2015

# The relationship between second-generation antipsychotic medication adherence and negative symptoms in first-episode schizophrenia

Elisha R. Agee

Pepperdine University

Graduate School of Education and Psychology

# THE RELATIONSHIP BETWEEN SECOND-GENERATION ANTIPSYCHOTIC MEDICATION ADHERENCE AND NEGATIVE SYMPTOMS IN FIRST-EPISODE SCHIZOPHRENIA

A clinical dissertation submitted in partial satisfaction

of the requirements for the degree of

Doctor of Psychology

by

Elisha R. Agee, M.A.

July, 2015

Stephanie Woo, Ph.D. – Dissertation Chairperson

This clinical dissertation, written by

Elisha Agee, M.A.

under the guidance of a Faculty Committee and approved by its members, has been submitted to and accepted by the Graduate Faculty in partial fulfillment of the requirements for the degree of

DOCTOR OF PSYCHOLOGY

Doctoral Committee:

Stephanie M. Woo, Ph.D., Chairperson

Kenneth L. Subotnik, Ph.D.

Carolyn Keatinge, Ph.D.

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# DEDICATION

This dissertation is dedicated to my mother and father.

I am forever grateful for your guidance and support. You have always been by my side and I would not be where I am without your words of encouragement and continual faith in my abilities. Without you, none of this would have been possible.

# ACKNOWLEDGEMENTS

I would like to acknowledge and thank my wonderful committee members, Dr. Stephanie Woo, Dr. Kenneth Subotnik, and Dr. Carolyn Keatinge. Thank you for generously giving your time and expertise to teach and guide me throughout this strenuous process.

Dr. Woo, thank you for believing in me and giving me multiple opportunities to succeed at new endeavors and grow over the last six years. You have been a wonderful mentor who has always supported and believed in me. Thank you for always being available despite how insanely busy you are, and for reading and editing my dissertation when I sent you drafts at the eleventh hour. You have intellectually challenged me and enriched my ideas, and the guidance you have given me is still very present in my mind. You have tremendously influenced my personal growth and experience at Pepperdine, and it is very meaningful to me that you have been a part of my graduate experience from start to finish.

I would like to extend my great appreciation and gratitude to Dr. Subotnik and the UCLA Aftercare Research Program, as this dissertation would not have been possible without their support, guidance, and resources. Dr. Subotnik, thank you for the opportunity to be a part of the Aftercare family. I have learned an enormous amount from you, and the knowledge I acquired about first episode psychosis and clinical research often guides my thinking and is a frequent part of my current clinical work. I would also like to acknowledge Dr. Gerhard Hellemann, the statistical mastermind who helped immensely with conducting the analyses for this dissertation and in the process greatly deepened my understanding of statistics.

Thank you Dr. Keatinge for your tremendous mentorship and consistent optimism and belief in what I am capable of achieving, which has driven me in times when I have doubted myself. The dedication and unmistakable caring that you have for your students pushed me to do

my absolute best. The passion you have for assessment emanates from you, and I believe your enthusiasm greatly contributed to me developing my own passion and enthusiasm for psychological evaluations. You have provided me great wisdom and guidance as I navigated my path through graduate school and decided that I wanted to work in the field of forensics. You also opened my eyes to career possibilities and opportunities that I had never considered.

I would like to express my immense gratitude to my family and friends for putting up with me and supporting me through this arduous but rewarding journey of graduate school. You have seen me at my best and worst through this process and your support has been unwavering. In particular, to my parents and Emily, I believe you deserve honorary doctorates yourselves for all the hours you have put in over the years listening to my trials and tribulations, and managing my stress. Thank you.

Lastly, I would like to express my gratitude and appreciation to the Pepperdine Graduate School of Education & Psychology community, which readily accepted me and created a supportive academic home for me to learn and thrive over the course of the last six years. Through my experiences at Pepperdine I have experienced immense personal growth, and have developed close, strong and life-long friendships. In particular, I am extremely grateful that I had Kenny, Kristen, and Jackie by my side as companions, classmates, study partners, stress-relievers, Starbucks-run buddies, carpool buddies, and reality-checkers during the ups and downs of our doctoral program. Thank you for being a part of this experience.

# VITA

## EDUCATION

**Pepperdine University, Graduate School of Education & Psychology**
West Los Angeles, CA
**Doctor of Psychology, Clinical Psychology** *expected* May 2015

- Accredited by the American Psychology Association
- Dissertation: *The relationship between second-generation antipsychotic medication adherence and negative symptoms in first-episode schizophrenia*

**Pepperdine University, Graduate School of Education & Psychology**
Malibu, CA
**Master of Arts, Clinical Psychology, Emphasis: Marriage & Family Therapy** April 2011

**University of California, San Diego (UCSD)**
La Jolla, CA
**Bachelor of Science, Psychology, Emphasis: Clinical Psychology** June 2007
**Minor in Visual Arts Photography**

## CLINICAL EXPERIENCE

**Saint Elizabeths Hospital**
Washington, District of Columbia July 2014 – Present
**Predoctoral Psychology Intern**
Training Supervisors: Richard Gontang, Ph.D., Christine Kelley Psy.D., Pamela Barrigher, Ph.D., Shilpa Krishnan, Ph.D., Wendy Olson, Ph.D.
Setting Type: Forensic/Civil Psychiatric Inpatient Hospital; APA Accredited Psychology Internship

- Patient Population: 300 bed forensic/civil psychiatric hospital with multiple levels of security (maximum and minimum) housing judicially committed patients under the following commitment types: not guilty by reason of insanity, not competent to stand trial, and various civil commitments.
- Complete two rotations participating as an integral part of an interdisciplinary treatment team for a unit: 1) six months on a maximum-security post-trial unit housing men who have been found Not Guilty by Reason of Insanity; 2) six months on a maximum-security pre-trial unit housing men who have been deemed incompetent to proceed with current legal charges
- Attend interdisciplinary recovery plan meetings, write 60-day treatment updates, develop and implement Initial Behavioral Intervention plans, meet individually with patients to discuss aspects of treatment, complete initial psychological assessments
- As part of the Forensic Consult Service, conduct competency evaluations, write letters to D.C. Superior Court opining competency status, and serve as a consultant for civil commitment hearings
- Administer, score, interpret, and write integrated psychological assessment reports (including assessment of risk for future violence, malingering, and cognitive, neuropsychological, and personality measures) detailing a comprehensive clinical interview, data interpretation, diagnostic clarification (as needed), and treatment recommendations.
- Provide individual and group psychotherapy (specifically, facilitating competency restoration, mock trial, and anger management groups)

**Patton State Hospital**
California Department of State Hospitals, Patton, CA September 2013 – June 2014

**Psychology Assessment Clerk**
Training Supervisors: Annette Ermshar, Ph.D., MSCP, ABPP (Forensics); Allen Kilian, Ph.D.; Andrew Tamanaha, Ph.D.
Setting Type: Maximum Security Forensic Psychiatric State Hospital

- Patient Population: 1,500 bed maximum security forensic psychiatric hospital housing judicially committed patients under the following commitment types: not guilty by reason of insanity, not competent to stand trial, mentally disordered offender, mentally disordered sex offender, and various civil commitments.
- Administered, scored, interpreted, and wrote 25 comprehensive assessment reports (psychodiagnostic, neuropsychological, and integrated) detailing assessments administered, data interpretation, diagnostic clarification (as needed), and treatment recommendations.
- Co-facilitated group psychotherapy for patients in the Sexual Offender Commitment Program (SOCP) by implementing the Good Lives Model/Self-Regulation Model, enhancing skills acquisition and application to male and female sex offenders.
- Conducted comprehensive clinical intakes and consult with multidisciplinary treatment team.

## Pepperdine Educational & Psychological Counseling Clinic

West Los Angeles, CA February 2013 – June 2014
**Psychology Extern**
Training Supervisors: Aaron Aviera, Ph.D.; Carol Falender, Ph.D.; Dity Brunn, Psy.D.
Setting Type: Community Clinic

- Patient Population: Adults, adolescents, and children presenting with an array of Axis I and Axis II disorders on an outpatient basis and receiving individual, couples, and family therapy.
- Conducted clinical intake assessments, and administered weekly individual and couples psychotherapy utilizing a primarily Cognitive Behavioral Therapy orientation.
- Recorded progress notes, developed therapy goals, and created treatment plans.
- Administered and assessed outcome measures to evaluate therapeutic progress.
- Reviewed video-recordings of therapy sessions during supervision to improve clinical skills and provide better treatment.

## Los Angeles County + University of Southern California Medical Center (LAC+USC)

Augustus Hawkins Campus, Los Angeles, CA September 2012 – September 2013
**Clinical Psychology Clerk**
Training Supervisors: Elaine Eaton, Ph.D.; Lucy Erickson, Ed.D.
Setting Type: Public County Hospital and Medical School

- Patient Population: A fast-paced and intensive program that admits adults and adolescents on involuntary (5150) legal holds for being a danger to self, danger to others, or gravely disabled. Patients present with severe psychopathology such as psychotic disorders, mood disorders, substance use disorders, OCD, PTSD, eating disorders, personality disorders, and cognitive disorders. Comorbid general medical conditions are also typical (i.e., cancer, autoimmune diseases, seizures, pregnancy, recent limb amputations).
- Facilitated group therapy, intake interviews, and individual crisis consultations for adults.
- Administered, scored, interpreted, and completed psychodiagnostic and neuropsychological assessment reports for diagnostic clarification, discharge planning, and medication modifications.
- Presented findings to referring physicians, patients, and at grand rounds with a 2-5 day turnover rate from point of referral to completion of report.

**University of California, Los Angeles (UCLA), Aftercare Research Program**
Los Angeles, CA September 2012 – June 2013
**Psychology Extern**
Training Supervisors: Luana Turner, Psy.D; Kenneth Subotnik, Ph.D.
Setting Type: Clinical Research Program within a university focusing on First Episode Psychosis

- Patient Population: Young adults with recent onset psychosis (within two-years of their first psychotic episode).
- Co-facilitated a psychoeducational group titled Tools for Successful Living (TSL).
- Assisted with development of treatment manual for group therapy program titled Tools for Successful Living (TSL) focusing on (but not limited to) the role of social support, wellness, insight, and substance use's impact on the brain, in individuals with schizophrenia.
- Attended supervision groups to discuss progress of patients and modifications of treatment protocol as part of a pilot study.

**Union Rescue Mission – Conrad Hilton Foundation**
Los Angeles, CA September 2011 – August 2013
**Psychology Extern/Fellow**
Training Supervisor: Aaron Aviera, Ph.D.
Setting Type: Homeless Shelter and Residential Substance Use Rehabilitation Facility

- Provided individual and group therapy to improve coping skills, relationships, and overall functioning to residents of the Union Rescue Mission homeless shelter, specifically individuals with long histories of addiction, mood disorders, psychotic disorders, and personality disorders.
- Co-founded and co-facilitated a psychoeducational support group for individuals with chronic medical conditions, to assist with management of healthy lifestyles and coping with grief, addiction, and anger exacerbated by their medical conditions.
- Completed intake assessments, individual session progress notes, as well as advocated for clients by means of frequent interactions with chaplains, parole officers, social workers, and other individuals to facilitate comprehensive treatment.
- Reviewed audio-recordings of therapy sessions during supervision to improve clinical skills and provide better treatment.

**Sports Concussion Institute**
Los Angeles, CA June 2012 – August 2012
**Psychology Extern**
Training Supervisor: Mari Davies, Ph.D.
Setting Type: Private Medical Clinic

- Administered neuropsychological assessments to collect baseline data for youth and adolescent athletes as a measure for assessing potential damage should traumatic brain injury occur during athletic season.
- Observed and assisted with cognitive rehabilitation for individuals with traumatic brain injury.

**Brotman Medical Center**
Culver City, CA January 2010 – May 2011
**Marriage & Family Therapist Practicum Trainee**
Training Supervisor: Jan Boczan, LMFT
Setting Type: Private Hospital

- Provided individual therapy, group therapy, and psychoeducation to the chronically mentally ill population, specifically those with schizophrenia, schizoaffective disorder, and mood disorders in the Intensive Outpatient Program, Behavioral Health Unit, and Chemical Detoxification Unit.

- Completed patient treatment plans, psychosocial assessments, as well as advocated for patients; wrote group and individual session progress notes addressing and evaluating each patient's mood, affect, and progress towards treatment goals.

## MENTAL HEALTH EMPLOYMENT EXPERIENCE

**San Diego Center for Children Learning Academy**
San Diego, CA May 2009 – July 2009
**Interim Special Education Teacher**
Supervisor: Nancy Macnamera, M.Ed.
Setting Type: Non-Public School

- Taught multiple-subject fifth and sixth grade combination special education class for children with emotional, developmental, and behavioral disabilities (bipolar disorder, autism spectrum disorder, PTSD, and mood and impulse control disorders).
- Created lesson plans, led class discussions and small groups to teach students reading, writing, and math.
- Worked closely with team of speech and occupational therapists, social workers, school therapists, and psychiatrists to develop and implement Individualized Education Plans (IEP).

**San Diego Center for Children**
San Diego, CA July 2007 – May 2009
**Child Development Counselor**
Supervisor: Pamela Hansen, LMSW
Setting Type: Residential Treatment Facility (Level 12 & Level 14)

- Counseled children and adolescents diagnosed with emotional and behavioral disabilities (mood disorders, autism spectrum disorders, ODD, PTSD, and psychotic symptoms) to facilitate adaptive coping skills, social skills, and anger management by working individually and leading small groups.
- As part of a multidisciplinary team, implemented treatment plans, documented observations, and tracked progress of client behavior, incidents, and prevention interventions.
- Applied behavior modification as well as Crisis Prevention Intervention (CPI) including verbal intervention and manual restraints on agitated and unsafe clients to ensure their well-being and the safety of others.

**San Diego Center for Children**
San Diego, CA December 2007 – May 2009
**Medication Technician**
Training Supervisor: Tracy Lee Brenner, LVN
Setting Type: Residential Treatment Facility

- Prepared and administered prescribed medications (i.e., antipsychotics, mood stabilizers, antidepressants) to residents (98% of the residents were prescribed medications).
- Assessed the psychological state, behaviors, and vitals of clients in physical restraints and determined whether the Psychiatric Emergency Team (PET) needed to be contacted to transport clients to the hospital.

## RESEARCH EXPERIENCE

**Los Angeles County + University of Southern California Medical Center (LAC+USC)**
Los Angeles, CA June 2013 – Present

**Research Assistant**
Principal Investigator: John Briere, Ph.D.

- Assist with revision of *Principles of Trauma Therapy: A Guide to Symptoms, Evaluation, and Treatment* to accommodate DSM-5 revisions for publication of the third edition of the text.
- Review and analyze dataset for development of paper regarding the effects of multiple types of trauma on the etiology of Posttraumatic Stress Disorder.
- Write sections of paper for multiple publications, specifically the introduction and discussion section.

## University of California, Los Angeles (UCLA), Aftercare Research Program

Los Angeles, CA June 2012 – Present
**Research Assistant**
Principal Investigator: Keith Nuechterlein, Ph.D.
Senior Research Psychologists: Kenneth Subotnik, Ph.D.; Joseph Ventura, Ph.D.

- Analyze and interpret data on medication adherence and negative symptoms in first episode psychosis.
- Write sections and develop tables/appendices for paper presentations, contracted research, and journal publications.
- Conduct literature searches, evaluate appropriateness of journal articles, and compile data for meta-analysis on social cognition, neurocognition, and insight in schizophrenia.
- Enter, review, edit, and manage SPSS Statistics and online databases of collected assessment data.
- Met with statistician on a weekly basis to discuss decisions related to analysis of datasets, and preparation of datasets for analysis (November 2013 – June 2014).

## Pepperdine University

Malibu, CA January 2012 – June 2014
**Research Assistant**
Faculty Supervisors: Stephanie Woo, Ph.D. & Carolyn Keatinge, Ph.D.

- Assisted in preparing new edition/revision of a textbook for advanced psychopathology and treatment
- Reviewed and edited chapters.
- Conducted literature searches and retrieve reference materials to aid in the development of revisions of book chapters to update and revise to DSM-5 criteria.

