Schizophrenia Research 159 (2014) 95–100

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

# The impact of second-generation antipsychotic adherence on positive and negative symptoms in recent-onset schizophrenia

Kenneth L. Subotnik [a,*], Joseph Ventura [a], Denise Gretchen-Doorly [a], Gerhard S. Hellemann [a], Elisha R. Agee [a], Laurie R. Casaus [a], John S. Luo [a], Kathleen F. Villa [b], Keith H. Nuechterlein [a,c]

[a] UCLA Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, UCLA Aftercare Research Program, University of California, Los Angeles, CA, USA
[b] Genentech, Inc., South San Francisco, CA, USA
[c] UCLA Department of Psychology, University of California, Los Angeles, CA, USA

ARTICLE INFO

*Article history:*
Received 10 March 2014
Received in revised form 30 June 2014
Accepted 3 July 2014
Available online 6 August 2014

*Keywords:*
Negative symptoms
Antipsychotic medication
Adherence
Longitudinal study
Cross-lagged panel design
Mediation

ABSTRACT

*Objective:* The aim of the study was to explore the extent to which initial severity of positive or negative symptoms in patients with recent-onset schizophrenia is related to medication nonadherence during the first outpatient year.
*Methods:* The study involved 64 first-episode schizophrenia patients treated with the second-generation oral antipsychotic medication, risperidone, for 12 months. Symptoms were evaluated using the SANS and SAPS completed every 3 months. Pearson correlations between medication adherence and symptoms were examined over each 3-month interval during 12 months of follow-through treatment. Possible causality was inferred from cross-lagged panel analyses.
*Results:* As expected, higher levels of adherence with antipsychotic medication were generally associated with lower levels of concurrent reality distortion (mean of SAPS delusions and hallucinations). Greater adherence during the 3-month baseline interval was generally associated with lower levels of avolition–apathy as well as alogia throughout the first outpatient year. However, medication adherence was not significantly associated with *decreases* in avolition–apathy or alogia over time. Cross-lagged panel analyses based on correlation coefficients are consistent with a causal relationship between initial medication adherence and lower levels of alogia. A test of mediation confirmed that an indirect path through reality distortion mediated the relationship between medication nonadherence and alogia.
*Conclusions:* The associations between greater medication adherence and lower levels of negative symptoms appeared to be accounted for by the relationship of both variables to positive psychotic symptoms. The findings suggest that the impact of second-generation antipsychotic medication on suppression of negative symptoms might be mediated via a reduction in positive symptoms.



## 1. Introduction

Patients with prominent negative symptoms who are also medication non-adherent typically have poorer outcomes (Morken et al., 2008; Tsang et al., 2010). It is possible that patients with negative symptoms lack distress about having schizophrenia and are therefore less motivated to participate in treatment. Given that medication nonadherence in schizophrenia patients is perhaps the single most preventable cause of psychotic relapse, examination of this relationship is very important. However, only a very few studies have empirically examined this question, and the findings have been equivocal.

Individuals with schizophrenia who had significantly higher overall SANS scores and higher avolition–apathy and alogia SANS item scores, were shown to have lower levels of first-generation depot antipsychotic medication adherence (Tattan and Creed, 2001). The authors hypothesized that the lethargy and lack of motivation associated with avolition and apathy led to the greater nonadherence with clinic visits required for depot antipsychotic medication injections, and speculated that alogia could interfere with treatment and developing greater insight into the need for treatment. The presence of higher levels of negative symptoms on the PANSS (Kay et al., 1987) was shown to be moderately positively correlated with lower oral antipsychotic medication adherence (Kao and Liu, 2010). Baloush-Kleinman et al. (2011) found that higher levels of negative symptoms were *not* directly related to antipsychotic medication adherence, but did indirectly impact medication

* Corresponding author at: University of California, Los Angeles, Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience & Human Behavior, 300 UCLA Medical Plaza, Room 2240, Los Angeles, CA 90095-6968, USA. Tel.: +1 310 825 0334; fax: +1 310 206 3651.
*E-mail address:* ksubotnik@mednet.ucla.edu (K.L. Subotnik).

http://dx.doi.org/10.1016/j.schres.2014.07.008
0920-9964/

adherence by influencing attitudes towards medication, which in turn were associated with lower adherence. Using structural equation modeling to test the Health Belief Model, they found that the presence of negative symptoms predicted negative attitudes (related to insight, medication costs, and medication benefits) towards medication, which then in turn predicted nonadherence. In contrast, findings for a large first-episode schizophrenia sample suggested that negative symptoms do not interfere with medication adherence, but on the contrary are associated with continued adherence to the antipsychotic medication regimen (Steger et al., 2012). In that study, resolution of positive symptoms was associated with continued medication adherence.

No effective treatments for negative symptoms of schizophrenia have been clearly established. Current antipsychotic medications are apparently ineffective or only minimally effective in treating negative symptoms of schizophrenia (Erhart et al., 2006; Moller, 2007; Carpenter and Davis, 2012; Levine and Leucht, 2012). There have been some reports of limited efficacy of clozapine, iloperidone, asenapine, amisulpride, and risperidone for reduction of negative symptoms, but the specificity for treatment of negative symptoms has not been clearly established (Danion et al., 1999; Makinen et al., 2008; Hanson et al., 2010; Levine and Leucht, 2012, 2013).

