



## Antipsychotic medication and social cue recognition in chronic schizophrenia

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### ABSTRACT

Social cognition has received increased attention in schizophrenia research because it is associated with functional outcomes. Psychosocial interventions are being developed to enhance social cognition, however less attention has been paid to the association between antipsychotic medication use and social cognition. This study evaluated whether individuals treated with olanzapine ( $n=117$ ) or quetiapine ( $n=106$ ) achieved improvements in social cognition. Participants were drawn from a larger 6-month, multi-site, randomized, double-blind clinical trial. Social cognition was assessed using signal detection analysis of performance on the Social Cue Recognition Test. Social functioning was measured with an interpersonal functioning index and a broader quality of life measure. Results revealed that participants in both medication groups improved significantly but modestly on three out of four social cognition subscales. The small observed effect in this trial is generally consistent with previous studies, and supports the need for ongoing research into the biological mechanisms of social cognitive dysfunction in schizophrenia.

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### 1. Introduction

Social cognition consists of “the mental operations underlying social interaction, which includes the human ability and capacity to perceive the intentions and dispositions of others” (Brothers, 1990). In the last decade, a growing body of literature has shown that social cognition is impaired in schizophrenia (Penn et al., 2006), is relatively independent of basic cognitive domains (e.g. attention, memory, executive functioning; Couture et al., 2006; Sergi et al., 2007b), and may be the strongest predictor of functional outcome in this illness (Couture et al., 2006; Brüne et al., 2007). These findings suggest that improving social cognition in schizophrenia may lead to improved social functioning. To this end, an array of psychosocial and medication interventions have been studied.

Psychosocial approaches can be divided into three categories. “Targeted” interventions focus on improving a circumscribed social cognitive domain, such as emotion perception (e.g., Choi and Kwon, 2006; Silver et al., 2004). “Comprehensive” interventions seek to improve the range of social cognitive domains that have been found to be abnormal in psychosis (Horan et al., 2009; Penn et al., 2007). “Broad-based” interventions incorporate social cognitive training within multi-component treatment suites that also include cognitive

remediation and social skills training (Brenner et al., 1992; Hogarty et al., 2004; van der Gaag et al., 2002). All of these approaches have shown promise, but all have important limitations. Targeted interventions improve performance on laboratory-based measures, but lack evidence that these gains generalize to improvements in social functioning. Comprehensive interventions show evidence of generalization (Combs et al., 2007; Roberts and Penn, 2009), but still require large-scale replication. Broad-based interventions have also shown generalization (Hogarty et al., 2004), but it is unclear what portion of the benefit comes from the social cognitive treatment component. Additionally, the time, labor, and cost-intensiveness of broad-based programs beg the question of whether social functioning gains can be achieved with less expensive, more disseminatable social cognitive treatments.

To that end, several studies have investigated whether antipsychotic treatment improves social cognition in schizophrenia. The potential for medications to improve social cognition in schizophrenia is supported by modest evidence that antipsychotics improve neurocognition (Keefe et al., 2007; Sergi et al., 2007a), which, in turn, shows an association with social cognition (Addington et al., 2006; Brekke et al., 2005). Kee et al. (1998) randomized 20 treatment-resistant patients to either haloperidol or risperidone and found that the latter was associated with improved social perception after 8 weeks of medication. In a non-randomized trial, Littrell et al. (2004) converted 22 patients from typical antipsychotics to olanzapine. After 12 weeks, this group showed significant improvement on a social

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perception task while 30 patients who stayed on conventional antipsychotic medication did not. Herbener et al. (2005) assessed facial emotion perception in 13 unmedicated individuals experiencing their first psychotic episode, and then again after they were clinically stabilized (mean = 31 days) on antipsychotic medication (typical or atypical). Patients exhibited deficits relative to a control sample at both time points, and did not exhibit improvement after medication. All of the studies described above are limited by small sample size.