## Pepperdine University

West Los Angeles, CA May 2010
**Research Assistant**
Supervisor: Doctoral Student Shannon Curry, M.A.

- Assisted on dissertation regarding utilization of expressive writing as an intervention strategy for adolescents exposed to on-going trauma in Peru.
- Scored questionnaires and surveys, and entered results into a database.

## University of California, San Diego (UCSD), Operant Laboratory

La Jolla, CA September 2006 – June 2007
**Research Assistant**
Principal Investigator: Edmund Fantino, Ph.D.

- Administered and proctored psychology experiments such as Prisoner's Dilemma and other decision making, token-economy exercises, with experiment conditions frequently changing.

- Assigned credit and scheduled appointments for the UCSD Experimetrix computer program for psychology experiments.
- Participated in weekly lab meetings.

**University of California, San Diego (UCSD), Autism Laboratory**
La Jolla, CA April 2005 – September 2006
**Research Assistant**
Principal Investigator: Laura Schreibman, Ph.D.

- Worked under a federal grant awarded by the NIMH to improve speech and language development of children with autism.
- Worked one on one with children in home sessions, filmed and scored therapy sessions to provide documentation and establish reliability.
- Utilized Pivotal Response Therapy, Picture Exchange Communication System, and Discrete Trial Training therapy models.

## TEACHING EXPERIENCE

**Pepperdine University**
Malibu, CA September 2012 – April 2014
**Graduate Level Teaching Assistant**
Faculty Supervisors: Susan Himelstein, Ph.D. & Carolyn Keatinge, Ph.D.

- Provided assistance for doctoral and master's level courses: *Advanced Assessment* (doctoral level), *Cognitive Assessment* (doctoral level), *Personality Assessment* (doctoral & master's level).
- Conducted WISC, WAIS-IV, and Rorschach labs for students, evaluating and providing feedback on their assessment administration abilities.
- Graded exams and student's assessment scoring while providing substantial feedback.

**Pepperdine University**
Malibu, CA September 2010 – April 2013
**Graduate Level Teaching Assistant**
Faculty Supervisor: Stephanie Woo, Ph.D.

- Provided assistance for doctoral and master's level courses: *Advanced Clinical Psychopathology* (doctoral level), *Assessment for Marriage & Family Therapists* (master's level), *Clinical Management of Psychopathology* (master's level).
- Graded exams and provided feedback to students regarding responses to exam questions to foster better understanding of material.
- Assisted with clerical duties related to student and lecture materials for class.

**Pepperdine University**
Malibu, CA January 2012 – April 2012
**Graduate Level Teaching Assistant**
Faculty Supervisor: Kristen Dial, Psy.D

- Provided assistance for master's level course: *Assessment for Marriage & Family Therapists.*
- Assisted and co-facilitated lectures to provide students with increased understanding of use of cognitive, personality, and relational assessments in psychotherapy.
- Graded exams and student assessment reports, compiled literature reviews as necessary for the professor.

**Pepperdine University**
Malibu, CA September 2011 – December 2011
**Graduate Level Teaching Assistant**
Faculty Supervisor: Charlene Underhill-Miller, Ph.D.

- Provided assistance for master's level course: *Techniques and Theories in Psychotherapy.*
- Met with students in one-on-one consultations to discuss therapeutic techniques and areas of growth in the student's videotaped therapy sessions.
- Graded exams and provided feedback to students to foster better understanding of material.

**Pepperdine University**
Malibu, CA April 2011 – June 2011
**Graduate Level Teaching Assistant**
Faculty Supervisor: Jorid Nygard, LMFT

- Provided assistance for master's level course: *Substance Abuse Evaluation and Treatment.*
- Assisted with lecture, prepared lecture materials as well as lectured in class.
- Graded exams, papers, and journal assignments; created spreadsheets to record grades and assisted with clerical duties related to student materials for class; provided feedback to and corresponded with students regarding exam and paper questions to increase understanding of the material.

**Pepperdine University**
Malibu, CA January 2011 – April 2011
**Graduate Level Teaching Assistant**
Faculty Supervisor: Dennis Lowe, Ph.D.

- Provided assistance for master's level courses: *Marriage & Family Therapy, Clinical Management of Psychopathology.*
- Planned and facilitated meetings with students regarding class presentations to answer questions and describe grading standards.
- Graded exams and edited papers for grammatical errors and APA format compliance.

## POSTER PRESENTATIONS

Subotnik, K.L., Ventura, J., Gretchen-Doorly, D., Hellemann, G.S., **Agee, E.R.,** Casaus, L.R., Luo, J.S., Villa, K.F., Nuechterlein, K.H. (2013). *Positive and negative symptom correlates of second-generation antipsychotic adherence in recent-onset schizophrenia.* Accepted for the fifty-second Annual Meeting of the American College of Neuropsychopharmacology, Hollywood, FL, December 11, 2013.

**Agee, E.R.,** Otte, K.A., Woo, S.M. (2013). *Increasing Clinicians' Awareness of 'Use of Force' Issues in Forensic/Inpatient Mental Health*. Presented at the one hundred twenty-first Annual Convention of the American Psychological Association, Honolulu, HI, August 3, 2013.

**Agee, E.R.,** Spezze, J.D., Underwood, J.J., Romero, E., Harrell, S.P., Mitchell, C. (2012). *God and Skid Row: Clinical Implications of Integrating Mental Health Services and Spirituality/Religion*. Presented at the one hundred twentieth Annual Convention of the American Psychological Association, Orlando, FL, August 4, 2012.

## INVITED TALKS

Subotnik, K.L., Nuechterlein, K.H., Ventura, J., Gretchen-Doorly, D., Hellemann, G.S., **Agee, E.R.** (2013). *Temporal sequencing of negative symptoms and medication nonadherence during the early course of schizophrenia*. Presented at Genentech, San Francisco, CA, September, 16, 2013.

**Agee, E.R**., Louie, B., Saiz, A. (2012). *When Your Child Has Autism*. Presented at the foster and kinship care program of the Los Angeles Mission College, Los Angeles, CA, April 21, 2012.

**Agee, E.R**. (2012). *Workshop on Scoring the Marital Status Inventory-Revised (MSI-R*). Guest lecturer for master's level course Assessment for Marriage & Family Therapists, CA, California, February 14, 2012.

## PAPERS

Briere, J., **Agee, E.**, & Dietrich, A. (submitted, 2014). *Cumulative trauma and current PTSD in general and inmate samples*.

**Agee, E.,** Spezze, J., Underwood, J. (2014). Parent education model for child and adolescent onset psychosis. *Graduate Student Journal of Psychology, 15,* 31 - 46.

Subotnik, K., Ventura, J., Gretchen-Doorly, D.R., Helleman, G.S., **Agee, E.R**., Casaus, L.R., Luo, J.S., Villa, K.F., Nuechterlein, K.H. (2014). The impact of second-generation antipsychotic adherence on positive and negative symptoms in recent-onset schizophrenia. *Schizophrenia Research, 159,* 95 -100. doi: 10.1016/j.schres.2014.07.008

Subotnik, K.L., Nuechterlein, K.H., Ventura, J., Gretchen-Doorly, D., Hellemann, G.S., **Agee, E**. (2013). *Temporal sequencing of negative symptoms and medication nonadherence during the early course of schizophrenia*. [internal report to Genentech, Inc., South San Francisco, CA 94080]

## LEADERSHIP EXPERIENCE

### Graduate School of Education & Psychology Clinical Training Program

Pepperdine University, Los Angeles, CA September 2013 – June 2014

**Peer-Supervisor of First and Second Year Doctoral Students**

Faculty Supervisor: Aaron Aviera, Ph.D.

- Selected by the Director of Clinical Training to mentor two first-year doctoral student therapists and one second-year doctoral student treating clients at the Union Rescue Mission, a residential homeless shelter providing comprehensive care to men, women, and children residing on Los Angeles' "Skid Row."
- Provided weekly support to students by reviewing their progress notes, intakes, and audiotaped therapy sessions and providing feedback regarding areas of strength and areas for improvement.
- Assisted with crisis intervention issues as needed to ensure proficiency and appropriate practice of legal and ethical principles.

### Los Angeles County + University of Southern California Medical Center (LAC+USC)

Los Angeles, CA September 2013

**Assessment Peer-Supervisor**

Supervisors: Elaine Eaton, Ph.D., Lucy Erickson, Ed.D.

- Provided training, mentorship, and guidance for incoming psychology assessment clerks on inpatient units.
- Demonstrated and co-facilitated inpatient group psychotherapy sessions, reviewed techniques and guidelines for working with an acute population.
- Served as model for demonstrating intake skills and assessment administration.
- Assisted with utilizing electronic medical records, reviewed scoring, interpretation and report writing for integrated assessments.

**Pepperdine University**
Student Government Association, Los Angeles, CA May 2013 – June 2014
**Vice President**

- Operated as part of the Executive Board to develop goals for student government and oversee actions and ideas of the students in the student government association.
- Co-led monthly meetings and assisted in the planning and execution of monthly events for the student body, including community philanthropy events, self-care activities, professional growth didactics, and fundraisers.
- Maintained the annual budget and allocated financial resources for events and the expenditures needed for the student body.

**Pepperdine University**
Forensic Psychological Association, Los Angeles, CA May 2012 – June 2014
**Executive Committee Member**

- Created and developed workshops and panel events throughout the year to provide students with knowledge and didactics about pursuing careers in the realm of forensic psychology.
- Met bi-monthly with executive committee, contacted alumni working at forensic sites to connect with current students to establish mentorship relationships.

**Pepperdine University**
Student Government Association, Los Angeles, CA September 2011 – May 2013
**Class Representative**

- Second Year Class Representative (September 2012 – May 2013)
- First Year Class Representative (September 2011 – August 2012)
- Served as liaison between class cohort and student government association in order to voice student's concerns, needs, and created cohesion among psychology program and student body.
- Created and planned activities and programming to further students' academic growth, maintained self-care, and fostered community philanthropic efforts.
- Attended monthly meetings and reported progress updates to class cohort.

**Pepperdine University**
Psi Chi International Honor Society in Psychology, Malibu, CA September 2010 – August 2011
**Vice President of Graduate School of Education & Psychology (GSEP), Malibu Chapter**

- Maintained regulations and traditions of the Psi Chi Honor Society for graduate students.
- Managed membership applications and attended monthly executive committee meetings.
- Planned student events to foster academic growth in extracurricular didactics.

## OTHER EXPERIENCE

**West LA Lacrosse**
West Los Angeles, CA September 2009 – June 2014

**Lacrosse Coach**
Supervisor: Caroline Goldzweig, M.D.
- Coached youth, middle, and high school girls in the mechanics and basics of lacrosse; taught sportsmanship, leadership, and teamwork.
- Interacted with officials and league coaches to schedule games and organize practice schedules.
- Assisted with recruiting, hiring, scheduling, and delegating responsibilities to coaches.

### Pepperdine University
Malibu, CA September 2009 – August 2011
**Graduate Assistant for Program Administrator**
Supervisor: Andrea Lipinski, M.A.
- Assisted Program Administrator by visiting practicum sites to evaluate appropriateness of site and establish stronger working relationships on behalf of the university.
- Acted as an ambassador of the Graduate School of Education and Psychology by leading tours, and communicating with students, prospective applicants, administration and faculty addressing questions and daily concerns.

### San Diego Unified School District
San Diego, CA February 2008 – June 2009
**Head Coach of Varsity Lacrosse Program**
Supervisor: Karen Quiros
- Coached the Patrick Henry High School Varsity lacrosse team.
- Planned and taught adolescents sportsmanship, teamwork, leadership, and the game of lacrosse while developing strategies to win according to game conditions.
- Planned, scheduled, led daily practices, prepared game line-ups to effectively coach a competitive varsity high school team.

### Braille Institute
La Jolla, CA September 2003 – June 2007
**Volunteer**
- Assisted individuals who are blind and visually impaired in various classes such as cooking and dancing.
- Assisted individuals in the Braille library by rewinding and replacing audio tapes and finding particular audio books of interest.

### Kearny Educational Complex
San Diego, CA January 2006 – April 2006
**Academic Tutor & Mentor**
- Tutored socially and economically disadvantaged high school students in geometry and algebra.
- Mentored students with emotional disabilities regarding college and life decisions.

## HONORS & AWARDS

Colleagues Grant, Pepperdine University, 2009 – Present
Conrad N. Hilton Foundation Fellowship, Union Rescue Mission, 2011 – 2012
Dean's List, University of California at San Diego, 2004

## PROFESSIONAL AFFILIATIONS

- Psi Chi International Honor Society in Psychology, 2010 – Present
  Psy.D Program Representative 2011 – 2012
  Vice President of GSEP Chapter Malibu Campus 2010 – 2011
- American Psychological Association (APA)
  Graduate Student Member 2007 – Present
- Forensic Psychological Association, 2012 – 2014
- Pepperdine GSEP Student Government Association, 2011 – 2014
- National Alliance on Mental Illness (NAMI), April 2011 – 2013
- California Association of Marriage and Family Therapists (CAMFT)
  Graduate Student Member 2009 – 2012
- Research and Practice Team (RAPT), September 2009 – April 2011
- Delta Gamma Sorority
  Alumni Member 2007 – Present
  Active Member 2003 – 2007
  Vice President Communications 2006 – 2007
  Director of Public Relations 2005 – 2006

## CREDENTIALS & CERTIFICATIONS

- California Basic Educational Skills Test (CBEST) Credential 2008 – Present
- Crisis Prevention Intervention (CPI) 2007 – 2011

# ABSTRACT

Adherence to psychotropic medication is a critical aspect of treatment for the management of psychotic disorders. While the literature on the need for medication adherence is extensive, little research has explored the relationship between the negative symptoms of psychosis and medication adherence. Since negative symptoms are enduring, stable, and strongly correlated with poor outcome, it is vitally important for research to explore the role of negative symptoms in regards to adherence to psychotropic medication. Given its potentially significant consequences for treatment interventions, the purpose of this study was to contribute to the exceedingly limited body of research exploring the relationship between the negative symptoms seen in psychosis and medication adherence. This study examined if there is a relationship between the two and whether causality could be determined should a significant relationship exist between medication adherence and negative symptoms. This study utilized data previously collected at the UCLA Aftercare Research Program for studies examining aspects of outpatient psychiatric treatment. The 148 participants had a mean age of 22.5 years and were in the midst of their first psychotic episode upon study entry. Data from the Brief Psychiatric Rating Scale, Scale for the Assessment of Negative Symptoms, and medication adherence ratings were collected over the course of 12 months. Analyses revealed a significant relationship between the presence of negative symptoms and medication nonadherence. Analyses examining the temporal relationship between the two variables revealed that initial medication nonadherence was significantly associated with subsequent negative symptoms. However, once the impact of positive symptoms was controlled for as a potential mediating variable, the strength of the relationship between medication adherence and negative symptoms dissipated. After controlling for the role of reality distortion, the only negative symptoms significantly associated with

medication nonadherence were the BPRS Negative Symptom Factor, BPRS Emotional Withdrawal, and BPRS Self-Neglect. Consequently, it appears that negative symptoms are more strongly associated with positive symptoms than with medication adherence. Replication of these findings and further research exploring the relationship between positive and negative symptoms as they relate to medication adherence is needed in order to improve treatment interventions focused on medication adherence.

# Chapter 1: Review of the Literature

## Introduction

Schizophrenia is a life-long and often debilitating illness, impacting all aspects of one's life. Adding to the difficulty and complexity of treating the disorder is the reality that the presentation of the illness can be highly varied in terms of the specific constellation of symptoms displayed and their severity. As a result, understanding the relationship between aspects of the illness and treatment effectiveness can be challenging. Although the terminology of *positive* vs. *negative* symptoms originated with the neurologist Hughlings Jackson in the 1930s, the observation that schizophrenia symptoms can be conceptualized into two general clusters has been made for over 150 years (Berrios, 1985; Crow, 1985; Hughlings-Jackson, 1931; Tandon et al., 2013). Positive symptoms are exaggerations and distortions of normal perception and thinking, such as paranoia, delusions, and hallucinations (Fernandez, Gomez, Homero, & Lopez-Ibor, 2013; Rollins, Bond, Lysaker, McGrew, & Salyers, 2010). Positive symptoms are among the features of schizophrenia that the public most often associates with psychosis and may be more intrusive than negative symptoms; however, negative symptoms are more highly correlated with poor outcome and long-term impairment in functioning (Hanson, Healey, Wolf, & Kohler, 2010). Although positive symptoms are a core feature of schizophrenia, for the purposes of this dissertation, emphasis will be placed on negative symptoms, with little further reference to positive symptoms.

