Published in final edited form as:

Schizophr Res. 2014 October ; 159(1): 95–100. doi:10.1016/j.schres.2014.07.008.

The Impact of Second-Generation Antipsychotic Adherence on Positive and Negative Symptoms in Recent-Onset Schizophrenia

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Abstract

Objective—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-

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Contributors

Keith H. Nuechterlein, Kenneth L. Subotnik, and Joseph Ventura participated in the overall design of the longitudinal studies described here and, with Elisha R. Agee, Denise Gretchen-Doorly, Gerhard S. Helleman, and Kathleen F. Villa, planned the data analyses reported in this manuscript. Gerhard S. Helleman, Kenneth L. Subotnik, and Elisha R. Agee conducted the data analyses. Laurie R. Casaus and John S. Luo were the psychiatrist investigators who supervised the medication administration. All authors read, edited, and approved of the manuscript.

Conflict of Interest

Denise Gretchen-Doorly, Ph.D., Gerhard S. Helleman, Ph.D., Elisha R. Agee, Laurie R. Casaus, M.D., and John S. Luo, M.D., have no financial conflicts of interest to disclose.

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.

Keywords

Negative symptoms; Antipsychotic medication; Adherence; Longitudinal study; Cross-lagged panel design; Mediation

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 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 (Carpenter and Davis, 2012; Erhart et al., 2006; Levine and Leucht, 2012; Moller, 2007). 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; Hanson et al., 2010; Levine and Leucht, 2012, 2013; Mäkinen et al., 2008).

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; Nuechterlein et al., 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 to 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 two 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 $< \frac{1}{2}$ 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 one-to two 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 (Andreasen, 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).

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 4 intervals.

Phase II: Cross-lagged Panel Analysis—In Phase II, cross-lagged panel analyses were used to examine evidence suggestive of possible causality. Cross-lagged panel analysis involves measuring two variables simultaneously at two time points to examine possible evidence of temporal reciprocal causality (Kenny, 1975; Kenny and Harackiewicz, 1979; Oud, 2012). There are two autocorrelations, one for each of the two variables correlated with itself at two points in time. The two synchronous correlations are between the two variables correlated with each other at the same point in time. Lastly, there are two cross-lags, which involve each variable correlated with the other at different points in time (Kenny, 1975; Kenny and Harackiewicz, 1979). When the two cross-lagged correlations are compared by subtracting one from the other, the result is called the cross-lagged differential.

Phase III: Examining the Influence of Psychosis as a “Third Variable”—The cross-lagged panel analyses cannot rule out the influence of “third variables” on both medication adherence and negative symptoms. Given that positive symptoms are known to be associated with both antipsychotic medication nonadherence as well as negative symptoms (Subotnik et al., 2011; Ventura et al., 2004), any significant cross-lagged panel analyses were further tested for the effects of positive symptoms as a potential mediating third variable.

3. Results

The demographic and clinical characteristics of the study participants are representative of the greater Los Angeles region (presented in Table 1). Participant symptom levels during the four time intervals are presented in Table 2.

3.1. Phase I, Correlational and GLMM Analyses

Adherence and positive symptoms—Adherence with antipsychotic medication was generally significantly associated with lower concurrent levels of psychotic symptoms (reality distortion), as well as with psychotic symptoms at subsequent time intervals (Table 3).

Adherence and negative symptoms—Adherence with antipsychotic medication was significantly associated with lower levels of two negative symptoms, avolition-apathy and alogia (see Table 4). Higher levels of initial medication adherence were associated with lower levels of avolition-apathy during months 1–3, as well as lower levels of Avolition-apathy at later time intervals (months 7–9 and months 10–12). Similarly, higher levels of medication adherence were, in general, associated with lower levels of alogia in subsequent time intervals.

Although initial medication adherence appears to predict levels of avolition-apathy and alogia throughout much of the subsequent time intervals, the initial level of medication adherence did not predict a general downward trend for these symptoms over the 12-month follow-through period. In a General Linear Mixed Model (GLMM), initial levels in adherence did not predict decreasing levels of either avolition-apathy ($F(1, 270)=1.3, p=.25$) or alogia ($F(1, 270)=2.0, p=.15$) over the 4 time intervals. Similarly, changes in adherence over the 4 time intervals were not associated with changes in avolition-apathy ($F(1, 190)=0.31, p=.58$) or alogia ($F(1, 189)=2.3, p=.13$) over the 4 time intervals in GLMM analyses. It is possible that high levels of stability of both medication adherence and symptoms over the time intervals obscured any possible relationships between adherence and symptom change. Antipsychotic medication adherence was highly stable over the four time intervals (range of r 's was .55 to .85, $N=66$). The levels of reality distortion were also highly stable over time (range of r 's was .65 to .89, $N=66$). The four negative symptoms showed moderate to high stability over the one-year follow-through period: Avolition-apathy, range of r 's was .41 to .85, $N=64$; alogia, range of r 's was .59 to .67, $N=63$; affective flattening, range of r 's was .65 to .78, $N=64$; and anhedonia-asociality, range of r 's was .49 to .80, $N=63$.