Two larger studies with greater statistical power failed to find evidence that medication improves social cognition. In a randomized, double-blind design, Sergi et al. (2007a) assigned 73 participants to receive either risperidone, olanzapine, or haloperidol for an 8-week period. No group showed improvement on an aggregate index of social cognition. Harvey et al. (2006) conducted a randomized, double-blind comparison of the effects of quetiapine and risperidone on neurocognition, social competence, and social cognition among 289 patients with schizophrenia. Both medications were associated with improvements in social competence and some neurocognitive domains. However, neither group showed improvement in emotion perception.

This literature is limited by the fact that there is a dearth of appropriately-powered studies and the findings are equivocal. The current study sought to address this limitation. We assessed changes in social cognition and social functioning within a large sample of individuals with schizophrenia or schizoaffective disorder who received antipsychotic medication for up to six months. Our research questions were: (1) Does social cognition improve over the course of medication treatment? And (2) Does it change differentially on the basis of medication type?

## 2. Methods

This study is part of a multi-site, randomized, double-blind trial comparing the effects of olanzapine and quetiapine among patients with poor functioning and prominent negative symptoms. This parent study demonstrated significant improvement in both groups in the primary outcome domain of negative symptoms, as well as most secondary outcome domains, including treatment tolerability, quality of life, and case-manager ratings of functioning (Kinon et al., 2006).

### 2.1. Participants

Participants were recruited from 29 outpatient treatment facilities throughout the United States. Participants consisted of 223 outpatients who met DSM-IV criteria for schizophrenia or schizoaffective disorder, had prominent negative symptoms, and had at least moderate social or occupational functioning impairment. Inclusion criteria for negative symptoms was defined as a Positive and Negative Syndrome Scale (PANSS) score of 4 or greater (moderate) on 3 or more of the 7 negative scale items, or 5 or greater (moderately severe) on 2 or more of these items. Inclusion criteria for social/occupational impairment was defined as a Global Assessment of Functioning (GAF) score of 60 (moderate difficulties) or less. Additionally, only study participants for whom Social Cue Recognition Test (SCRT) data were available from baseline assessment and their final visit were included in the present study. Using this criterion, 119 of the original 342 participants were excluded, reducing the number of participants to 223.

### 2.2. Procedure

After recruitment and consent, participants were randomly assigned either to the olanzapine (OLZ) or quetiapine (QUE) group. Participants then entered a 2-week titration period during which they were switched from their current medication to OLZ or QUE. This was followed by a 22-week phase during which participants worked with their psychiatrists to arrive at their optimal medication dose. Optimal dosage and titration rate were determined within a double-blind paradigm that followed dosing guidelines for each medication (for OLZ, 10–20 mg/day in 5-mg increments; for QUE, 300–700 mg/day in 100-mg increments). In the full study sample (Kinon et al., 2006) the mean modal dose for OLZ-treated participants was  $15.6 \pm 4.3$  mg/day, and for QUE-treated patients was  $455.8 \pm 156.3$  mg/day. Chlorpromazine equivalents of these doses are 312 mg/day and 607.7 mg/day, respectively (Woods, 2003). Regarding co-medication, participants were permitted to remain on antidepressant or mood stabilizing medication provided they were already on the medication prior to randomization and no adjustments were made during the study. Rescue benzodiazepines were also permitted. Last, all participants also received standard outpatient treatment coordinated by case managers at community mental health centers.

## 2.3. Measures

### 2.3.1. Social cognition

Social cognition was assessed at baseline and study endpoint, or, for participants who discontinued treatment early, at the participant's final visit. Social cognition was operationalized as participants' sensitivity to social cues (regarding others' thoughts, feelings, and intentions) as measured with the Social Cue Recognition Task (SCRT) (Corrigan and Green, 1993), a video-based test of social information processing. The SCRT is scored using signal detection analysis (Green and Swets, 1966), which quantifies respondents' ability to identify a meaningful stimulus against a backdrop of distractor stimuli. Previous research using the SCRT has demonstrated poorer sensitivity to social cues among individuals with schizophrenia compared to healthy controls (Corrigan and Green, 1993). A follow-up study replicated this finding and showed that this deficit was evident among individuals with both low and high psychotic symptomatology (Corrigan and Nelson, 1998).