Negative symptoms reflect the absence or reduction of certain social abilities and emotions that are normally present (Hanson et al., 2010; Moller, 2007). Although the inclusion of negative symptoms as an example of active phase symptoms of schizophrenia in the DSM system is of relatively recent origin (American Psychological Association [APA], 2000),

historically there has been an understanding of the importance of negative symptoms in the disease process of schizophrenia. For example, Bleuler prioritized negative symptoms over positive symptoms as primary aspects of schizophrenia (Hanson et al., 2010). A challenge in identifying negative symptoms is determining whether they are primary features of the illness or secondary to factors such as hospitalization, depression, environmental understimulation, and medication side effects (Chang et al., 2011; Flaum & Andreasen, 1995). If it is determined that the presence of negative symptoms is due to any other factor, then the negative symptoms should not be considered a factor for the diagnosis of schizophrenia (APA, 2013). Since secondary symptoms can be due to several factors, they often fluctuate based on the changes of the influencing factors (Hanson et al., 2010).

This dissertation will explore the relationship between negative symptoms of first episode schizophrenia and medication nonadherence. As such, the following includes a review of various aspects of negative symptoms, including types and examples of negative symptoms, clinical significance and prognosis, and the relationship between negative symptoms and medication adherence.

**Negative Symptoms**

Negative symptoms are important in understanding and treating schizophrenia because there is robust evidence that outcome is predicted by severity of negative symptoms and cognitive impairment (Brier & Berg, 1999; Ventura, Hellemann, Thames, Koellner, & Nuechterlein, 2009). Although research has established the effectiveness of antipsychotic medications on treating positive symptoms (Kozuki & Schepp, 2005; Leucht et al., 2003; Salimi, Jarskog, & Lieberman, 2009), these agents are not as effective in treating negative symptoms or cognitive deficits (Breier & Berg, 1999; Erhart, Marder, & Carpenter, 2006; Salimi et al., 2009).

Despite negative symptoms being less responsive to treatment, persistent, and worsening over time, they are typically viewed as less disruptive and distressing than positive symptoms because they do not usually lead to hospitalization (Hanson et al., 2010). Negative symptoms associated with schizophrenia tend to be fairly stable throughout the course of the illness and are less likely to characterize cases with later illness onset (Woo & Keatinge, 2008). Additionally, negative symptoms manifest in many ways, which adds to the complexity of the clinical presentation of schizophrenia and its treatment (Moller, 2007). It can be particularly difficult for the individual with schizophrenia and their loved ones because oftentimes negative symptoms can seem very similar to clinical depression since both share a lack of motivation, decreased interests, or just an inability to be interested in anything; these similarities can make it challenging for clinicians to properly distinguish between schizophrenia and a mood disorder (Green, 2001). Additionally, negative symptoms may be particularly difficult for loved ones because individuals with mostly negative symptoms of schizophrenia often appear interpersonally disconnected, bland, or "zombie-like" (Woo & Keatinge, 2008, p. 477). One psychologist, John Briere, has even likened it to talking to someone with "a sheet of plastic" (personal communication, December 17, 2012) between oneself and an individual with schizophrenia.

**Types of negative symptoms.** There are many types of negative symptoms that can be a part of schizophrenia. To better understand the breadth negative symptoms have in an individual's overall functioning, the most common ones will be identified and described: Affective flattening, alogia, apathy, anergia, avolition, anhedonia, and asociality.

*Affective flattening,* also called blunted affect, involves restrictions in the range and intensity of one's emotional expression and is characterized by poor eye contact, immobility in the face, and reduced body language (APA, 2000; Green, 2001). The individual may smile or

warm up to someone occasionally, but mostly there is a restricted and diminished range of emotional expressiveness that is present most of the time (Tattan & Creed, 2001). Reduction of spontaneous movements and lack of voice modulation may also be present with affective flattening (Makinen, Miettunen, Isohanni, & Koponen, 2008).

*Alogia*, also known as poverty of speech, consists of restrictions or a decrease in the fluency and productivity of thought or speech and may be manifest by brief, concise, empty replies that are not attributable to factors such as an unwillingness to speak (APA, 2000; Green, 2001; Rollins et al., 2010; Tattan & Creed, 2001). Individuals with alogia tend to talk little and say few words (Makinen et al., 2008).

*Apathy* refers to the absence, suppression, or withdrawal of emotions or feelings (Rollins et al., 2010; Tattan & Creed, 2001). Apathy reflects a lack of motivation and a decrease in goal-directed behavior not attributable to cognitive impairment, emotional distress, or decreased consciousness (Kiang, Christensen, Remington, & Kapur, 2003). When an individual demonstrates apathy, it may look like she or he has an indifference to everything – relationships, long-term goals, or the future in general. Those with schizophrenia may also be unable to articulate or only poorly describe their feelings (Woo & Keatinge, 2008).

*Anergia* is a physical symptom that consists of a reduction in movement or a lack of energy (Green, 2001; Woo & Keatinge, 2008). Anergia may look like motor retardation and disorientation (Laroi et al., 2000). It consists of slow or restricted physical movement, and may also relate to poor mental focus (Moller, 2007).

*Avolition*, also known as amotivation, refers to a restriction in the initiation or persistence of goal-directed behavior or activities (APA, 2000; Foussias & Remington, 2010). Avolition also includes reduced motivation, which may be evidenced by behaviors such as poor hygiene

(Makinen et al., 2008). Individuals with this symptom may display a decreased willingness to or interest in work, school, social, treatment, or recreational activities and may instead sit for long periods of time (APA, 2000; Baier et al., 2000; Leo, Jassal, & Bakhai, 2005). Since avolition may include spending days sitting and watching television, having no interest in helping with basic household chores, or seeming unwilling to return to school or obtain a job, it can sometimes be viewed as a personality flaw instead of a symptom of schizophrenia (Green, 2001).

*Anhedonia* represents a loss of interest or pleasure in activities (APA, 2000; Baier et al., 2000; Foussias & Remington, 2010; Loas, Noisette, Legrand, & Boyer, 2000). It is also thought of as a diminished capacity for experiencing pleasure, and can manifest not just as loss of interest but also less engagement in social or pleasurable activities (Buck & Lysaker, 2013; Makinen et al., 2008). The inability to experience closeness with others is also associated with anhedonia (Makinen et al., 2008).

*Asociality* is social withdrawal due to a lack of motivation to engage in social interactions, and a preference for solitary activities (Tattan & Creed, 2001; Woo & Keatinge, 2008). Individuals experiencing asociality may have few friends, poor relations with friends, and reduced social interactions with others (Makinen et al., 2008).

**Deficit syndrome.** *Deficit syndrome* is a term coined by Carpenter and his colleagues in 1988 that is intended to reflect primary negative symptoms that are characterized by an enduring stability and persistence over time that are not attributable to secondary symptoms (APA, 2000; Carpenter, Heinrichs, & Wagman, 1988; Chang et al., 2011). The deficit syndrome is associated with anticipatory anhedonia (i.e., lack of motivated behavior and a desire for something in the future; Buck & Lysaker, 2013) and cognitive dysfunction, and those with the deficit syndrome tend to have more neurocognitive deficits than individuals with schizophrenia who do not have

the deficit syndrome (Beck et al., 2011; Green, 2001; Hanson et al., 2010). Additionally, the deficit syndrome has been associated with lower socio-economic status, irrespective of ethnicity (Hanson Healey, Wolf, & Kohler, 2010). The deficit syndrome has been found to be directly related to functional outcomes including decreased employment and social functioning, lower socio-economic status, and overall worse prognosis (Green, 2001; Hanson et al., 2010). Notably, one study showed that when receiving social skills training, individuals with the deficit syndrome benefited less than individuals without deficit syndrome (Erhart et al., 2006). Overall, the estimated prevalence of the deficit syndrome is 15% for first episode schizophrenia, and 25-30% in chronic schizophrenia (Hanson et al., 2010; Kirkpatrick, Buchanan, Ross, & Carpenter, 2001).

**Clinical Significance of Negative Symptoms**

Negative symptoms are typically stable and enduring features of schizophrenia, lasting throughout the course of the illness (Hanson et al., 2010; Rollins et al., 2010). Approximately 50-90% of individuals with schizophrenia experience negative symptoms during their first episode of psychosis, and 20-40% of individuals with schizophrenia have persistent negative symptoms (Makinen et al., 2008). Further, overall functioning, quality of life, and aspects of everyday life are profoundly affected by negative symptoms (Makinen et al., 2008; Rollins et al., 2010). Negative symptoms tend to go unnoticed by the patient, but as previously noted are very noticeable to the individuals around the patient, and may worsen over time (Hanson et al., 2010; Rollins et al., 2010).

**Association Between Negative Symptoms and Outcome**

Although the presence of negative symptoms is generally agreed upon to indicate poor prognosis, evidence for the responsiveness of negative symptoms to medication is mixed (Erhart,

Marder, & Carpenter, 2006). First generation antipsychotic medications were first developed in the 1940s, and consisted of chlorpromazine, haloperidol, thioridazine, and fluphenazine (Green, 2001). Although these medications revolutionized the treatment and prognosis for schizophrenia, they mostly treated positive symptoms and were not very effective at reducing negative symptoms (Carpenter & Davis, 2012). In the 1990s a new generation of antipsychotic medications, referred to as atypical antipsychotics, were introduced to the market and found to be more effective than previous agents in treating negative symptoms as well as the anxiety and depression that often accompany schizophrenia; however, such medication did not effectively treat negative symptoms (Green, 2001; Hanson et al., 2010). To clarify, it appears that atypical antipsychotics minimize secondary negative symptoms; however, they have no significant impact on primary negative symptoms (Hanson et al., 2010). Even up to recently, available pharmacological treatments have had limited benefits in reducing the burden of negative symptoms (Erhart, Marder, & Carpenter, 2006; Makinen, Miettunen, Isohanni, & Koponen, 2008). However clozapine appears to be the most effective atypical antipsychotic medication for treatment of negative symptoms, but comes with a serious risk of agranulocytosis (Makinen et al., 2008). The second-generation antipsychotic iloperidone, appears to be superior to haloperidol or risperidone in improving negative symptoms, but appears to have a greater effect on secondary and not primary negative symptoms (Hanson et al., 2010). Asenapine has demonstrated some efficacy for persistent negative symptoms when compared to olanzapine, though superiority has not been demonstrated (Hanson et al., 2010). When compared to haloperidol, both olanzapine and risperidone demonstrate clinically significant improvement for the extent of negative symptoms (Hartling et al., 2012; Salimi, Jarskog, & Lieberman, 2009). Overall, research seems to indicate that clozapine, olanzapine, and risperidone are more effective

in treating negative symptoms than typical antipsychotics (Makinen et al., 2008). In one study, olanzapine and risperidone were each associated with moderate improvements in avolition and apathy, with a mild, but non-significant effect for asociality and anhedonia (Salimi, Jarskog, & Lieberman, 2009). Affective flattening and poverty of speech appear to be more stable and less responsive to pharmacologic treatment (Kelley, van Kammen, & Allen, 1999). Although second-generation antipsychotics generally have fewer side-effects than first-generation antipsychotics, it must be acknowledged that clozapine and olanzapine can cause serious side effects such as diabetes and weight gain (Thomas, Nandhra, & Singh, 2012). Limited positive findings have been associated with N-methyl-D-aspartate agonists, and cognitive enhancers have had mixed results for reducing negative symptoms (Hanson et al., 2010). Promising preliminary results for treating negative symptoms have been found with minocycline and omega fatty acids (Hanson et al., 2010).

As previously mentioned, it is generally agreed upon that the presence of negative symptoms in schizophrenia, particularly in the earlier stages of the illness, is associated with poor prognosis and functional outcome, and limited response to medication (Makinen et al., 2008; Ventura et al., 2009). In fact, individuals with persistent negative symptoms are significantly more likely to be male, have more prominent symptoms, less insight, worse vocational outcome, and spend less time in full-time employment (Chang et al., 2011). Individuals with persistent negative symptoms have also been found to have longer duration of untreated psychosis and poorer premorbid functioning in academic and occupational function than individuals without primary negative symptoms (Chang et al., 2011). Thus negative symptoms can be extremely detrimental to an individual's future and can impair the overall level of functioning. Even after a psychotic episode has resolved, negative symptoms often remain,

making it hard for individuals to reestablish a sense of interpersonal connectedness with others (Green, 2001). So far, no treatment appears to significantly treat and improve the negative symptoms of schizophrenia (Carpenter & Davis, 2012; Moller, 2007).

**Medication Adherence**

It is important to discuss the role of medication adherence in the treatment of schizophrenia. Steger, Cassidy, Rabinovitch, Joober, & Malla (2012) found that within first episode psychosis, medication adherence has been associated with faster remission of positive symptoms, better social and occupational functioning, and fewer relapses (Coldham, Addington, & Addington, 2002). In general, strong medication adherence has been shown to improve overall outcomes in psychosis by reducing the risk of relapse and rehospitalization (Steger et al., 2012). Additionally, individuals who have a history of nonadherence or who are initially nonadherent to medication are much more likely to be inadequately adherent throughout the course of the illness, as past nonadherence is predictive of future nonadherence (Leo et al., 2005; Steger et al., 2012).

There are a range of definitions of medication adherence and measures used to assess this construct, which can make comparison of findings difficult (Novak-Grubic & Tavcar, 2002). Some of the many measures of medication adherence are electronic compliance monitors, pill counts, direct observation, prescription renewals, patient or relative report, and biological measurements such as blood assays (Coldham et al., 2002). For the purpose of this paper, the definition of medication adherence will be, “the extent to which a person’s behavior cooperates with the medical suggestions he or she has been provided” (Kao & Liu, 2010, p. 557), a definition consistent with the one used at the UCLA Aftercare Research Program (Kampman & Lehtinen, 1990).

**Prevalence of Medication Nonadherence**

Estimates of the rate of medication nonadherence among individuals with schizophrenia range from 4-89%, and on average medication adherence is only around 50% (Fleischhacker, Oehl, & Hummer, 2003; Lacro, Dunn, Dolder, Leckband, & Jeste, 2002). Many studies have reported differing levels of nonadherence, depending on the stage of the course of illness. Within the first psychiatric admission, up to 50% of individuals will be non-adherent to psychiatric medications (Verdoux et al., 2000), and one-third of patients will be medication non-adherent within six months of their first psychotic episode (Kamali et al., 2006). Some studies have found that within the first year of treatment 26-53% of patients in early psychosis terminate treatment, and within 1-2 years of follow-up, medication nonadherence rates are estimated to be 40% or more (Fenton, Blyer, & Heinssen, 1997; Steger et al., 2012). However, Steger et al. (2012) reported 33-63% of the participants with schizophrenia displayed inadequate levels of adherence. Data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) clinical trials for chronic schizophrenia, a benchmark study in the field of schizophrenia, found that 74% of participants discontinued medication during the 18-month trial (Lieberman et al., 2005). The CATIE study was pivotal for the field of schizophrenia research in many ways. It was a study sponsored by the National Institute of Mental Health and involved three phases using 1,460 patients compiled from 57 sites in 24 states within the United States (Nasrallah, 2007). Many aspects of the studies were innovative for the time, most notably assessing the effectiveness of antipsychotic medications by measuring the time until medication discontinuation or switch in medication as the primary outcome (Weiden, 2007).