3.2. Phase II, Cross-Lagged Panel Analyses

As planned, the correlations between adherence and each of the negative symptom items were examined for evidence consistent with possible causal relationships using cross-lagged panel design analyses. These analyses suggest that adherence during months 1 to 3 may have led to lower levels of alogia during the 10–12 month interval, not that less severe initial alogia led to better adherence during the 10–12 month interval ($z=3.1, N=63, P=.002$, see Figure 1). Cross-lagged panel design analyses for the adherence and SANS items avolition-apathy ($z=1.0, N=64, p=.16$), affective flattening ($z=1.6, N=64, p=.11$), and anhedonia-asociality ($z=1.2, N=63, p=.11$) did not identify significant suggestive causal directions, although their correlation patterns were also in the direction of medication adherence contributing to lower levels of negative symptoms.

3.3. Phase III, The Influence of a Third Variable, Mediation Analyses

Neither correlational nor cross-lagged panel design analyses can rule out the possibility that a third variable that is related to both adherence and negative symptoms is primarily responsible for the observed relationships between the two. Positive symptoms of schizophrenia are known to be associated with both antipsychotic medication nonadherence as well as higher levels of negative symptoms. Further, adherence with antipsychotic medication would be expected to directly impact positive symptoms. Therefore, we identified reality distortion (the mean of hallucinations and delusions) at each time interval as a potential third variable that might influence both adherence and negative symptoms. Most of the significant correlations between antipsychotic medication adherence and negative symptoms were no longer statistically significant after partialling out the variance associated with concurrent levels of reality distortion. Only one of the relationships between medication adherence and lower levels of negative symptoms (Alogia at the 4–6 month interval, $r=.26, p=.04$) remained significant after controlling for reality distortion during the same interval. Conversely, the general magnitude, as well as the significance levels, of the

correlations between adherence and reality distortion were mostly unaffected after partialling out the variance associated with levels of alogia at each of the time intervals (r values ranged from 0.11 ($p=.38$) to 0.44, $p<.01$).

Given that the associations between medication adherence and lower levels of negative symptoms appeared to be statistically accounted for by the relationship of both variables to positive symptoms, we tested this hypothesis further in a mediation analysis. A Sobel test of mediation (Sobel, 1982) was performed to confirm the apparent mediation by positive symptoms. Figure 2 illustrates the indirect path from medication adherence to lower alogia *through* reality distortion (Sobel test=2.1, $N=63$, $p=.04$). Figure 3 illustrates that the alternative model in which the relationship between medication adherence and reality distortion is mediated by alogia is not a likely scenario (Sobel test=1.3, $N=63$, $P=.21$). These analyses demonstrate that the relationship of antipsychotic medication adherence to lower levels of alogia can be accounted for by this indirect path through reality distortion.

4. Discussion

In this sample of first-episode schizophrenia patients, higher levels of antipsychotic medication adherence were associated with lower levels of positive symptoms as well as lower levels of two forms of negative symptoms. Specifically, greater adherence to the second-generation oral antipsychotic medication, risperidone, was associated with lower levels of reality distortion (delusions and hallucinations), avolition-apathy, and alogia in zero-order bivariate correlations. However, contrary to our hypothesis that negative symptoms would lead to lower medication adherence, the pattern of longitudinal correlations are consistent with the possibility that initial adherence contributed to lower levels of alogia up to one year later. However, it is possible that the relationship between antipsychotic medication adherence and negative symptoms reflects their common relationship with one or more additional factors that are known to be associated with both variables. Given the known relationships between antipsychotic medication adherence and lower levels of positive symptoms (Alvarez-Jimenez et al., 2012; Subotnik et al., 2011) as well as the evidence for a temporal relationship between positive and negative symptoms (Ventura et al., 2004), we explored whether positive symptoms served as such a third variable. Indeed, we found that most of the significant correlations between antipsychotic medication adherence and negative symptoms became nonsignificant after controlling for reality distortion. A statistical test confirmed that an indirect path through reality distortion mediated the relationship between medication nonadherence and alogia. This pattern is consistent with the view that the impact of antipsychotic medication nonadherence on alogia is likely to be secondary to its impact on reality distortion.

