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Identification of clinically meaningful relationships among cognition, functionality, and symptoms in subjects with schizophrenia or schizoaffective disorder☆

Gahan Pandina [a,*], Robert Bilder [b], Ibrahim Turkoz [a], Larry Alphs [c]

[a] Janssen Research & Development, LLC, Titusville, NJ, USA
[b] Department of Psychiatry, University of California—Los Angeles, Los Angeles, CA, USA
[c] Janssen Scientific Affairs, LLC, Titusville, NJ, USA

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ABSTRACT

Introduction: Cognitive impairment in schizophrenia and schizoaffective disorder is a major determinant of disability. This study explored the relationships among cognitive functioning, clinical symptoms, overall functionality, and demographic characteristics.
Methods: This was a post hoc analysis of a 52-week, prospective, randomized, double-blind study (N = 323) comparing 2 doses of risperidone long-acting injectable (RLAI) in stable subjects with schizophrenia or schizoaffective disorder. Cognitive evaluations were performed and standardized using a healthy age- and sex-matched comparison group. Simple and multiple regression models were used to identify relationships among neurocognitive composite scores (NCS), clinical symptom end points (Positive and Negative Syndrome Scale [PANSS] total and factor scores), overall functionality (Personal and Social Performance [PSP] score), and demographics.
Results: A simple regression model identified significant relationships between the NCS at end point and PANSS total score, PANSS disorganized thoughts factor score, functioning (PSP) and age. A 1-point decrease on PANSS total score and PANSS disorganized thoughts factor score corresponded to an increase in NCS of 0.126-point, and 0.81-point increases, respectively. A 1-point increase on the PSP corresponded to a 0.186-point increase in the NCS T-score. Among the demographic variables, only age correlated significantly with cognition (10-year increase in age corresponded to 1.1-point decrease in NCS T-score) in a multiple regression model.
Conclusion: Improved cognition was associated with beneficial changes in functional status and clinical symptoms (particularly disorganization symptoms) in subjects with schizophrenia/schizoaffective disorder. Older subjects showed less overall cognitive improvement. Improved cognitive and functional outcome is correlated with symptom improvements in RLAI-treated patients with schizophrenia.

1. Introduction

Cognitive dysfunction is a core symptom domain associated with schizophrenia. Up to 75% of patients with schizophrenia have mild to moderate cognitive impairments, which often predate the illness (O'Carroll, 2000). Various cognitive functions are affected in schizophrenia, particularly memory, attention, motor skills, executive function, and intelligence (Heinrichs and Zakzanis, 1998). Neurocognitive deficits have been reported to account for 20% to 60% of the variance in functional outcomes (Green et al., 2000), and better cognitive functioning is associated with improved quality of life (Schretlen et al., 2000; Savilla et al., 2008). Deficits in executive function and working memory appear to have direct impact on patients' perceptions of quality of life with negative effects on patients' ability to work and function in a social environment (Alptekin et al., 2005). Neurocognitive performance is more important than clinical symptoms in predicting employment status (Kaneda et al., 2009). Deficiencies in verbal memory and vigilance may prevent optimal adaptation by patients and may act as rate-limiting factors for rehabilitation (Green, 1996; Green et al., 2000). Consequently, improving cognitive function may improve quality of life through improved social interactions and increased employment.

Oral antipsychotics (atypical and typical) and long-acting atypical antipsychotics are effective in improving clinical symptoms of schizophrenia (Lewis, 1998; Pajonk et al., 2002; Lindenmayer et al., 2004), with modest improvements in cognitive performance (Keefe et al., 2007a,b; Crespo-Facorro et al., 2009; Cuesta et al., 2009; Davidson et al., 2009; Kim et al., 2009). However, the ability to investigate the effects of treatment on cognition is hampered by the heterogeneity of cognitive impairment across individuals, lack of standardized tests to measure cognition (Heinrichs and Zakzanis, 1998), and methodological issues

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* Corresponding author at: Psychiatry, Janssen Research & Development, 1125 Trenton-Harbourton Road, Titusville, NJ 08560, USA. Tel.: +1 609 730 2324; fax: +1 609 730 2069.
E-mail addresses: gpandina@its.jnj.com (G. Pandina), RBilder@mednet.ucla.edu (R. Bilder), ITurkoz@its.jnj.com (I. Turkoz), LAlphs@its.jnj.com (L. Alphs).

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that confound interpretation (Davidson et al., 2009). Nonetheless, although not clearly established, important relationships among cognitive performance, functioning, and clinical symptoms are apparent.