The variability in the rate of medication nonadherence may be attributable to the naturally fluctuating nature of medication adherence over time, as well as differing definitions of

and methods to assess this phenomenon (Lacro et al., 2002). Such variability notwithstanding, medication nonadherence remains a significant clinical issue in the treatment of schizophrenia. The costs of nonadherence, in terms of factors such as rehospitalization due to increased symptoms and associated impairment, has been estimated range from $106 million to $1,400 million per year in the United States alone (Dilla, Ciudad, & Alvarez, 2013). Despite improvements in the science of antipsychotic medication, such as the abovementioned increased effectiveness and decreased side effects of the second generation antipsychotics, such advancements will be in vain if patients do not take them (Beck, Cavelti, Wirtz, Kossowsky, & Vauth, 2010; Leo et al., 2005). Little is known about why medication nonadherence is so prevalent in routine clinical practice, although research exploring the causes of nonadherence has significantly increased over the past two decades (Baloush-Klienman et al., 2011). Essentially, despite the varying numbers of medication adherence across dozens of studies, the trend across all of the findings is that medication nonadherence is unacceptably high in the treatment of schizophrenia, and due to the considerable detrimental consequences of nonadherence, more information needs to be gathered to help navigate productive changes in treatment.

**Effects of Medication Nonadherence**

As mentioned, medication nonadherence is a major risk factor for relapse and hospitalization for individuals with schizophrenia (Kao & Liu, 2010). There are many negative outcomes that have been linked to medication nonadherence, such as exacerbation of psychotic symptoms, increased clinic and emergency room visits, rehospitalization, greater impairment in daily functioning, and poorer quality of life (Baloush-Kleinman et al., 2011; Lacro et al., 2002). The costs of psychiatric hospitalizations for schizophrenia patients in the U.S. are estimated to be over $10 billion annually (Wu et al., 2005).

**Predictors & Correlates of Poor Medication Adherence**

Medication nonadherence in schizophrenia is likely influenced by multiple factors and several correlates of poor medication adherence have been identified in the literature. These correlates vary depending upon where an individual is in the course of schizophrenia. For example, individuals with first episode psychosis who are consistently non-adherent with antipsychotic medication tend to have had better premorbid adjustment and neurocognitive functioning (Robinson, Woerner, Alvir, Goldman, & Lieberman, 1999). As mentioned previously, they also typically have a later onset of psychotic symptoms. This suggests that perhaps better functioning individuals are more likely to deny the need for ongoing treatment, including medication, related to their schizophrenia (Robinson et al., 1999).

**Medication related factors.** Some factors commonly found to have an association with medication nonadherence are related to the medication itself (Tattan & Creed, 2001). Possible medication-related reasons for nonadherence include being prescribed an ineffective dosage (either too much or too little), palatability, medication duration, or even complexity of medication regimen (Leo et al., 2005). Also, individuals may have adverse side effects from medications, which subsequently may provoke nonadherence. Such adverse side effects might be caused by current medications, although they may even be caused by previous medications with which the patient had a negative experience (Kao & Liu, 2010; Leo et al., 2005). An individual's level of subjective distress related to extrapyramidal side effects is also strongly correlated with inadequate medication adherence (Kao & Liu, 2010).

Another medication related factor of nonadherence is the cost of care and the individual's ease of access to health care providers, because when it is difficult to access a doctor for prescription refills, it is likely that nonadherence will follow (Velligan et al., 2009). Even depot

(injectable) medications do not ensure perfect medication adherence since an individual can fail to receive the injection at the prescribed time interval (Kane & Malhotra, 2003).

**Mental illness related factors.** There are also illness related factors associated with medication nonadherence (Tattan & Creed, 2001). For example, certain thought processes associated with schizophrenia, such as disorganized thinking, and baseline positive symptoms, have been associated with medication nonadherence (Leo et al., 2005; Novak-Grubic & Tavcar, 2002). More positive symptoms of schizophrenia, particularly grandiosity, along with a higher number of total symptoms, are also correlated with medication nonadherence (Coldham et al., 2002; Kamali et al., 2006; Novak-Grubic & Tavcar, 2002; Steger et al., 2012). Perhaps counter-intuitively, despite initial adequate medication adherence, Steger et al. (2012) showed that oftentimes in schizophrenia, once symptoms resolve as a result of medication, adherence to medication decreases. One may hypothesize that this is because an individual may feel better, and no longer believe they need medication. Comorbidity (e.g., mood disorders and substance disorders) is also strongly correlated with medication nonadherence (Coldham et al., 2002; Steger et al., 2012). Substance abuse is a strong predictor of medication nonadherence in general; and Kamali et al. found that the presence of a substance use disorder predicted medication nonadherence at the six-month mark of treatment (Kamali et al., 2006).

There is a significant correlation between medication compliance and the duration of time an individual has been on psychotropic medications, specifically, the shorter the length of time the individual has been on medication, the less likely they are to be adherent (Tattan & Creed, 2001). In other words,

> Patients who were poorly compliant did seem to have had a shorter, more severe course of illness with greater severity of negative symptoms and the same number of hospital

admissions in a shorter period of time compared with patients who were more compliant. (Tattan & Creed, 2001, p. 153)

**Individual related factors.** The presence of cognitive impairment is related to medication adherence because attention and memory deficits may impact an individual's ability to develop a medication routine (Kozuki & Schepp, 2005; Lacro et al., 2002; Leo et al., 2005). In addition, an individual's beliefs about the risks and benefits of medication, and how such beliefs may align with personal values and goals, may directly and poorly impact medication adherence (Leo et al., 2005). For example, if an individual believes that the risks of medication outweighed the benefits, he or she may be less willing to take medication. Or if an individual has particular cultural beliefs regarding the use of medication, such as believing homeopathic remedies should be utilized instead of prescription medication, medication adherence would also be adversely impacted.

Insight into having a mental illness is also correlated to medication adherence (Buckley et al., 2007). If an individual is aware of and accepts having schizophrenia, and is able to recognize and label their symptoms, they will likely have a more positive attitude toward treatment, subsequently increasing the probability of medication adherence (Kao & Liu, 2010). A major factor that has been shown to hinder medication adherence is poor insight, as 50% of individuals with schizophrenia lack insight into their illness (Coldham at al., 2002; Kamali et al., 2006; Novak-Grubic & Tavcar, 2002).

Personality characteristics, stigma associated with having schizophrenia, and personal priorities (such as wanting to have a sex drive and stopping medication because of its often negative effects on libido), are all more examples of individual-related factors associated with medication nonadherence (Kao & Liu, 2010; Leo et al., 2005). An individual's beliefs regarding

the effectiveness of medication, the importance of treatment, and the significance of adherence, are also directly related to medication adherence (Kao & Liu, 2010; Steger et al., 2012; Velligan et al., 2009). Additionally those with less education, of younger age, and male gender are more likely to be medication non-adherent (Coldham et al., 2002; Kao & Liu, 2010; Steger et al., 2012).

**Physician & treatment related factors.** Sometimes, physician or treatment team related factors can negatively impact an individual's medication adherence (Lacro et al., 2002; Tattan & Creed, 2001). Physicians who do not give the optimal dosage for treatment of schizophrenia, or physicians who do not provide patients with adequate medication psychoeducation regarding the role of medication in treating their illness, can undermine patient adherence (Leo et al., 2005). Also, sometimes medication nonadherence is increased because physicians do not tell their patients their diagnosis or medication schedule (Leo et al., 2005).

Leo et al. (2005) also identify the role patient and physician communication may play in impacting overall medication adherence. Compatible communication styles and strong rapport or alliance, are likely to improve adherence, whereas with less rapport the individual may be more likely to abandon treatment (Leo et al., 2005; Velligan et al., 2009). If a patient perceives that their clinician is genuinely interested in their wellbeing, and willing to dedicate time to their treatment, medication adherence is likely to be better. In contrast, nonadherence may result from a patient fearing abandonment by their physician if their symptoms improve (i.e., wondering if their doctor will discharge them). Nonadherence may also serve as a way to express discontent, frustration, or anger with treatment or the physician or treatment team (Leo et al., 2005).

**Social & environmental factors.** Lastly, social and environmental factors may play a significant role in medication adherence for individuals with schizophrenia (Leo et al., 2005;

Tattan & Creed, 2001). Social and family support and involvement have been shown to increase medication adherence for individuals with schizophrenia (Coldham et al., 2002; Kao & Liu, 2010; Velligan et al., 2009). When a person with schizophrenia lives with other people, medication adherence is generally better than when an individual lives independently because of the structure and support provided (Leo et al., 2005). Financial factors and access to treatment may hinder medication nonadherence (Kozuki & Schepp, 2005). For example, medication nonadherence likely would be greater when an individual has limited financial resources, is facing prohibitive medication costs, or has transportation difficulties limiting access to pharmacies or healthcare providers.

**Consequences of Poor Medication Adherence**

Among the significant negative consequences of medication nonadherence in schizophrenia are higher relapse rates and more frequent and longer hospitalizations (Tattan & Creed, 2001), which in turn are associated with increased care costs (Leo et al., 2005; Morken, Widen, Grawe, 2008). In particular, there is a correlation between medication nonadherence and violence perpetuated by psychotic individuals (Alia-Klein, O'Rourke, Goldstein, & Malaspina, 2007). Medication nonadherence can also have a significantly negative impact on academic and occupational functioning, social adaptation, and long-term functional adaptation (Leo et al., 2005). Patients with more prominent negative symptoms who are medication non-adherent typically have a worse course of illness and poor prognostic outcome (Morken et al., 2008).

**Relationship Between Negative Symptoms & Medication Adherence**

The research exploring the relationship between negative symptoms and medication is mixed and limited. It has been shown that having the ability to manage a medication regimen is

"at best a weak and non-specific correlate" (Heinrichs, Goldberg, Miles, & McDermid, 2008, p. 50) with the presence of negative symptoms, suggesting that, if negative symptoms are associated with poor medication adherence, it is not because the negative symptoms limit an individual's capacity to manage their medication. As mentioned, research indicates that having insight into having schizophrenia is negatively correlated with the presence of negative symptoms (Chang et al., 2011; Mintz, Dobson, & Romney, 2003). As such, there may be a relationship between insight and negative symptoms, and their conjoined impact on medication adherence. Due to minimal insight regarding the benefits of medication on symptom remission, the preventative effect of antipsychotics does not enhance medication adherence in those with significant negative symptoms (Beck et al., 2011). Such studies also indicate that the lack of insight regarding the benefits of medication and the steps needed for symptom remission are related to the high cognitive disorganization and anticipatory anhedonia associated with negative symptoms. In other words, negative symptoms may serve a moderating role in the impact of insight on medication adherence.

As of now, there appear to be five studies with significant findings regarding a relationship between medication adherence and negative symptoms. Each study will be described in terms of setting, sample, measures, and findings:

Tattan & Creed published a study in 2001 exploring the relationship between negative symptoms and medication adherence in 58 individuals attending a depot clinic in Withington Hospital, South Manchester. Tattan and Creed stated that their purpose for the study was because a "possible association between negative symptoms of schizophrenia and compliance with medication has not been studied methodically" (p. 150). They elaborated that although it may seem common sense to believe that individuals who experience negative symptoms would have

better medication adherence than those with positive symptoms because they may lack "assertion of will" (p. 150) that is not the case. Tattan and Creed hypothesized that negative symptoms would be related to poorer medication compliance because of potential lethargy and lack of motivation associated with negative symptoms. For the individuals in the sample, the duration of the illness averaged from 9 – 22 years, and individuals in the study were required to attend the clinic for at least the preceding year to be included in the study. Medication adherence was measured for one year by means of depot prescription cards and was rated in terms of good (complete compliance), intermediate (missed no more than one month of injections), and poor (medication missed for more than one month). The study instruments used were a clinical interview, convenience questionnaire (assessing convenience to clinic), Mini Mental Status Examination (assessing cognitive impairment), and the Scale for Assessment of Negative Symptoms (SANS; to assess the presence and severity of negative symptoms). Upon analyses of the results, the individuals in the study who fell in the poor compliance group had significantly higher SANS scores for avolition, apathy, and alogia (Tattan & Creed, 2001). Additionally, the overall SANS score was higher for individuals with poor compliance. Another finding was that the individuals who were poorly compliant appeared to have a shorter, more severe, course of illness with greater severity of negative symptoms. The authors recognized that one of the limitations of their study was that the sample did not include individuals who were completely nonadherent to medication.

In 2010, Kao and Liu published a study exploring the variables associated with antipsychotic treatment in those with schizophrenia. They hypothesized that medication adherence would be positively associated with insight and negatively correlated with symptoms and side effects of medication. The sample included 113 participants who had been diagnosed

with schizophrenia for longer than one year. All 113 participants were receiving antipsychotic medication treatment prior to the start of the study. The study instruments were the Medication Adherence Rating Scale (MARS), Self-Appraisal of Illness Questionnaire (SAIQ), Positive and Negative Syndrome Scale (PANSS), Extrapyramidal Symptoms Rating Scale (ESRS), Beck Depression Inventory, Beck Hopelessness Scale, Scale for Suicide Ideation, Anxiety Checklist, and the Global Assessment of Functioning (GAF). The study found that subjective response to medication and medication adherence are the two factors influencing medication adherence. The study shared many findings related to the role of insight in medication adherence and indicated that medication adherence was significantly predictive by the positive component of the PANSS, depressive symptoms, outcome of illness, and severity of extrapyramidal side effects. Kao and Lui also found that the presence of negative components of Kay, Flazbein, and Opler's (1987) Positive and Negative Syndrome Scale (PANSS) was statistically significantly related to MARS scores assessing medication nonadherence, in that the negative symptom components of the PANSS were positively correlated with medication nonadherence.

Baloush-Kleinman and colleagues published a study in 2011 exploring the usefulness of the Health Belief Model in explaining antipsychotic medication nonadherence in early schizophrenia. The study included 112 individuals who were earlier in the course of their illness, but were not in their first psychotic episode. Medication adherence was assessed with the Visual Analog Scale for Assessing Treatment Adherence, and symptom severity was assessed with the Clinical Global Impression. The Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) were also administered to assess severity of positive and negative symptoms. The Cognitive Appraisal of Health Scale and Scale to Assess Unawareness of Mental Disorder were administered to assess health beliefs and insight

into their psychotic illness, respectively. The MacArthur Competence Assessment Tool, Extrapyramidal Symptom Rating Scale, Liverpool University Neuroleptic Side Effect Rating Scale, Drug Attitude Inventory, and Trust in Physician Scale were also administered. The results suggested that in comparison to partially or completely nonadherent individuals, medication adherent individuals have increased insight into their illness and the need for treatment, and more awareness of the illness' social consequences. Additionally, adherent individuals appeared to have more positive views of their doctor-patient alliance, and had families with more positive attitudes towards medication. Interestingly, Baloush-Kleinman et al. found that negative symptoms did not directly impact, but rather indirectly impacted medication adherence. Specifically, by means of structural equation modeling, they found that the presence of negative symptoms predicted attitudes (related to insight, medication costs, and medication benefits) towards medication, which then in turn predicted adherence.

In 2012, Steger et al. published a study exploring symptom resolution's impact on medication adherence in first episode psychosis. Given that the sample for the study was a first episode psychosis population, the authors hypothesized that rapid symptom improvement would be associated with subsequent medication adherence. Participants in the study were recruited from the Prevention and Early Intervention in Psychosis Program in Montreal (PEPP-Montreal) in Quebec, Canada. The 216 participants did not have more than one-month exposure to and treatment with antipsychotic medication prior to the start of the study. The study instruments were the Scale for Assessment of Positive Symptoms (SAPS), Scale for Assessment of Negative Symptoms (SANS), Calgary Depression Scale for Depression in Schizophrenia, Barnes Akathisia Scale, and the Extrapyramidal Symptom Rating Scale. Medication adherence was determined based on client and case manager report and pill counts. Adherence was converted to

a percentage and categorized as: Never Adherent (0%), Very Infrequently Adherent (1-25%), Sometimes Adherent (26-50%), Quite Often Adherent (51-75%), or Always Adherent (>75%). Any adherence less than 75% was deemed "inadequate" (p. 46). The authors found that at the three-month mark of the study most participants whose negative symptoms had resolved also had lower levels of positive symptoms. At the six-month mark there were even a greater number of participants with resolved negative symptoms than at the three-month mark. Another finding was that early resolution of negative symptoms was associated with less adequate adherence, whereas those whose negative symptoms persisted were more likely to be adherent to their medication regimen. Steger at al. found that individuals whose negative symptoms had resolved after three months were less likely to have adequate adherence at six months. This may be due to the individual's belief that a substantial improvement in symptoms may indicate readiness to stop taking medication. This effect may also be due to the fact that negative symptoms often cause significant functional impairment. Therefore, one may believe that negative symptom reduction is associated with returning to normal functioning, consequently deciding that medication is no longer needed (Quach et al., 2009; Steger et al., 2012). Of the participants who had early resolution of negative symptoms, the ones who were adequately adherent were compared with those who were inadequately adherent. The comparison revealed that there was a greater presence of alogia and affective flattening in medication nonadherent individuals (Steger et al., 2012). Further analyses explored whether the reduction in negative symptoms was due to a reduction in parkinsonian side effects associated with ceasing medication, and the authors determined this was not a significant factor.