The aim of this report is to explore the extent to which the severity of negative symptoms in patients with recent-onset schizophrenia is related to medication nonadherence during the first outpatient year. A secondary aim is to explore potential "causal" relationships between oral antipsychotic medication adherence and negative symptoms. We hypothesized that the presence of negative symptoms is a primary contributing factor in decreased medication adherence.

## 2. Methods

### 2.1. Participants

This study involved patients with a recent first episode of schizophrenia drawn from two National Institute of Mental Health-funded longitudinal protocols ("Sample 3" and "Sample 4") conducted at the Aftercare Research Program at the University of California, Los Angeles (Nuechterlein et al., 1992, 2008; Subotnik et al., 2011). All patients received treatment with second-generation antipsychotic medication, regular visits with the treating psychiatrist, individual case management, and group psychosocial interventions and/or cognitive training interventions. Sample 3 participated in an 18-month study for which oral risperidone was the standard antipsychotic treatment. Sample 4 participated in a 12-month study comparing long-acting injectable risperidone to oral risperidone. To maintain comparability with Sample 3, the current analyses will examine data only from those Sample 4 patients who were randomized to the oral risperidone group.

The UCLA Aftercare Research Program recruits its participants from a variety of local Los Angeles psychiatric hospitals and clinics. Study inclusion and exclusion criteria were: 1) the first major psychotic episode began within the last 2 years; 2) DSM-IV diagnosis of schizophrenia, schizoaffective disorder, depressed type, or schizophreniform disorder; 3) 18–45 years of age; 4) no evidence of a known neurological disorder; 5) no evidence of significant and habitual drug abuse or alcoholism in the 6 months prior to hospitalization and no evidence that the psychosis was accounted for by substance abuse; 6) no premorbid IQ < 70; 7) sufficient acculturation and fluency in the English language to avoid invalidating research measures; 8) residence within commuting distance of the UCLA; and 9) treatment with risperidone was not contraindicated. There were no entry criteria based on symptom severity, and there were no symptom selection criteria for inclusion in the data analyses.

Previous level of medication adherence was not a consideration when recruiting participants. Most participants entered the study after a psychiatric hospitalization and all had their first psychotic episode within the 2 years prior to study entry. This study was reviewed and approved by the UCLA Institutional Review board. All participants provided written consent to participate after being given oral and written information about the research procedures.

### 2.2. Measurement of medication adherence

Antipsychotic medication adherence, rated on a 1–5 scale (1: never missed medication (100% adherence); 2: missed a few times, essentially took all prescribed doses (approximately 76–99% adherence); 3: missed several times, took at least half of all doses (approximately 50–75% adherence); 4: took <½ of prescribed doses (approximately 1–49% adherence); 5: stopped taking all medication (0% adherence)). The sources of adherence information were every 2 week pill counts, plasma concentrations measured every 4 weeks, patient report, clinician assessment, and the Medication Event Monitoring System (MEMS-6 [Sample 4 only]) which continuously measures pill bottle opening and closing "events". Adherence ratings were made on every 1 to 2 weeks even when all sources of information were not available during a rating period. Each patient's weekly or bi-weekly medication adherence ratings were then averaged into 3-month interval ratings.

### 2.3. Symptom assessment

Positive symptoms and negative symptoms were rated every 3 months, covering the prior 3-month interval. Positive symptoms were rated on the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen (1984b), a 35-item measure evaluating the presence and severity of disorganized and positive symptom dimensions. Our report focused on "reality distortion" which we defined as the mean of the global ratings of Delusions and that of Hallucinations. Negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a), a 23-item rating scale (Hanson et al., 2010). It consists of five subscales: Affective flattening, alogia, avolition–apathy, anhedonia–asociality, and attention (Andresaen, 2008). The attention item was not examined here because of its overlap with cognitive impairment (McGorry et al., 2013). This report used the global ratings for each of the four symptoms of interest. Each SAPS and SANS rater achieved a median intraclass correlation coefficient (ICC) of 0.80 or higher across all items compared with the criterion ratings, and participated in a quality assurance program to maintain inter-rater reliability.

### 2.4. Data analytic plan

There were three phases of data analyses. Phase I involved bivariate Pearson correlations between medication adherence and the four negative symptoms as well as General Linear Mixed Model Analyses (GLMM) analyses of change in symptoms over the four time intervals using SPSS version 21. In Phase II, any patterns of significant relationships from Phase I were further examined using cross-lagged panel analyses using the formulas provided by Kenny (1975). Because cross-lagged panel analyses cannot rule out the influence of "third variables", Phase III explored the impact of a mediating variable that may influence relationships between medication adherence and negative symptoms following Sobel (1982).

#### 2.4.1. Phase I: Correlational and general linear mixed model analyses (GLMM)

Phase I utilized Pearson correlations to assess the strength of the relationship between medication adherence and negative symptoms. Correlations between medication adherence and symptoms were examined over each 3-month interval during 12 months of follow-through treatment. GLMM analyses examined prediction of symptom change over the four intervals.