Computerized testing provides a basis for cognitive assessment with the potential for assessing constituent domains with respect to time and supports administration standardization (Kertzman et al., 2008). The Cogtest® Neurocognitive System (Cogtest® battery) is effective in measuring cognition in patients with schizophrenia. The Cogtest® battery was used to assess cognition in a randomized double-blind study evaluating 1-year outcomes in stable subjects with schizophrenia or schizoaffective disorder who transitioned directly from oral antipsychotics to risperidone long-acting injectable (RLAI) every 2 weeks (Simpson et al., 2006). The study showed that long-term treatment with RLAI was associated with low relapse and rehospitalization rates, and that subjects experienced statistically significant improvements in psychotic symptoms and functioning, despite being identified as stable. No significant differences in any of the relevant efficacy measures were observed between the two doses (Simpson et al., 2006). This post hoc analysis of the original study described by Simpson et al. aimed to describe changes in cognitive function observed during this 1-year study, as assessed using the Cogtest® battery, as well as explore the relationships among changes in cognition and demographic characteristics, changes in symptoms and changes in functioning. To aid interpretation, normative data were collected in healthy volunteers to determine whether anticipated changes in cognition were clinically meaningful and not due to practice effects.

2. Methods

2.1. Data sources

2.1.1. Normative control sample

Psychiatrically and physically healthy participants aged 18 to 65 years, inclusive, were selected to match, as closely as possible, the demographic characteristics (age, sex, education, and ethnicity) of the schizophrenia study population (Section 2.1.2). These volunteers completed 3 study visits: screening (≤4 weeks before baseline visit), baseline, and follow-up (5–7 weeks after baseline visit). The sample was planned to include approximately equal numbers of men and women in 4 age strata (ages 18–35, 36–50, 51–65, and >65 years) with approximately 30 individuals per stratum. Within each age stratum, individuals were matched to the samples participating in the studies, based on group distributions of education and ethnicity.

During the baseline and follow-up visits, healthy volunteers completed the Cogtest® battery of neurocognitive tests. Two different testing sequences with counterbalanced order were used to minimize test-order effects. Based on the neurocognitive tests described in Table 1, 6 cognitive domains were created: processing speed, attention/vigilance, reasoning/problem solving, working memory, declarative memory, and social cognition (test composition outlined in Fig. 1).

2.1.2. Schizophrenia/schizoaffective study sample

Post hoc analyses were conducted on data from a 52-week, prospective, randomized, multicenter (United States [US], Canada, Chile, and Argentina), double-blind study comparing 2 doses (25 mg and 50 mg) of RLAI; results of this study have been presented previously (Simpson et al., 2006). Subjects were aged 18 to 70 years, inclusive, and met *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, criteria for schizophrenia or schizoaffective disorder. Subjects were known to be clinically stable (i.e., no hospitalization, clinically relevant worsening of symptoms, or aggressive behavior) for a minimum of 4 months immediately preceding study enrollment. Cognitive assessments were performed at baseline and at weeks 12, 24, and 52 using the Cogtest® battery of selected neurocognitive tests.

2.2. Statistical analyses

2.2.1. Normative control sample

T-scores were computed for cognitive item scores, and domain scores for the normative population. Outliers (i.e., values representing impossible responses or erroneous data) were excluded before

Table 1
Description of the neurocognitive tests.

Test	Description
AX continuous performance test	• Participant presses right mouse button whenever an X is preceded by an A and left mouse button for all other stimuli
Flanker continuous performance test	• Participant presses right or left mouse button depending on whether middle element in a 5-line display has an arrowhead pointing to right or left; 3 types of trials used
Face memory test	• Computer generates pictures of human faces • Original face is paired with a distracter face (i.e., novel face) • Participant must identify original face
Identical pairs continuous performance test	• Computer presents 2- versus 4-digit numbers • Participant responds whenever 2 identical stimuli appear in a row
Object working memory	• Participant matches a target stimulus to 1 of 2 alternatives, which vary systematically in their perceptual similarity to the target • Test is repeated using a short (1-s) and a long (4-s) delay
Penn emotional acuity test	• Computer displays faces with happy (10), sad (10), and neutral (20) expressions • Participant rates emotion of each face on 7-point Likert scale
Set shifting test	• Participant presses keys on right or left side of keyboard, corresponding to side of screen on which a square (the stimulus) appears • Participant required then to learn a test sequence, which is reversed as test progresses
Strategic target detection test	• Participant crosses out target stimuli embedded among distraction elements • Participant is not told in advance which stimuli are the target and must learn by choosing 1 stimulus and observing feedback indicating whether choice was right or wrong
Tapping speed test	• Computer captures total number of taps a participant does with index finger of each hand and the latency to each response
Word list memory	• Participant tries to recall 16 words presented by computer • Computer then repeats only words not recalled, and participant is asked to try to recall all 16 words again