Subotnik et al. published a study in 2014 exploring the extent to which the severity of initial positive and negative symptoms is related to medication nonadherence in individuals with

recent-onset schizophrenia. The sample consisted of 66 individuals all of whom experienced their first major psychotic episode within two years of the study entry. The study instruments were the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS). Medication adherence ratings were on a scale from 1 to 5, with lower scores indicating nonadherence and higher scores indicating better adherence. The medication adherence rating was determined based on data collected from pill counts, plasma concentrations, patient report, clinician assessment, and the Medication Event Monitoring System (MEMS-6). The study spanned 12 months and data analyses explored the relationship between symptoms and medication adherence in addition to whether there was a temporal relationship between the two variables in order to infer causality. It appears that this is the only prior study exploring a potential temporal relationship between negative symptoms and medication adherence. The results suggested that higher levels of medication adherence were generally associated with lower levels of reality distortion. Lower levels of avolition-apathy and alogia were associated with better medication adherence during the three-month baseline interval. Data analyses exploring potential causality suggested that there is a causal relationship between initial medication adherence and lower levels of alogia. While this study revealed that adherence to medication led to lower negative symptoms, it appeared that this relationship was mediated by a reduction in positive symptoms.

**Statement of Problem**

Individuals with schizophrenia who have more prominent negative symptoms typically have a poor prognostic outcome compared to those without such symptoms. Although little research has looked at the relationship between medication adherence and negative symptoms of schizophrenia, the few critical findings have been described above. It appears that current

antipsychotic medications are only minimally effective in treating negative symptoms. Furthermore, current research suggests that individuals with schizophrenia with significant negative symptoms have poorer medication adherence than those who do not have negative symptoms of schizophrenia. Many studies appear to have high attrition rates, and it is likely that patients who have missing data in studies or drop out of studies are nonadherent with medication and typically do not show up for end of study evaluations (Steger et al., 2012). Related to negative symptoms, Steger et al. (2012) found that individuals whose negative symptoms had resolved by the three-month mark of the study, were subsequently more likely to have missing data at the six-month mark. Additionally, the effect of subjects withdrawing from studies and the effect of missing data in studies on overall findings related to medication adherence in schizophrenia is unknown, thus there are potentially still many gaps in the literature. Since medication adherence has consistently been found to be predictive of better outcomes, it is critical that this area is further explored.

**Significance of Proposed Study**

Medication nonadherence is perhaps the single most preventable cause of psychotic relapse in schizophrenia. Intuitively, negative symptoms would appear to lead to medication nonadherence, but the very few studies that have empirically examined this question did not consistently observe this relationship. Identification of predictors of medication nonadherence might lead to useful interventions that could have a huge public health significance. This study will gain more information about a potentially causal relationship between negative symptoms and medication adherence.

**Research Question**

Exploring the relationship between medication adherence and negative symptoms could have significant consequences for treatment interventions. This study will primarily be exploring the question: is the presence of negative symptoms in schizophrenia related to decreased medication adherence? The temporal relationship of negative symptoms and medication nonadherence will be examined for the appearance of a causal relationship between the two. It is hypothesized that the presence of negative symptoms is a primary contributing factor in decreased medication adherence.

# Chapter 2: Methodology

## Participants

The study sample was gathered from participants receiving treatment for first-episode psychosis at the UCLA Aftercare Research program. The sample consists of 148 individuals who qualified as being in the midst of their first psychotic episode, meaning individuals within the first two years of their first psychotic episode. All participants were followed clinically at the UCLA Aftercare Research Program and received outpatient psychiatric treatment as part of studies sponsored by NIMH grants MH37705 and MH66286 to K. Nuechterlein, Ph.D., P.I. (ClinicalTrials.gov identifiers NCT00203788 and NCT00333177). Treatment included regular psychiatrist visits, antipsychotic medication, and individual case management and therapy by Master's and Doctoral level therapists. The second-generation antipsychotic medication, risperidone, was used as the first line medication to stabilize participants at baseline (provided by Janssen Scientific Affairs, Janssen RIS-SA-67 and RIS-NAP-4009). The program was the participant's primary source of mental health treatment, and typically involved 1-2 clinic visits per week.

Participants at the UCLA Aftercare Research Program were recruited from a variety of settings including Los Angeles area psychiatric hospitals and clinics, and the UCLA outpatient service at the Resnick Neuropsychiatric Hospital at UCLA. The analysis examined the period beginning at outpatient stabilization and covered the subsequent 12 months or until the medication trial was terminated due to a switch of the primary antipsychotic medication or withdraw from the study. The participants were not recruited or referred to the program based on previous level of medication adherence. Participants provided written informed consent and were given both oral and written information about the research procedures prior to receiving

services from the program. The UCLA Institutional Review Board approved both longitudinal protocols.

In order to meet criteria for the UCLA Aftercare Research Program, and be included in this sample, participants (a) were within two years of the onset of their first major psychotic episode; (b) had a diagnosis of schizophrenia or schizoaffective disorder, mainly schizophrenic subtype, based on the Research Diagnostic Criteria (RDC; Sample 3), or Schizophrenia, Schizophreniform, or Schizoaffective Disorder, Depressed Type (DSM-IV, for Sample 4); (c) were between the ages of 18 and 45 years; (d) had no evidence of a known neurological disorder; (e) had no evidence of significant and habitual illicit substance abuse or alcoholism in the six months prior to admission to the program, no evidence that substance use accounted for the psychosis, and no evidence that substance use would be a prominent factor in the course of illness; (f) had no premorbid mental retardation; (g) had sufficient acculturation and English language fluency to avoid invalidating research measures of symptomology; (h) lived within commuting distance of the UCLA Aftercare Program; and (i) did not have a contraindication for risperidone (e.g., allergic reaction, intolerable side effects experienced in a previous trial, failed trial that was of sufficient length and in which patient was considered adherent), the initial standardized antipsychotic medication used in the study.

The sample of this dissertation study consisted of 148 individuals: 65 individuals in Sample 3, and 83 individuals in Sample 4, all of whom have had schizophrenia and the onset of their illness was within two years of study entry. Both samples were a part of an NIMH-funded project entitled, “Developmental Processes in Schizophrenic Disorders,” with Sample 3 participants also enrolled in a study called, “Improving and Predicting Work Outcome in Recent-

Onset Schizophrenia," and Sample 4 participants enrolled in a study called, "Cognitive Remediation, Medication Adherence, and Work Outcome in Recent-Onset Schizophrenia."

**Design**

This study involves exploratory analyses of previously collected data as part of a larger study. Once admitted to the UCLA Aftercare Research Program, participants were stabilized on oral risperidone, an FDA approved second-generation antipsychotic medication and randomized to an intervention. One sample, that will be referred to as Sample 3, consisted of an 18-month study comparing two psychosocial interventions to which patients were randomly assigned: an Individual Placement and Support (IPS) and Workplace Fundamentals Module intervention condition, or a Brokered Vocational Rehabilitation condition (consisting of vocational rehabilitation through referral to outside agencies). The details of the two psychosocial interventions are provided elsewhere (Subotnik et al., 2011; Subotnik et al., 2015), as this study is focusing on medication adherence and negative symptoms specifically, within the greater study. The other sample, which will be referred to as Sample 4, participated in a 12-month study comparing long-acting injectable risperidone to oral risperidone. Each participant began the study with oral risperidone as the only antipsychotic medication for a minimum of three weeks. Subsequently, participants were randomized to either continued oral risperidone treatment or the long-acting injectable form of risperidone (RLAI). To maintain comparability, this study will only examine data from those in Sample 4 who were randomized to the oral risperidone group. Sample 4 participants were also randomized to either a cognitive remediation or healthy lifestyle skills training as part of a fully crossed 2x2 design. For a summary of the psychosocial interventions see Subotnik et al. (2015). Additionally, as Sample 3 was of longer duration than

Sample 4, for consistency the present study will only be examining data from the first 12 months of adherence and symptom data from all participants.

**Institutional Review Board (IRB) approval.** The original UCLA Aftercare Research Program studies from which data were used for this dissertation received full IRB approval from UCLA. This author also received approval for IRB exemption from the Pepperdine University Graduate and Professional Schools IRB (GPS IRB) because this study used archived, de-identified data (see Appendix A). Lastly, this author obtained permission from the UCLA Aftercare Research Program to use their de-identified, archived data for this dissertation (see Appendix B).

## Measures

**Medication adherence.** Medication adherence was assessed by considering a variety of factors and developing a numerical value to represent level of adherence to prescribed medication. Each factor comprising medication adherence was categorized and rated to evaluate the level of medication adherence for each two-week interval of time. The factors, or source of information, comprising medication adherence were: pill counts (typically assessed bi-weekly); plasma concentrations of risperidone and 9-hydroxyrisperidone (nonadherence was flagged by nondetectable levels of 9-hydroxyrisperidone; typically assessed every 4 weeks); self-report of nonadherence to a member of the treatment team (typically assessed every 1 to 2 weeks); assessment by a clinician based on occurrence of side effects (typically assessed every 1 to 2 weeks); and Medication Event Monitoring System (MEMS-6®, Sample 4 only). The Medication Event Monitoring System is a medication bottle whereby the lid electronically tracks the date and time that the bottle has been opened and closed since the last time the cap was monitored. Adherence ratings were made on a bi-weekly basis even when all sources of information were

not available during a rating period. Each participant's medication adherence was rated on a 1 - 5 scale, with one representing perfect adherence (100%) and 5 representing lowest adherence (0%). Medication adherence ratings also consist of the rater identifying his or her level of confidence in the accuracy of their rating (on a scale of 1 to 5, with 1 = very little confidence and 5 = very confident). Each patient's weekly medication adherence ratings were then averaged into one-month, as well as 3-month interval ratings. Patient participants in Sample 4 who were randomly assigned to long-acting injectable medication were excluded from these analyses because the level of adherence tended to be nearly perfect across patients and across time points, which would preclude analyses of temporal relationships among adherence and symptoms measures. Further, the long-acting nature of the injectable medication would hamper the examination of the relationship of short-term changes in adherence and symptoms.

**Symptom assessment.** Symptoms were assessed by trained raters administering measures beginning at study entry and throughout the longitudinal treatment and assessment follow-through period.

***Brief Psychiatric Rating Scale (BPRS)***. Psychiatric symptoms were assessed using the expanded 24-item version of the Brief Psychiatric Rating Scale, which is semi-structured and requires self-report and clinician observation to establish ratings (see Appendix C; BPRS Version 4.0; Overall & Gorham, 2008; Ventura et al., 1993). The BPRS was created by John E. Overall and Donald R. Gorham in 1962 and is a clinician-rated measure designed to provide a comprehensive description of significant symptom characteristics in individuals with psychotic illnesses (Overall & Gorham, 2008; Ventura et al., 1993). The expanded version was created in 1993 by the Clinical Research Center for Schizophrenia and Psychiatric Rehabilitation, UCLA Department of Psychiatry and Biobehavioral Sciences, and the West Los Angeles VA Medical

Center (Ventura et al., 1993). The expanded version includes six new scales for more comprehensive assessment of serious mental illness symptoms, and allows for multiple sources of information, such as from the patient, parents or relatives, mental health professionals, medical chart, or other sources – such as police reports (Ventura et al., 1993). The BPRS specifically monitors symptom frequency and severity, and each item is rated from 1 - 7 (1 = not present, 7 = extremely severe; see Appendix C for scoring record form). Although the manual has descriptions for each anchor point, for specific examples that are not included in the anchor points, the scoring system essentially can be understood as ratings of 2 - 3 representing nonpathological, yet mild and observable symptomatology; ratings of 4 - 5 representing moderate and clinically significant symptomatology; and ratings of 6 - 7 representing the presence of severe and clinically significant symptomatology (Ventura et al., 1993). Symptoms rated in the severe range (6 - 7) typically represent pathological experiences. The BPRS typically takes 20-30 minutes to administer, with the first 14 items of the measure rated based on the patient's self-report, and the last 10 items rated based on observed behavior or speech of the patient during the interview (Overall & Gorham, 2008; Ventura et al., 1993).

The BPRS was administered at the point of outpatient medication stabilization, every two weeks during the first year of enrollment in the UCLA Aftercare Research Program. The raters for the BPRS all participated in a quality assurance program and achieved a median Intraclass Correlation Coefficient (ICC) of .80 or higher across all items compared with the criterion ratings (Ventura et al., 1993). Means of one-month intervals of BPRS ratings were established, which constitute the BPRS data that will be used in this report. Further, for the purpose of this study (to address negative symptoms specifically), items related to self-neglect, blunted affect, emotional withdrawal, motor retardation will be of primary focus.

The Self- Neglect scale of the BPRS Version 4.0 assesses level of hygiene, grooming, and meeting basic needs (i.e., showering and eating) to determine whether such behaviors are at an acceptable level based on socially acceptable standards (Ventura et al., 1993). This relates to the negative symptom, avolition. The BPRS Version 4.0 scale Blunted Affect pertains to the patient's range of emotional expressiveness of their face, voice, or gestures. The more restricted the affect, the higher the rating. A blunted affect may also manifest in marked indifference or flatness when discussing upsetting or stressful topics. Oftentimes, blunted affect is referred to as affective flattening. The Emotional Withdrawal scale assesses the patient's capacity to relate emotionally to the interviewer during the assessment. The more deficient an individual's ability is to relate emotionally, the higher the rating on the scale. The BPRS scale Motor Retardation assesses the negative symptom of anergia. This scale evaluates the patient's energy level, specifically whether there is a reduction in energy level, which is often evidenced by slowed movements and speech, reduced body tone, and decreased frequency of spontaneous body movements.

With substantial time and effort, good interrater reliability can be achieved with the BPRS (ICC > 0.80; Overall & Gorham, 2008). It is typically more difficult to receive higher levels on interrater reliability on observational items than on items requiring the patient's self-report (Overall & Gorham, 2008). Additionally, the detailed anchor descriptors often aid in increasing interrater reliability. The BPRS also has good internal consistency for positive and negative symptoms (Cronbach $\alpha = 0.81, 0.91$, respectively; Overall & Gorham, 2008). The BPRS has good validity when compared to other symptom measures for general psychopathology, such as the SANS, SAPS, and PANSS (Overall & Gorham, 2008). The BPRS is correlated with scales on both the SANS, and SAPS ($r = 0.63$), as well as the positive,

negative, and total symptom scales of the PANSS ($r$ = 0.92, 0.82, 0.84, respectively; Overall & Gorham, 2008). Overall, the BPRS is a sound instrument that has been extensively used dating back to the 1970s, and is commonly used in research studies (Overall & Gorham, 2008).

