total words recalled at trial 5; WLL LD, Word List Learning total words recalled after 20-minute delay interval; CPT *d′*, signal detection continuous performance test number of errors of omission; PASAT, Paced Auditory Serial Addition Test total number of correct responses; DOT 30s delay, Dot test distance error at the 30 sec delay minus the distance error in the copy condition.