The SCRT requires participants to view short (1 to 2 min) videos of four interpersonal vignettes, two of which are characterized by "high emotion" between the characters (e.g. an argument), and the other two by "low emotion" (e.g. a casual conversation). For each vignette, participants must respond with "True" or "False" to a series of propositions pertaining to both concrete (i.e. behavioral) and abstract (i.e. emotional or cognitive) aspects of the interaction. An example of a concrete proposition is, "Sally remained seated throughout the scene." An abstract proposition is, "Carl felt excited about what he was going to say." Abstract cues require greater inferential and intentional processing, whereas concrete cues require accurate encoding of objective social information. "Hits" (i.e. the rate of correct "True" responses) and "False Positives" (FP; the rate of incorrect "True" responses) are calculated separately for abstract and concrete questions across each of the four vignettes. Aggregate sensitivity indices are then computed for the following data categories: (1) Low emotion vignette, concrete cues; (2) Low emotion vignette, abstract cues; (3) High emotion vignette, concrete cues; and (4) High emotion vignette, abstract cues. "Sensitivity" refers to the proportion of actual True's which are correctly identified as such.

Following previous research using the SCRT in this population (Corrigan and Green, 1993), sensitivity ( $A'$ ) was calculated non-parametrically, using the following index (Pollack and Norman, 1964):

$$A' = \frac{1}{2} + \frac{(\text{hits} - \text{FP})(1 + \text{hits} - \text{FP})}{4 \times \text{hits}(1 - \text{FP})}$$

Sensitivity scores vary between 0 (low) and 1 (high). Previous research using the SCRT has found that individuals with schizophrenia achieve significantly lower sensitivity scores than healthy controls (Corrigan and Green, 1993).

### 2.4. Data analysis plan

#### 2.4.1. Imputation of missing data

All of the 223 participants were administered the SCRT at baseline. Sixty-five percent of the sample completed the SCRT at study endpoint. The remaining 35% of the sample discontinued treatment early. Data from these participants' final visit were carried forward and analyzed as post-test data. This method, Last Observation Carried Forward, is a commonly-used, conservative data imputation technique that is more vulnerable to Type II than Type I error (Heyting et al., 1992).

#### 2.4.2. Primary analyses

The primary research questions (improvement in SCRT score from pre- to post-test, and differential improvement across medication type) were evaluated using an Analysis of Covariance (ANCOVA) model comparing the effects of olanzapine versus quetiapine on the change scores of the SCRT sensitivity indices. Four variants of the model were run, corresponding to the four SCRT indices. For each, the pre-test SCRT sensitivity score was entered as a covariate in the analysis. Additionally, to control for the effect of treatment site on outcome, analogous tests were conducted in which site was added as an additional factor in the model. For variables in which site was found to be statistically significant, the two-factor results are reported (as noted) below. For other variables, results of the univariate ANCOVAs are reported.

## 3. Results<sup>1</sup>

Table 1 summarizes participant baseline characteristics. Participants in the two treatment groups did not differ significantly in any domains.

Table 2 summarizes results from the ANCOVA analyses conducted on the four SCRT sensitivity indices. No statistically significant between-group differences emerged. Within-subjects change scores

<sup>1</sup> All pre-, post-test, and change score sensitivity variables were analyzed under the assumption of normality of distribution. Skewness and Kurtosis were below 1.0 for all variables, with one exception. The low emotion, concrete change score had a Kurtosis of 1.04. Non-parametric (Wilcoxon) analyses on this variable were in agreement with the ANCOVA test, and therefore are not reported.

**Table 1**  
Participant baseline characteristics.\*

	Olanzapine (N = 117)	Quetiapine (n = 106)
Sex (% male)	68.4	69.4
Age (M, [S.D.])	41.30 (9.41)	40.13 (9.31)
Race (%)		
White	49.6	50.0
African American	38.5	38.9
Hispanic	9.4	8.3
Other	2.6	2.8
Diagnosis (%)		
Schizophrenia	64.1	58.3
Schizoaffective bipolar	29.1	27.8
Schizoaffective depression	6.8	13.9
Age of illness onset (M [S.D.])	24.07 (8.00)	22.63 (7.93)
Duration of illness (M [S.D.])	17.20 (9.62)	17.36 (9.16)
PANSS positive symptoms (M [S.D.])	18.85 (4.48)	19.02 (4.68)**
PANSS negative symptoms (M [S.D.])	25.40 (3.93)	25.19 (3.63)
PANSS general symptoms (M [S.D.])	41.74 (7.77)	40.39 (7.90)