***Scale for the Assessment of Negative Symptoms (SANS).*** The Scale for the Assessment of Negative Symptoms (SANS) is a 23-item measure used to assess the presence of the negative symptoms associated with psychotic disorders (see Appendix D). It is currently considered the gold standard for assessing the presence and severity of negative symptoms (Andreasen, 1983; Hanson et al., 2010). It takes approximately 30-minutes to administer and consists of five subscales: Affective Flattening or Blunting, Alogia, Avolition-Apathy, Anhedonia-Asociality, and Attentional Impairment (Andreasen, 2008). Affective Flattening is assessed by evaluating an individual's affect, such as whether the individual has poor eye contact, inappropriate affect, unchanging social expression, minimal expressive gestures, and so forth (Andreasen, 2008). The Alogia category consists of whether an individual is demonstrating poverty of speech, thought blocking, or a long latency for responding in conversation. The Avolition-Apathy category is evaluated by assessing an individual's grooming, hygiene and physical anergia. The Anhedonia-Asociality category includes assessing an individual's interest and activity level, ability to feel close and intimate with others, and quality and frequency of relationships with friends and others. Lastly, the Attention category includes whether the individual is socially attentive, and attentive during the testing of their mental status (Andreasen, 2008). The SANS is clinician rated based on all information available, including observation and reports from the previous month, which may limit the measure's ability to detect rapid symptom changes (Hanson et al., 2010). Each subtest assesses specific behaviors, which are rated from 0 to 5 (0 = not present), and also has a Global Rating item evaluating categories of symptoms in general. In order to increase inter-

rater reliability, each SANS rater achieved a median ICC of 0.75 or higher across all items compared with the criterion ratings, and participated in a quality assurance program. The SANS was administered to participants every three months.

Overall, there are mixed findings in the literature regarding the interrater reliability of SANS, ranging from fair to very good (ICC = 0.60 – 0.84; Andreasen, 2008). The interrater reliability of the five domains covered in the SANS ranges from 0.86 – 0.93, with the interrater reliability of the Total Score being 0.92 (Andreasen, 2008). The interrater reliability of the individual items on the SANS ranges from 0.70 to 0.92 (Andreasen, 2008). Findings suggest that the SANS has moderate test-retest reliability, with the Total Score test-retest reliability being 0.45, and the test-retest of the different domains ranging from 0.13 – 0.40 (ICCs; Andreasen, 2008). The modest test-retest reliability for the SANS is likely due to the nature of how symptom severity typically fluctuates within schizophrenia (Andreasen, 2008). The SANS has high internal consistency (Cronbach α = Alogia, 0.63; Affective Flattening, 0.83; Avolition-Apathy, 0.74; Anhedonia-Asociality, 0.77; Attention, 0.75; Andreasen, 2008). Internal consistency is also high within the five domains of the SANS (Cronbach α = 0.86). Overall, given that the SANS is the gold-standard for assessing negative symptoms, is widely known and used, and has fair- to-good psychometric properties, it is appropriate for use for assessing negative symptoms in this study.

**Procedures**

The UCLA Aftercare Research Program recruits its participants from a variety of local Los Angeles psychiatric hospitals and clinics. Additionally, participants were obtained through referrals from the UCLA outpatient service at the Resnick Neuropsychiatric Hospital at UCLA. Previous level of medication adherence was not a consideration when recruiting participants. As

this program was the participant's primary source of mental health treatment, participant's typically attended the clinic at least one time per week. All participants consented to oral and written information about the research procedures involved in this study, and provided written consent. Most participants entered the study after a psychiatric hospitalization, and at the time of study entry diagnostic, demographic, psychiatric, social history, and functional capacity data were collected for each participant. This study was reviewed and approved by the UCLA Institutional Review board.

Data were collected in a variety of ways. Medication adherence was converted to a numerical value on a scale of 1 - 5, as previously mentioned, and utilized a number of sources of information to form a consensus rating of the level of adherence for every week of the follow-through. In addition to confidence and overall compliance ratings, information was collected and documented related to the participant's daily prescribed dose, number of milligrams consumed, changes in medication prescriptions, percentage of adherence, and reasons for missed doses.

As mentioned above, the BPRS was administered bi-weekly and the SANS was administered every three months.

**Data Analysis Plan**

Descriptive analyses will be completed on the demographics of the sample. The primary data analysis of medication adherence and negative symptom data will involve Pearson correlations and repeated measures analysis of variance (ANOVA), specifically Generalized Linear Mixed Models (GLMM). The analyses will have three phases. Phase I will utilize Pearson correlations to assess the strength of the relationship between medication adherence and negative symptoms. Then bivariate correlations will be completed with time lags to explore a potential temporal relationship between negative symptoms and medication nonadherence. Phase II will

consist of a GLMM to examine how the strength of the relationship between medication adherence and negative symptoms changes when controlling for multiple observations within subjects. A GLMM will then analyze the temporal relationship between medication adherence and negative symptoms using time lags (similar to the Pearson correlations) but while controlling for multiple observations within subjects. The last phase of data analysis (Phase III) consists of using a GLMM with a mediational term to explore the impact of a third variable (Reality Distortion) mediating the potential relationship between negative symptoms and medication adherence. The three phases will examine data comprised into one-month intervals. Specifically, intervals of time were used rather than specific time-points during the course of the 12-month study. This data analyses plan was selected to order to determine the optimal temporal gap to examine the relationship between medication nonadherence and negative symptoms.

**Phase I: Pearson Correlations**

The concept of Pearson correlations dates back to the 19th century, when Sir Francis Galton published an article in 1888 about the correlation; however, it adopted its name when Karl Pearson introduced the idea of correlation coefficients (Chen & Krauss, 2004). Pearson correlations, also referred to as Pearson product-moment correlations, refer to examining the strength of a linear relationship between two variables (Chen & Krauss, 2004). The correlation is given a numerical value, ranging from 0 to 1, called the correlation coefficient ($r$), and the larger the number, the stronger the relationship between the two variables (Chen & Krauss, 2004). For the purposes of this study, Pearson correlations will be used to assess the significance of correlations between medication adherence and negative symptoms. Whether the coefficient is positive or negative, relates to the direction of the relationship (either positive, negative, or null). A positive coefficient means that an increase in one variable, is associated with an increase in the

other variable (or decrease in one variable is associated with a decrease in the other; Chen & Krauss, 2004). A negative coefficient means that an increase in one variable is associated with a decrease in the other variable (or a decrease in one variable is associated with an increase in the other variable; Chen & Krauss, 2004). A null relationship between the two variables indicates that an increase in one variable is associated with both an increase and decrease in the other, and vice versa (Chen & Krauss, 2004).

Pearson correlations will be deemed significant should the p-value equal less than or equal to 0.05 ($p < 0.05$). The p-value represents the probability of obtaining a test statistic at least as extreme as the correlation co-efficient ($r$) that was obtained (in the same direction) when the null-hypothesis is assumed to be true (Gibbons, 2004). It is important to note that Pearson's correlation coefficients of greater magnitude and significance does not suggest causality between the two variables. For this study, Pearson correlations will initially be completed in Phase I to examine the strength of the overall relationship between negative symptoms and medication adherence. Then Pearson bivariate correlations will be completed with time lags to determine whether there is a temporal relationship between negative symptoms and medication adherence. For example, since data will be divided among one-month intervals, Pearson correlations will be completed to examine the strength of the relationship between medication adherence and subsequent negative symptoms one month later, two months later, and so on up to twelve months later. Reversely, Pearson correlations will be completed to examine the strength of the relationship between negative symptoms subsequent medication adherence one month later, two months later, etcetera, up to twelve months later. Bivariate correlations utilizing time lags will indicate the direction of a potential relationship between medication adherence and negative symptoms.

**Phase II: A Generalized Linear Mixed Model (GLMM)**

Analysis of variance (ANOVA) is a type of statistical analyses used to detect differences between two or more groups on an independent variable with repeated measures for subjects (Witte & Witte, 2004). The Generalized Linear Mixed Model (GLMM) is a generalized form of ANOVA that is useful for controlling for multiple observations per subjects. This form of analysis can easily accommodate missing data and is well suited for a longitudinal study such as this. In the current study, there are repeated measures of both negative symptoms and medication adherence over the course of twelve months (Witte & Witte, 2004). Repeated measures ANOVA is used when all participants comprising a sample are measured under multiple conditions (such as at multiple time points). As with ANOVA, the subject's ratings are compared to their own ratings, and therefore key estimates of variability are not inflated by variability due to differences between individuals (Witte & Witte, 2004).

The null hypothesis for GLMM is that the independent variable does not impact the dependent variable, and therefore the dependent variable will be similar despite differing values of the independent value. Whether or not the null hypothesis of an ANOVA is false depends on whether there is evidence of an effect of the independent variable. If the variability between groups (e.g., symptom ratings at different intervals of time) exceeds variability within groups (e.g., symptom ratings of different participants at the same interval of time) the null hypothesis can be rejected.

The null hypothesis for the GLMM is tested by means of an F test. An F test refers to the F ratio, which is the variability between groups divided by the variability within groups (Witte & Witte, 2004). Specifically, the numerator is the observed differences between all sample means and the denominator is the estimated error or combined variance estimate (Witte & Witte, 2004).

The F test assumes that if the null hypothesis is actually true, both the numerator and the denominator of the F ratio will be approximately the same. If the null hypothesis is false, the numerator will be larger than the denominator. Therefore, if an F value is approximately (or less than) one, there is no significant association between the independent and dependent variable (e.g., no treatment effect). The larger the F value, the smaller the level of significance between the independent and dependent variable. F values will be deemed significant should the p-value equal less than or equal to 0.05 ($p < 0.05$).

For this study, Phase II will consist of completing GLMM analyses as a means of examining the strength of association between medication adherence and negative symptoms while controlling for multiple observations within subjects.

**Phase III: Generalized Linear Mixed Model (GLMM) including a Mediational Term**

In order to solidify the causality of the bivariate correlation and mixed model GLMM, the null-hypothesis should be explored, which suggests that the relationship between the independent variable (*X*) and dependent variable (*Y*) is not causal but rather due to an unmeasured third variable, a mediator, *M* (Kenny, 1975). Without testing for mediating variables, variable X is considered the causal variable that causes the outcome (*Y*). The path from the independent variable to the dependent variable (*X* to *Y*) is called the total effect (*C*; see Figure 1). However, it is possible that there is third variable, or mediating variable (*M*) that is affecting *Y*, initially making the impact of *X* on *Y* appear stronger than it is in actuality.

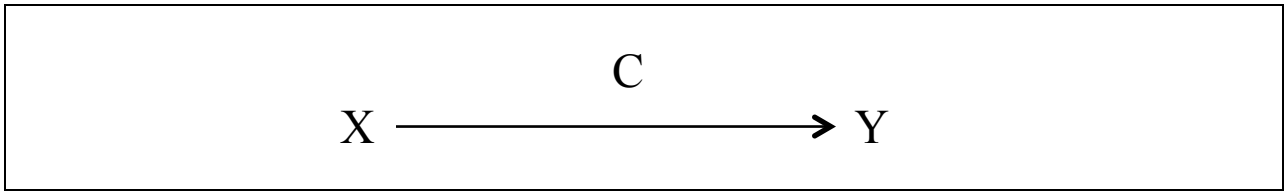


*Figure 1*. Description of a causal relationship between an independent (*X*) and dependent variable (*Y*).

For the current analyses, the mediation effect will be estimated through the inclusion of the mediating variable in the GLMM analyses and by estimating *c*' and comparing this parameter estimate with an estimate of *c*. In Subotnik et al. (2014), it was observed that the relationships between antipsychotic medication adherence on negative symptoms in this same sample was mediated by the effect of medication adherence on positive symptoms, which subsequently led to improvement in negative symptoms. This potential mediation process will be explored in the current sample, utilizing much short time periods for assessing both adherence and negative symptoms. Thus the GLMM will analyze whether *X* causes *Y*, or rather whether *M* is an intervening variable and thus *X* has a significant relationship to *M*, and *M* has a significant relationship with *Y* (see Figure 2; Kenny, 2014). Should the independent variable no longer affect the dependent variable once the mediator has been controlled for, then it is called complete mediation and the mediating variable is solely causing the significant relationship observed between the independent and dependent variables (in which case *c'* would be zero). If when controlling for *M* the direct effect (*c'*) is reduced in size (but not zero), i.e. *c'* < *c* then partial mediation is occurring.

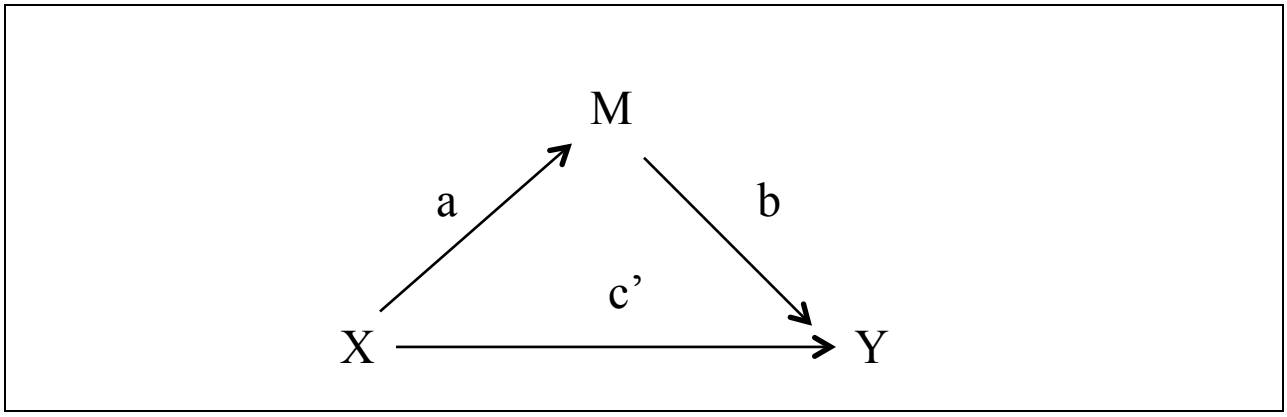


*Figure 2*. Demonstration of the role of mediating variables (*M*) in the impact of the independent variable (*X*) on the dependent variable (*Y*).

# Chapter 3: Results

As stated in Chapter 1, the study reported here examined the relationship between medication adherence and negative symptoms of schizophrenia in first episode psychosis. This chapter is organized in terms of the three phases of data analyses listed in Chapter 2. It reports the (a) characteristics of the study sample, (b) the relationship between negative symptoms and medication adherence using bivariate correlational methods that specifically examine different time lags between the measurements of adherence and symptoms, (c) a mixed model ANOVA (GLMM) approach that will examine the relationships between medication adherence and negative symptoms while controlling for multiple observations within subjects, and (d) a mixed model ANOVA (GLMM) approach that will examine the relationships between medication adherence and negative symptoms controlling for reality distortion, which is a likely third variable that could potentially mediate the main relationships.

## Characteristics of the Study Sample

The study sample consisted of a total of 148 participants: 65 Sample 3 participants, and 83 Sample 4 participants. All had been diagnosed with either schizophrenia, schizoaffective disorder, or schizophreniform, according to the DSM-IV (demographics provided in Table 1). To be included in the sample, the onset of their illness was within two years of study entry. The gender of the sample (combined Sample 3 and Sample 4) participants was as follows: 73% male ($n$ = 108) and 27% female ($n$ = 40; see Table 1). The mean age of the sample was 22.5 years, with a standard deviation of 4.0. In terms of race, 48% ($n$ = 71) of the sample participants described themselves as Caucasian; 25% ($n$ = 37) described themselves as African American; 11% ($n$ = 16) described themselves as Asian; 2% ($n$ = 3) described themselves as Pacific Islander; 3% ($n$ = 5) described themselves as American Indian/Alaskan; 11% ($n$ = 16) described

themselves as Biracial or Multiracial (Mixed). 42% of the sample ($n$ = 62) had a Hispanic ethnicity. The mean level of education was 12.8 years, with a standard deviation of 1.9. Additionally, in terms of marital status, 95% ($n$ = 141) of the sample was single, 4% ($n$ = 6) were married, and 1% ($n$ = 1) were separated. The average time since onset of first psychotic episode at the initial point of the study was 8.0 months, with a standard deviation of 8.6. Regarding diagnosis, 59% ($n$ = 87) were diagnosed with Schizophrenia, 14% ($n$ = 21) were diagnosed with Schizoaffective Disorder, and 27% ($n$ = 40) were diagnosed with Schizophreniform.