The two negative symptoms that were significantly correlated with medication adherence in the bivariate analyses, avolition-apathy and alogia, were the same negative symptoms identified by Tattan and Creed (Tattan and Creed, 2001) as associated with first-generation depot antipsychotic medication adherence. They speculated a directional interpretation wherein avolition and apathy might interfere with a patient's initiative to attend clinic appointments, and that alogia might interfere with the ability to engage in psychotherapy, which in turn would disrupt adherence with the medication regimen. Whereas this

interpretation makes intuitive sense to those who provide treatment to individuals with schizophrenia, our cross-lagged panel analyses suggest that the opposite direction of effect is more likely. Further, the current evidence suggests that the relationship between nonadherence and negative symptoms might be secondary to control of psychotic symptoms. The Kao and Liu (2010) findings that negative symptoms were correlated with lower antipsychotic medication adherence should similarly be reconsidered in light of this potential mediation effect.

Limitations of this study include relatively low levels of negative symptoms among these recent-onset schizophrenia patients. The relative lack of change over time of both medication adherence and negative symptoms limited our ability to detect predictors of change in the four negative symptom domains. Only a moderate sample size (66 participants) had complete follow-through data on any of the symptoms examined, limiting the statistical power to detect subtle relationships. Further, experimental manipulation of antipsychotic medication adherence was not feasible and experimental manipulation of negative symptoms is not possible. Potential third variables could only be controlled statistically. Therefore, this study relied on correlational analyses to infer possible causality of pseudo-independent variables. This allows testing of promising models but precludes any definitive conclusions about potential causal direction.

Thus, these findings suggest that any benefit of second-generation antipsychotic medication for negative symptoms might be secondary to control of positive symptoms. Further, it is a cautionary tale, reinforcing the need for research designs that can separate the effects of drugs on negative versus positive symptoms when examining promising treatments for negative symptoms. In this study it appeared that early medication adherence was specifically associated with later lower levels of alogia. Upon further exploration it was revealed that the adherence was not specifically related to alogia but was primarily related to psychotic symptoms and secondarily to alogia. Future research should explore other “third variables” known to be related to both medication adherence and negative symptoms that might similarly serve as mediators of this relationship. For example, Baloush-Kleinman et al. (2011) identified attitudes toward antipsychotic medication as such a third variable. Other candidate third variables are insight (Chang et al., 2011; Mintz et al., 2003), neurocognition (Ventura et al., 2013), and social cognition (Ventura et al., 2011).

Acknowledgments

We gratefully acknowledge the caring UCLA Aftercare Research Program case managers Kimberly Baldwin, M.F.T., Rosemary Collier, M.A., Nicole R. DeTore, M.A., Yurika Sturdevant, Psy.D., and Luana Turner, Psy.D.. We also thank the medication adherence raters, Elizabeth Arreola, B.A., Manjot Bains, Miriam Barillas, B.A., Ashton Christian, Kassandra Coronel, Jing Gong, Liset Cristino Crespín, M.S.W., Angie Sung Hyun Lim, Lilian Medina, B.A., Sabiha Kaiser, B.S., Steven Kwong, B.S., Angie Lim, B.S., Gabriella Pasqual, Leila Sims, M.D., Gabriel Swerdlow, John Tran, Andres Victoria, B.A., Yejin Yoo, B.S., and Liang Zhu, B.A..

Role of Funding Sources

This research was primarily funded by the National Institute of Mental Health (NIMH research grant MH037705 and NIMH Center grant P50 MH066286 to K.H. Nuechterlein). Medication and supplemental support was provided by Janssen Scientific Affairs, Inc, through an investigator-initiated grant. An investigator-initiated grant from Genentech, Inc, provided supplemental funding to support the data analyses presented here.

Kenneth L. Subotnik, Ph.D., has received research funding from Janssen Scientific Affairs, LLC, and Genentech, Inc through grants to Drs. Nuechterlein and Ventura. He is a consultant to Otsuka America Pharmaceutical, Inc. Keith H. Nuechterlein, Ph.D., has received funding from Janssen Scientific Affairs, LLC, Brain Plasticity, Inc., and Genentech, Inc. He has served as a consultant to Genentech, Inc., Janssen Scientific Affairs, and Otsuka America Pharmaceutical, Inc. Joseph Ventura, Ph.D., has received funding from Janssen Scientific Affairs, LLC, Brain Plasticity, Inc., and Genentech, Inc. He has served as a consultant to Brain Plasticity, Inc., and Boehringer-Ingelheim GmbH. Kathleen F. Villa, M.A., was an employee of Genentech, Inc., and is now an employee of Jazz Pharmaceuticals, plc.