\* There were no significant differences between groups in baseline characteristics.  
\*\* N = 105.

differed significantly from zero on three of the four dependent variables (low emotion-concrete, low emotion-abstract, and high emotion-concrete). Analysis of change scores within the separate medication groups revealed that each medication was associated with significant pre- to post-test improvement in one of the four data categories; olanzapine was associated with significant improvement in performance for low emotion-concrete cues, while quetiapine was associated with improvement in high emotion-abstract cues.

Because participants were selected on the basis of prominent negative symptoms, we conducted post-hoc bivariate correlations examining associations between baseline PANSS-rated symptoms and SCRT performance. As shown in Table 3, negative symptoms showed a small but consistent negative association with all four SCRT variables. Less association was evident for positive and general PANSS symptoms. Based on this finding, we examined correlations between pre- to post-treatment change scores on SCRT and PANSS variables. There were no significant correlations.

#### 4. Discussion

The present study evaluated whether social cognitive performance improved among individuals with schizophrenia receiving antipsychotic medication. Modest but significant evidence emerged in support of this question. Participants improved significantly on three out of four social cue recognition subscales. Although statistically significant, effect sizes of pre- to post-test SCRT improvements

**Table 3**  
Correlations between baseline social cue recognition and symptoms.

(N = 223)	PANSS positive*	PANSS negative	PANSS general
	r	r	r
Low emotion concrete	−0.151**	−0.194***	−0.154**
Low emotion abstract	−0.083	−0.168**	−0.033
High emotion concrete	−0.018	−0.153**	−0.060
High emotion abstract	−0.082	−0.167**	0.005

\* N = 222.

\*\* P < 0.05.

\*\*\* P < 0.01.

were quite small (See Table 2; Cohen, 1988), and not likely to be clinically significant (Jacobson and Truax, 1991). This evidence of a questionable association between antipsychotic treatment and social cognitive improvement does not serve to clarify the equivocal literature reviewed above. Several smaller, less controlled studies have found evidence of an association (Kee et al., 1998; Littrell et al., 2004), whereas larger studies have not (Harvey et al., 2006; Sergi et al., 2007a,b). This small effect may not be surprising in light of the fact that antipsychotic medications were not developed to target social cognitive deficit. In contrast, targeted psychosocial interventions have yielded more robust findings (e.g. Combs et al., 2007).

Results did not reveal a notable differential association with social cue recognition for olanzapine versus quetiapine. This parity is consistent with the previous literature in that none of the appropriately-powered studies reviewed above has shown a differential effect on social cognition between atypical agents. This finding also is consistent with emerging data from the CATIE study. Penn and colleagues (2009) evaluated emotion perception data from 873 CATIE participants who were randomized to olanzapine, quetiapine fumarate, risperidone, ziprasidone or perphenazine. Participants completed the Face Emotion Discrimination Task (FEDT; Kerr and Neale, 1993) at baseline and after two months of treatment. Results revealed no differential improvement in FEDT performance across treatment groups. Additionally, observed improvements were quite small (*ds* ranged from 0.04 to 0.18) and non-significant.

It is worth noting that patients in the present study performed substantially worse (pre- and post-test average SCRT sensitivity score = 0.67) than those in previous research using the SCRT (average = 0.83; Corrigan and Green, 1993). This is particularly notable since previous participants were hospital inpatients. This discrepancy may be due to participants in previous research being younger (mean age of 34 versus 41 years) and therefore having experienced less illness-related social cognitive degeneration (Kucharska-Pietura et al., 2005; Silver et al., 2002). Alternatively, it may be due to the fact that the present participants were selected on