The 12 months of data analyzed for this study began once a participant was entered into the study protocol. The sample for this study was comprised of participants from two different protocols. Both protocols were part of an NIMH-funded project entitled, "Developmental Processes in Schizophrenic Disorders." One of the protocols (Sample 3) was for a study called "Improving and Predicting Work Outcome in Recent-Onset Schizophrenia" and was an 18-month study comparing two psychosocial interventions (either Individual Placement and Support and Workplace Fundamentals Module or a Brokered Vocational Rehabilitation). The other protocol (referred to as Sample 4) was for a study titled "Cognitive Remediation, Medication Adherence, and Work Outcome in Recent-Onset Schizophrenia" and was a 12-month study comparing long-acting injectable risperidone to oral risperidone. The 12-month period of data used for this study did not begin at the randomization baseline, rather it began once a participant started attending the Aftercare Program and the assessment of psychiatric symptoms and medication adherence commenced. Medication ratings, SANS and BPRS data gathered over the course of 12 months were analyzed for the purpose of this study. There was an attrition rate of approximately 24% over the course of the one-year study.

All adherence and symptom data were compiled into one-month intervals to facilitate alignment of the adherence and symptom data for 12 consecutive time periods during the follow through period. This approach also allowed for BPRS ratings, typically made every two weeks, and adherence ratings, typically made every one- to-two weeks, to be combined into somewhat longer one-month periods in order to provide greater stability of the ratings. All BPRS ratings periods less than two weeks and exceeding 13 weeks were excluded from analysis. Both long adherence and symptom intervals (rating periods that exceeded four weeks) were divided and included into the weighted means of multiple monthly means. BPRS ratings that crossed into more than one monthly interval were placed into the monthly interval that corresponded to the date of the rating. The same was done for medication adherence ratings.

Each variable for both medication adherence and symptom ratings were merged to create mean values for one-month intervals. Specifically, all of a participant's ratings for a particular variable were added together and a mean value was calculated to establish a single value for each variable to represent one month. Mean values for one-month intervals were calculated for each symptom variable and medication adherence ratings. However, the values were weighted based on the duration of the rating period. For example, if one rating period lasted 14 days, another 7 days, and another 7 days, the first rating would represent 50% of the monthly rating value, and the second and third ratings would both represent 25% of the total monthly rating. Intervals were determined based on four-week intervals following each individual's start date into the study. Some medication adherence rating periods covered multiple months of time. The average length of medication adherence rating periods was 20.0 days (SD = 16.6). The average time covered by the BPRS ratings was 17.9 days (SD = 6.1). To determine whether there were gaps in the period of time covered in both medication adherence and symptom ratings, the data set was arranged by

anchoring time periods to the end date of a rating period. The number of participants with more than 12 months of data was limited, so only the first 12 months of adherence data and symptom data were analyzed for each participant.

Table 1

*Sample Characteristics at Study Entry for Recent-Onset Schizophrenia Patients*

| | Sample 3 ($n$ = 65) | Sample 4 ($n$ = 83) | Combined ($n$ = 148) |
|---|---|---|---|
| Mean Age (SD) | 23.6 (4.0) | 21.6 (3.7) | 22.5 (4.0) |
| Mean Education (SD) | 13.3 (1.9) | 12.5 (1.8) | 12.8 (1.9) |
| Mean number of months since psychosis onset (SD) | 8.3 (9.8) | 7.8 (6.6) | 8.0 (8.2) |
| Gender | 69% Male | 76% Male | 73% Male |
| Marital Status | Single 94%<br>Married 3%<br>Separated 3% | Single 95%<br>Married 5%<br>Separated 0% | Single 95%<br>Married 4%<br>Separated 1% |
| Race | Caucasian 49%<br>Asian 12%<br>Pacific Islander 3%<br>Native American 0%<br>African-American 21%<br>Mixed 15% | Caucasian 48%<br>Asian 11%<br>Pacific Islander 1%<br>Native American 5%<br>African-American 28%<br>Mixed 7% | Caucasian 48%<br>Asian 11%<br>Pacific Islander 2%<br>Native American 3%<br>African-American 25%<br>Mixed 11% |
| Ethnicity | 43% Hispanic | 42% Hispanic | 42% Hispanic |
| Diagnosis | Schizophrenia 64%<br>Schizoaffective 15%<br>Schizophreniform 21% | Schizophrenia 55%<br>Schizoaffective 14%<br>Schizophreniform 31% | Schizophrenia 59%<br>Schizoaffective 14%<br>Schizophreniform 27% |

**Descriptive Analysis**

Descriptive analysis of the symptom ratings revealed that there was very little variance in the symptom levels. Table 2 provides descriptive summaries of the symptom ratings aggregated across all subjects and across all 12 rating periods. Thus, the relatively small standard deviations

represent both reduced variance between-subjects as well as within-subjects over the 12-month period of this study. BPRS Self-Neglect had the least amount of variance in ratings (SD = 0.70), while the most variance in symptom levels occurred with SANS Avolition-Apathy (SD = 1.58). Additionally, symptom levels were generally mild with negative symptom means ranging from 1.00 for SANS Alogia (as mentioned previously, on a scale of 0 – 5) to 2.35 for SANS Avolition-Apathy (also on a scale of 0 – 5). Additionally, as mentioned previously, the BPRS is rated on a scale of 1 (not present) to 7 (Extremely Severe).

Table 2

*Descriptive Analysis of Negative Symptom Levels*

| Negative Symptom | *N* | Minimum | Maximum | Mean | Standard Deviation |
|---|---|---|---|---|---|
| SANS Affective Flattening | 1722 | 0.00 | 5.00 | 1.39 | 1.28 |
| SANS Alogia | 1722 | 0.00 | 5.00 | 1.00 | 1.18 |
| SANS Avolition-Apathy | 1722 | 0.00 | 5.00 | 2.35 | 1.58 |
| SANS Anhedonia | 1722 | 0.00 | 5.00 | 1.85 | 1.39 |
| SANS Attention | 1721 | 0.00 | 5.00 | 1.07 | 1.33 |
| BPRS Motor Retardation | 1725 | 1.00 | 6.00 | 1.74 | 0.97 |
| BPRS Blunted Affect | 1726 | 1.00 | 6.00 | 2.28 | 1.25 |
| BPRS Self-Neglect | 1725 | 1.00 | 7.00 | 1.36 | 0.70 |
| BPRS Emotional Withdrawal | 1725 | 1.00 | 6.00 | 1.63 | 0.98 |

**Bivariate Correlations**

Analysis consisted of bivariate correlations to determine whether there was a significant relationship between negative symptoms and medication adherence. When analyzing 12-month averages of negative symptom and medication adherence ratings, analyses indicated that the presence of negative symptoms was significantly associated with medication nonadherence, suggesting that the more nonadherent an individual was with medication, the greater the presence of negative symptoms (see Table 3). Correlation coefficients ranged from .08 to .17, with the strongest association present between medication nonadherence and the BPRS Emotional

Withdrawal, and the weakest association present with the SANS Affective Flattening. When examining all SANS global items and BPRS negative symptom items, the only symptoms that were not significantly associated with medication nonadherence were SANS Attention ($r$ = .04) and BPRS Motor Retardation ($r$ = .01). Although included in the SANS, it should be noted that the Attention variable is often considered a cognitive symptom, as opposed to a negative symptom.

Table 3

*Pearson Correlations of Mean Values of Negative Symptoms and Mean Medication Nonadherence Levels*

| Negative Symptom Ratings | *N* | *r* | *p* |
|---|---|---|---|
| SANS Affective Flattening | 1223 | .08 | .007 |
| SANS Alogia | 1223 | .12 | .000 |
| SANS Avolition-Apathy | 1223 | .15 | .000 |
| SANS Anhedonia- Asociality | 1223 | .10 | .001 |
| SANS Attention | 1222 | .04 | .193 |
| BPRS Self-Neglect | 1226 | .13 | .000 |
| BPRS Blunted Affect | 1227 | .08 | .004 |
| BPRS Emotional Withdrawal | 1226 | .17 | .000 |
| BPRS Motor Retardation | 1227 | .01 | .817 |

Bivariate correlations were completed between negative symptoms and medication adherence at each time point (one-month intervals) across the course of 12 months to examine the possible temporal relationships of the negative symptoms and medication adherence. Specifically, negative symptoms were examined in relation to each data point for medication adherence (e.g., each monthly mean of ratings for negative symptoms were correlated with each monthly mean of ratings for medication adherence). Such analysis was to determine whether the presence of negative symptoms was more strongly associated with later medication nonadherence, or reversely, if medication nonadherence was more strongly associated with later negative symptoms. Generally, initial medication adherence was more strongly associated with

levels of negative symptoms in later months than concurrently rated levels of negative symptoms for both the SANS (see Table 4) and the BPRS (see Table 5).

**Initial nonadherence predicting later negative symptoms.** When examining SANS global items in relation to examining medication adherence over time, affective flattening, alogia, avolition-apathy, and anhedonia-asociality, all significantly were associated with predicting earlier medication nonadherence. In fact, the greater the lag time (e.g., the greater the time between the observations) the stronger the relationship between negative symptoms and prior medication adherence. Alogia and Avolition-Apathy most strongly predicted medication adherence 12 months prior (Alogia, $r = .23$; Avolition-Apathy, $r = .24$). Of the negative symptoms that significantly predicted previous medication nonadherence, Anhedonia-Asociality had the weakest association (1 – 12 months, $r = .10$ - $.19$).

Table 4

*Correlations of SANS Negative Symptoms with Previous Ratings of Medication Adherence*

| Adherence in the months prior to symptom ratings | Scale for the Assessment of Negative Symptoms (SANS) Symptom Ratings | | | | |
|---|---|---|---|---|---|
| | Affective Flattening | Alogia | Avolition-Apathy | Anhedonia-Asociality | Attention |
| 12 months prior N = 202 | $r = .20$ $p = .004$ | $r = .23$ $p = .001$ | $r = .24$ $p = .001$ | $r = .19$ $p = .008$ | $r = .09$ $p = .186$ |
| 11 months prior N = 289 | $r = .16$ $p = .007$ | $r = .24$ $p = .000$ | $r = .21$ $p = .000$ | $r = .15$ $p = .010$ | $r = .10$ $p = .088$ |
| 10 months prior N = 375 | $r = .16$ $p = .001$ | $r = .26$ $p = .000$ | $r = .22$ $p = .000$ | $r = .16$ $p = .002$ | $r = .06$ $p = .224$ |
| 9 months prior N = 460 | $r = .14$ $p = .004$ | $r = .24$ $p = .000$ | $r = .21$ $p = .000$ | $r = .12$ $p = .014$ | $r = .06$ $p = .239$ |
| 8 months prior N = 550 | $r = .15$ $p = .000$ | $r = .24$ $p = .000$ | $r = .19$ $p = .000$ | $r = .12$ $p = .003$ | $r = .04$ $p = .382$ |
| 7 months prior N = 639 | $r = .13$ $p = .001$ | $r = .21$ $p = .000$ | $r = .17$ $p = .000$ | $r = .13$ $p = .001$ | $r = .02$ $p = .542$ |
| 6 months prior N = 727 | $r = .11$ $p = .002$ | $r = .20$ $p = .000$ | $r = .16$ $p = .000$ | $r = .12$ $p = .001$ | $r = .03$ $p = .426$ |
| 5 months prior N = 818 | $r = .11$ $p = .002$ | $r = .18$ $p = .000$ | $r = .13$ $p = .000$ | $r = .10$ $p = .003$ | $r = .03$ $p = .356$ |

(continued)

| Adherence in the months prior to symptom ratings | Scale for the Assessment of Negative Symptoms (SANS) Symptom Ratings | | | | |
|---|---|---|---|---|---|
| | Affective Flattening | Alogia | Avolition-Apathy | Anhedonia-Asociality | Attention |
| 4 months prior N = 908 | *r* = .10 *p* = .002 | *r* = .19 *p* = .000 | *r* = .13 *p* = .000 | *r* = .11 *p* = .001 | *r* = .02 *p* = .603 |
| 3 months prior N = 999 | *r* = .08 *p* = .010 | *r* = .18 *p* = .000 | *r* = .14 *p* = .000 | *r* = .11 *p* = .001 | *r* = .04 *p* = .210 |
| 2 months prior N = 1097 | *r* = .09 *p* = .003 | *r* = .17 *p* = .000 | *r* = .16 *p* = .000 | *r* = .11 *p* = .000 | *r* = .04 *p* = .158 |
| 1 months prior N = 1190 | *r* = .09 *p* = .001 | *r* = .15 *p* = .000 | *r* = .18 *p* = .000 | *r* = .10 *p* = .001 | *r* = .03 *p* = .280 |

*Note.* Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

The general trend of initial medication nonadherence being strongly associated with later negative symptoms was also found when analyzing BPRS data. Specifically, the association between medication nonadherence and negative symptoms became stronger the greater the temporal distance. The strongest temporal relationship with medication nonadherence was the BPRS item Blunted Affect (1 – 12 months, *r* = .07 - .21). The weakest association was medication nonadherence and Self-Neglect, and it varied in significance over time. Specifically, the data suggests that initial medication nonadherence predicted BPRS Self-Neglect one, two, three, four, seven, and eight months later. There does not appear to be a clear explanation for this inconsistency in association. Overall, the strength of association between BPRS negative symptom variables and prior medication adherence ranged from *r* = .07 to *r* = .21.

Table 5

*Correlations of BPRS Negative Symptoms with Previous Ratings of Medication Adherence*

| Adherence in the months prior to symptom ratings | Brief Psychiatric Rating Scale (BPRS) Symptom Ratings | | | |
|---|---|---|---|---|
| | Self-Neglect | Blunted Affect | Emotional Withdrawal | Motor Retardation |
| 12 months prior N = 203 | *r* = .11 *p* = .116 | *r* = .21 *p* = .002 | *r* = .15 *p* = .030 | *r* = .13 *p* = .069 |
| 11 months prior N = 290 | *r* = .02 *p* = .684 | *r* = .19 *p* = .002 | *r* = .11 *p* = .056 | *r* = .08 *p* = .199 |

(continued)

| Adherence in the months prior to symptom ratings | Brief Psychiatric Rating Scale (BPRS) Symptom Ratings | | | |
|---|---|---|---|---|
| | Self-Neglect | Blunted Affect | Emotional Withdrawal | Motor Retardation |
| 10 months prior N = 376 | *r* = .08 *p* = .134 | *r* = .21 *p* = .000 | *r* = .14 *p* = .007 | *r* = .10 *p* = .049 |
| 9 months prior N = 462 | *r* = .08 *p* = .076 | *r* = .13 *p* = .005 | *r* = .16 *p* = .000 | *r* = .05 *p* = .330 |
| 8 months prior N = 552 | *r* = .08 *p* = .049 | *r* = .15 *p* = .000 | *r* = .16 *p* = .001 | *r* = .05 *p* = .256 |
| 7 months prior N = 641 | *r* = .11 *p* = .006 | *r* = .14 *p* = .000 | *r* = .18 *p* = .000 | *r* = .04 *p* = .364 |
| 6 months prior N = 729 | *r* = .05 *p* = .179 | *r* = .11 *p* = .002 | *r* = .16 *p* = .000 | *r* = .02 *p* = .510 |
| 5 months prior N = 820 | *r* = .04 *p* = .315 | *r* = .10 *p* = .004 | *r* = .16 *p* = .000 | *r* = -.00 *p* = .973 |
| 4 months prior N = 911 | *r* = .08 *p* = .021 | *r* = .09 *p* = .007 | *r* = .17 *p* = .000 | *r* = -.00 *p* = .906 |
| 3 months prior N = 1002 | *r* = .11 *p* = .000 | *r* = .07 *p* = .022 | *r* = .18 *p* = .000 | *r* = .01 *p* = .692 |
| 2 months prior N = 1100 | *r* = .12 *p* = .000 | *r* = .08 *p* = .010 | *r* = .18 *p* = .000 | *r* = .01 *p* = .759 |
| 1 months prior N = 1194 | *r* = .11 *p* = .000 | *r* = .09 *p* = .001 | *r* = .17 *p* = .000 | *r* = .01 *p* = .642 |

*Note.* Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

**Initial negative symptoms predicting later medication nonadherence.** Bivariate correlation data analysis also explored whether there was a general trend of association with the presence of negative symptoms predicting medication nonadherence at a later time. Overall, this data analysis indicated there was not a robust association between the presence of negative symptoms and medication nonadherence. Although SANS Apathy was suggested to precede medication nonadherence one, two, three, and four months later, the relationship was no longer significant when looking at temporal lags longer than four months. None of the other SANS variables were significantly related to medication adherence at a later date in time (see Table 6). BPRS Self-Neglect and BPRS Emotional Withdrawal were significant in each of the first four months and six months (respectively) preceding medication nonadherence (see Table 7). There was no directional relationship between medication nonadherence and BPRS Blunted Affect

over the course of one year. Although SANS Apathy was suggested to precede medication nonadherence one, two, three, and four months later, the relationship was no longer significant when looking at temporal lags longer than four months. None of the other SANS variables were significantly related to medication adherence at a later date in time (see Table 6).