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Figure 1.

Cross-lagged panel analyses showing a pattern consistent with a causal relationship between medication nonadherence at the Month 0–3 interval and SANS alogia at the Month 12 time interval. Note: Values are Pearson correlations.

Sobel test = 2.1, N=63, $p < 0.04$

Figure 2.

Sobel test showing that reality distortion is a mediator of the relationship between medication nonadherence and SANS alogia at the month 0–3 interval. Note: Values are standardized “Beta” coefficients.

Sobel test = 1.3, N=63, $p = 0.21$

Figure 3.

Sobel test to examine whether SANS alogia is a mediator of the relationship between medication adherence and reality distortion, at the month 0–3 interval. This test of the alternative model does not demonstrate mediation. Note: Values are standardized “Beta” coefficients.

Table 1

Participant Characteristics (N = 66)

Mean age, years (SD)	22.6 (3.6)
Mean education, years (SD)	13.2 (1.9)
Mean time since psychosis onset, months (SD)	10.2 (9.2)
Gender (%)	
Male	70%
Female	30%
Marital Status (%)	
Single	98%
Married	2%
Race (%)	
Caucasian	48%
African American	22%
Asian	12%
Pacific Islander	5%
Native American	5%
Mixed	8%
Ethnicity (%)	
Hispanic/Latino	34%
Diagnosis (%)	
Schizophrenia	63%
Schizoaffective Disorder	11%
Schizophreniform Disorder	25%
Psychotic Disorder, NOS	1%

Table 2

Participant Symptom Levels (N = 66)

	Follow-Through Months: Mean (SD)			
	Months 1–3	Months 4–6	Months 7–9	Months 10–12
Reality Distortion	1.2 (1.3)	1.1 (1.3)	1.0 (1.2)	1.0 (1.2)
Avolition-Apathy	2.9 (1.3)	2.5 (1.4)	2.5 (1.3)	2.4 (1.3)
Alogia	1.2 (1.2)	1.2 (1.2)	1.2 (1.2)	1.2 (1.3)
Affective Flattening	1.8 (1.4)	1.7 (1.4)	1.7 (1.3)	1.7 (1.4)
Anhedonia-Asociality	2.4 (1.4)	2.4 (1.4)	2.5 (1.3)	2.3 (1.4)

Table 3

Pearson correlations for the relationship between SAPS reality distortion (mean of hallucinations and delusions) and medication adherence at 3-month intervals (n = 66)

	Medication Adherence			
	Months 1–3	Months 4–6	Months 7–9	Months 10–12
Reality Distortion (n = 66)				
Months 1–3	0.47^c	0.25^b	0.12	0.09
Months 4–6	0.41^c	0.23 ^a	0.16	0.22 ^a
Months 7–9	0.46^c	0.30^b	0.21 ^a	0.22 ^a
Months 10–12	0.45^c	0.38^c	0.36^c	0.34^c

^a $P < 0.10$,

^b $P < 0.05$,

^c $P < 0.01$

Table 4

Pearson correlations for the relationship between SANS negative symptoms and medication adherence at 3-month intervals

	Medication Adherence			
	Months 1–3	Months 4–6	Months 7–9	Months 10–12
Avolition-Apathy (n =64)				
Months 1–3	0.27^b	0.18	0.13	0.16
Months 4–6	0.16	0.18	−0.01	−0.04
Months 7–9	0.24 ^a	0.17	0.13	0.07
Months 10–12	0.31^b	0.23 ^a	0.16	0.04
Alogia (n =63)				
Months 1–3	0.20	0.03	−0.05	−0.08
Months 4–6	0.32^c	0.31^b	0.06	0.14
Months 7–9	0.38^c	0.28^b	0.16	0.12
Months 10–12	0.35^c	0.27^b	0.19	0.16
Affective Flattening (n = 64)				
Months 1–3	0.19	0.14	0.03	0.00
Months 4–6	0.13	0.13	−0.04	−0.02
Months 7–9	0.11	0.08	−0.05	−0.09
Months 10–12	0.21 ^a	0.20	0.08	0.06
Anhedonia-Asociality (n = 63)				
Months 1–3	0.17	0.10	−0.05	−0.03
Months 4–6	0.13	0.22	0.01	0.04
Months 7–9	0.08	0.10	−0.04	−0.10
Months 10–12	0.16	0.17	0.02	−0.06

^a $P < 0.10$,

^b $P < 0.05$,

^c $P < 0.01$