**Table 2**  
One-way ANCOVA on pre-to-post sensitivity change score, with pre-test score as a covariate.

Variable	Olanzapine (N = 117)		Olanzapine pre-/post-test	Quetiapine (N = 106)		Quetiapine pre-/post-test	Overall pre-/post-test; effect size	Between treatment groups test
	Pre M (S.D.)	Post M (S.D.)		Pre M (S.D.)	Post M (S.D.)			
Low emotion concrete*	0.69 (0.11)	0.71 (0.12)	t = 2.64**	0.70 (0.11)	0.70 (0.12)	t = 1.18	t = 2.33** d = 0.098	F = 1.46
Low emotion abstract	0.65 (0.11)	0.66 (0.12)	t = 1.25	0.66 (0.11)	0.67 (0.13)	t = 1.63	t = 2.00** d = 0.097	F = 0.08
High emotion concrete	0.67 (0.11)	0.68 (0.12)	t = 1.11	0.69 (0.12)	0.70 (0.13)	t = 1.60	t = 1.86** d = 0.106	F = 0.26
High emotion abstract	0.64 (0.11)	0.65 (0.11)	t = 0.38	0.64 (0.09)	0.66 (0.11)	t = 2.25**	t = 1.67 d = 0.094	F = 1.61

M = mean; S.D. = standard deviation; *d* is the effect size estimated from the formula  $d = t[2(1-r)/n]^{1/2}$ , where *t* is *t*-statistic for the paired sample *t* test and *r* is the correlation across pairs, *n* is the total sample size (Dunlap et al., 1996).

\* Significance of treatment site as a fixed factor: *F* = 2.07; *P* = 0.002.

\*\* *P* < 0.05.

the basis of having prominent negative symptoms and poor functional status, both of which are associated with poor social cognition (Herbener et al., 2005; Couture et al., 2006; Sergi et al., 2007a,b). This possibility is supported by our post-hoc analysis showing a consistent, though small, negative association between baseline negative symptoms and SCRT performance. However, we failed to find correlations between pre- to post-treatment change scores in negative symptoms and any SCRT variables, despite the fact that both domains improved significantly over the course of treatment. Previous research on the link between SCRT performance and symptom status found that sensitivity scores did not vary as a result of low vs. high symptomatology (Corrigan and Nelson, 1998), however that study did not distinguish between negative and positive symptoms. More research is needed to elucidate potential links between symptom status and social cue recognition in schizophrenia.

This study has several limitations. Most importantly, it did not include a non-medication control group. Therefore observed improvements in social cue recognition may reflect practice effects. This limitation is due in part to the ethical problem of randomizing participants with schizophrenia to receive no medication. Thus, this same limitation is present in the three other large studies evaluating this topic (Harvey et al., 2006; Penn et al., under review; Sergi et al., 2007a). The possibility that observed improvements are due entirely to practice effects is limited, however, by the fact that previous studies that used repeated administration of social cognition measures typically have not observed practice effects (e.g., Combs et al., 2008; Penn and Combs, 2000; Russell et al., 2008). This limitation also is symptomatic of a broader problem facing social cognition research in schizophrenia: The bulk of extant measures have psychometric properties that are either poor or unknown (Green et al., 2008). Instrumentation is an important rate-limiting factor in this area of research.

A second limitation is that the SCRT differs from social cognition measures used in previous studies of the effects of medication on social cognition. The SCRT taps various aspects of emotion perception, social perception, and Theory of Mind. Convergent validity between the SCRT and other measures of these domains has not been established, which limits the ability to compare the current results to previous findings. This issue bespeaks a broader limitation in the field that was noted above. The psychometric properties of most commonly-used social cognition measures are not well established, and the relationships between social cognitive domains are poorly understood (Green et al., 2008). Addressing this issue will require ongoing psychometric work.

In summary, the present study is in good agreement with previous research in suggesting that antipsychotic medication may confer only small benefits on social cognition in schizophrenia. Emerging research in social neuroscience is beginning to uncover specific somatic mechanisms related to social cognitive dysfunction (e.g. Pinkham et al., 2003). This research holds promise for the development of specially targeted medication interventions that may yield more robust effects on social cognitive functioning in schizophrenia.

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