Table 6

*Correlations of SANS Negative Symptoms with Subsequent Ratings of Medication Adherence*

| Adherence in the months after symptom ratings | Scale for the Assessment of Negative Symptoms (SANS) Symptom Ratings | | | | |
|---|---|---|---|---|---|
| | Affective Flattening | Alogia | Avolition-Apathy | Anhedonia-Asociality | Attention |
| 12 months later N = 71 | *r* = .07 *p* = .561 | *r* = -.05 *p* = .662 | *r* = .15 *p* = .199 | *r* = -.09 *p* = .461 | *r* = -.02 *p* = .862 |
| 11 months later N = 153 | *r* = -.05 *p* = .568 | *r* = -.09 *p* = .291 | *r* = .08 *p* = .301 | *r* = -.01 *p* = .880 | *r* = -.03 *p* = .705 |
| 10 months later N = 237 | *r* = -.04 *p* = .514 | *r* = -.07 *p* = .317 | *r* = .11 *p* = .106 | *r* = -.01 *p* = .838 | *r* = -.06 *p* = .375 |
| 9 months later N = 321 | *r* = -.09 *p* = .120 | *r* = -.09 *p* = .130 | *r* = .11 *p* = .048 | *r* = .02 *p* = .748 | *r* = -.08 *p* = .167 |
| 8 months later N = 407 | *r* = -.09 *p* = .065 | *r* = -.10 *p* = .036 | *r* = .09 *p* = .062 | *r* = -.00 *p* = .991 | *r* = -.06 *p* = .209 |
| 7 months later N = 494 | *r* = -.08 *p* = .062 | *r* = -.08 *p* = .077 | *r* = .07 *p* = .108 | *r* = -.02 *p* = .721 | *r* = -.08 *p* = .068 |
| 6 months later N = 586 | *r* = -.07 *p* = .095 | *r* = -.05 *p* = .237 | *r* = .06 *p* = .126 | *r* = -.02 *p* = .633 | *r* = -.07 *p* = .118 |
| 5 months later N = 685 | *r* = -.08 *p* = .048 | *r* = -.03 *p* = .439 | *r* = .07 *p* = .066 | *r* = .02 *p* = .566 | *r* = -.03 *p* = .382 |
| 4 months later N = 782 | *r* = -.07 *p* = .053 | *r* = -.02 *p* = .602 | *r* = .09 *p* = .012 | *r* = .07 *p* = .068 | *r* = -.03 *p* = .357 |
| 3 months later N = 881 | *r* = -.02 *p* = .635 | *r* = .02 *p* = .563 | *r* = .10 *p* = .004 | *r* = .06 *p* = .096 | *r* = -.02 *p* = .548 |
| 2 months later N = 987 | *r* = .02 *p* = .570 | *r* = .05 *p* = .156 | *r* = .09 *p* = .005 | *r* = .06 *p* = .053 | *r* = .01 *p* = .845 |
| 1 month later N = 1102 | *r* = .05 *p* = .094 | *r* = .09 *p* = .002 | *r* = .12 *p* = .000 | *r* = .08 *p* = .009 | *r* = .04 *p* = .227 |

*Note.* Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

Table 7

*Correlations of BPRS Negative Symptoms with Subsequent Ratings of Medication Adherence*

| Adherence in the months after symptom ratings | Brief Psychiatric Rating Scale (BPRS) Symptom Ratings | | | |
|---|---|---|---|---|
| | Self-Neglect | Blunted Affect | Emotional Withdrawal | Motor Retardation |
| 12 months later N = 71 | *r* = -.02 *p* = .847 | *r* = .02 *p* = .866 | *r* = -.01 *p* = .916 | *r* = -.02 *p* = .899 |
| 11 months later N = 154 | *r* = -.00 *p* = .975 | *r* = -.04 *p* = .667 | *r* = .01 *p* = .916 | *r* = -.04 *p* = .624 |
| 10 months later N = 238 | *r* = .00 *p* = .961 | *r* = -.07 *p* = .263 | *r* = .06 *p* = .328 | *r* = -.05 *p* = .471 |
| 9 months later N = 322 | *r* = -.00 *p* = .955 | *r* = -.08 *p* = .159 | *r* = .03 *p* = .575 | *r* = -.04 *p* = .453 |
| 8 months later N = 408 | *r* = -.03 *p* = .510 | *r* = -.09 *p* = .065 | *r* = .03 *p* = .537 | *r* = -.07 *p* = .169 |
| 7 months later N = 496 | *r* = -.02 *p* = .613 | *r* = -.08 *p* = .069 | *r* = .08 *p* = .079 | *r* = -.09 *p* = .050 |
| 6 months later N = 588 | *r* = .03 *p* = .466 | *r* = -.06 *p* = .166 | *r* = .12 *p* = .004 | *r* = -.07 *p* = .076 |
| 5 months later N = 687 | *r* = .04 *p* = .283 | *r* = -.07 *p* = .073 | *r* = .12 *p* = .002 | *r* = -.08 *p* = .036 |
| 4 months later N = 784 | *r* = .12 *p* = .001 | *r* = -.07 *p* = .042 | *r* = .12 *p* = .001 | *r* = -.07 *p* = .050 |
| 3 months later N = 884 | *r* = .09 *p* = .005 | *r* = -.03 *p* = .437 | *r* = .13 *p* = .000 | *r* = -.03 *p* = .338 |
| 2 months later N = 990 | *r* = .07 *p* = .021 | *r* = .02 *p* = .633 | *r* = .13 *p* = .000 | *r* = -.02 *p* = .547 |
| 1 month later N = 1105 | *r* = .11 *p* = .000 | *r* = .05 *p* = .108 | *r* = .17 *p* = .000 | *r* = -.01 *p* = .772 |

*Note.* Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

**Generalized Linear Mixed Model (GLMM)**

GLMM was completed as a mixed model to analyze the amount of correspondence between adherence and negative symptoms, while controlling for repeated observations within-subjects (see Table 8). Therefore differences between related means of negative symptoms over the course of 12 months (and therefore 12 data points) in relation to medication adherence were analyzed. The negative symptoms that were significantly associated with medication adherence (as the independent variable) were the BPRS Negative Symptom Factor, $F(1,1214) = 5.1$, $p =$

.024; BPRS Blunted Affect F(1,1205) = 4.6, $p$ = .032; BPRS Emotional Withdrawal F(1, 1223) = 8.9, $p$ = .003; BPRS Self-Neglect F(1, 1222) = 14.7, $p$ = .000; SANS Alogia F(1, 1218) = 4.4, $p$ = .035; SANS Affective Flattening F(1, 1201) = 4.1, $p$ = .044; and SANS Attention F(1, 1217) = 4.5, $p$ = .035.

However, BPRS Motor Retardation, F(1, 1224) = 0.0, $p$ = .847; SANS Avolition-Apathy, F(1, 1214) = 1.0, $p$ = .313; and SANS Anhedonia-Asociality, F(1, 1202) = 1.4, $p$ = .231; over the 12 time intervals were not associated with levels of medication adherence over the 12 rating periods.

Table 8

*GLMM with Medication Adherence as the Independent Variable*

| Symptom Variable | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance ($p$) |
|---|---|---|---|---|---|
| BPRS | | | | | |
| Negative Symptom Factor* | .051 | .023 | (1, 1214) | 5.1 | .024 |
| Blunted Affect | .066 | .031 | (1,1205) | 4.6 | .032 |
| Emotional Withdrawal | .085 | .029 | (1,1223) | 8.9 | .003 |
| Motor Retardation | .005 | .027 | (1,1224) | 0.0 | .847 |
| Self-Neglect | .080 | .021 | (1,1222) | 14.7 | .000 |
| SANS | | | | | |
| Affective Flattening | .063 | .031 | (1,1201) | 4.1 | .044 |
| Alogia | .064 | .031 | (1,1218) | 4.4 | .035 |
| Avolition-Apathy | .039 | .039 | (1,1214) | 1.0 | .313 |
| Anhedonia | .038 | .032 | (1,1202) | 1.4 | .231 |
| Attention | .074 | .035 | (1,1217) | 4.5 | .035 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$
*Mean of BPRS Withdrawal and Motor Retardation variables

**Initial nonadherence predicting later negative symptoms.** Similar to the bivariate correlations, repeated measures Analysis of Variance was conducted in a mixed model (GLMM) approach in order to examine the temporal relationship between medication adherence and

negative symptoms. Specifically, analyses were conducted to examine whether there was a significant association with medication adherence in the months preceding negative symptoms (see Table 9; see Appendices E - X).

Table 9

*GLMM of Initial Medication Nonadherence Predicting Later Negative Symptoms*

| | Medication adherence months prior (F values) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Symptom | 12 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 |
| SANS | | | | | | | | | | | | |
| Affective Flattening | 6.7 | | | | | | | | 4.7 | | 3.4 | 5.6 |
| Alogia | 7.3 | 5.1 | | | | | | | 6.9 | 5.3 | 12.0 | 11.0 |
| Avolition-Apathy | 11.8 | | 6.7 | 6.8 | | | | | | | | 5.9 |
| Anhedonia-Asociality | 9.1 | | | | | | | | | | 3.9 | 6.2 |
| Attention | | | | | | | | | | 4.2 | 8.2 | 5.0 |
| BPRS | | | | | | | | | | | | |
| Negative Symptom Factor | 12.1 | | | | | | | | | | | 4.5 |
| Self-Neglect | 6.7 | | | 5.1 | | | | | | 10.4 | 11.7 | |
| Blunted Affect | 5.7 | | 4.6 | | | | | | | | | 4.4 |
| Emotional Withdrawal | 5.4 | | | | | 6.1 | | | | | 5.7 | 6.3 |
| Motor Retardation | 8.9 | | | | | | | | | | | |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

The data suggests that initial medication nonadherence was significantly associated with SANS Affective Flattening ratings one month, $F(1,1168) = 5.6$, $p = .018$; two months, $F(1,1073) = 3.4$, $p = .068$; four months, $F(1,878) = 4.7$, $p = .031$; and twelve months, $F(1,159) = 6.7$, $p = .011$ later (see Appendix E). There was a similar pattern when examining the relationship between initial medication nonadherence preceding later SANS Alogia ratings in that there was a significant association when medication nonadherence preceded negative symptoms by only a few months and then again with much longer gaps in time (see Appendix F). For example, SANS Alogia was significantly associated with medication adherence one month, $F(1,1183) = 11.0$, $p =$

.001; two months, F(1,1086) = 12.0, $p$ = .001; three months, F(1,985) = 5.3, $p$ = .022; and four months prior, F(1,893) = 6.9, $p$ = .009. Then medication adherence was significantly associated with SANS Alogia again when medication adherence preceded it by eleven months, F(1,253) = 5.1, $p$ = .024; and twelve months, F(1,141) = 7.3, $p$ = .008. SANS Avolition-Apathy was significantly associated with medication nonadherence one month, F(1,1178) = 5.9, $p$ = .015; nine months, F(1,427) = 6.8, $p$ = .010; ten months, F(1,341) = 6.7, $p$ = .010; and twelve months, F(1,157) = 11.8, $p$ = .001 prior (see Appendix G). In similar fashion, medication nonadherence was significantly associated with SANS Anhedonia-Asociality one, F(1,1162) = 6.2, $p$ = .013 and two, F(1,1067) = 3.9, $p$ = .047 months later, and then again twelve months later, F(1,180) = 9.1, $p$ = .003 (see Appendix H). Lastly, initial medication nonadherence was significantly associated with SANS Attention ratings one, F(1,1181) = 5.0, $p$ = .026; two, F(1,1088) = 8.2, $p$ = .004; and three, F(1,990) = 4.2, $p$ = .041 months later (see Appendix I).

Regarding the GLMM exploring the temporal relationship between medication adherence and BPRS ratings, some symptom variables demonstrated the same pattern observed with the SANS, in which initial medication nonadherence preceding negative symptoms was strongly associated with shorter lags of time (e.g., one, two, or three months) and then again with very long lags of time (e.g., twelve months). For example, medication nonadherence was significantly associated with BPRS Negative Symptom Factor one month, F(1,1182) = 4.5, $p$ = .033 and twelve months later, F(1,164) = 12.1, $p$ = .001 (see Appendix J). BPRS Self-Neglect was significantly associated with medication nonadherence in the preceding two, F(1,1097) = 11.7, $p$ = .001; three, F(1,998) = 10.4, $p$ = .001; nine, F(1,450) = 5.1, $p$ = .025; and twelve, F(1,201) = 6.7, $p$ = .011 months (see Appendix K). Medication nonadherence was significantly associated with BPRS Blunted Affect one month, F(1,1172) = 4.4, $p$ = .037; ten months, F(1,356) = 4.6, $p$ =

.033; and twelve months, F(1,152) = 5.7, *p* = .018 later (see Appendix L). Similar to other negative symptoms, BPRS Emotional Withdrawal was significantly associated with preceding initial medication nonadherence with a short time lag then also a long lag of time. Specifically, medication nonadherence was significantly associated with BPRS Emotional Withdrawal one month, F(1,1191) = 6.3, *p* = .013; two months, F(1,1097) = 5.7, *p* = .017; and twelve months, F(1,199) = 5.4, *p* = .021 later (see Appendix M). However, BPRS Emotional Withdrawal was also significantly associated with medication nonadherence seven months prior, F(1,635) = 6.1, *p* = .014. Notably, BPRS Motor Retardation was only significantly associated with prior medication nonadherence when it was twelve months prior, F(1,182) = 8.9, *p* = .003 (see Appendix N).

**Initial negative symptoms predicting later medication nonadherence.** Generalized linear mixed models were also conducted to examine the temporal relationship between negative symptoms and subsequent medication nonadherence (see Table 10). SANS Affective Flattening (see Appendix O) was only significantly associated with subsequent medication nonadherence when preceding medication nonadherence by four, F(1,779) = 5.9, *p* = .015; and five months F(1,681) = 6.0, *p* = .015. SANS Attention and SANS Alogia were only significantly associated with later medication nonadherence when preceding nonadherence by one month, F(1,1092) = 4.5, *p* = .034; and eight months, F(1,404) = 7.6, *p* = .006; respectively (see Appendices P and Q). There were no significant associations between negative symptoms and medication adherence when examining medication adherence in the months following SANS Avolition-Apathy (see Appendix R) and SANS Anhedonia-Asociality (see Appendix S).

Table 10

*GLMM of Initial Negative Symptoms Predicting Later Medication Nonadherence*

| | Medication adherence months later (F values) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Symptom | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| SANS | | | | | | | | | | | | |
| Affective Flattening | | | | 5.9 | 6.0 | | | | | | | |
| Alogia | | | | | | | | | 7.6 | | | |
| Avolition-Apathy | | | | | | | | | | | | |
| Anhedonia-Asociality | | | | | | | | | | | | |
| Attention | 4.5 | | | | | | | | | | | |
| BPRS | | | | | | | | | | | | |
| Negative Symptom Factor | | | | | | | | | | | | |
| Self-Neglect | | | | 13.8 | | | 8.0 | | | | | |
| Blunted Affect | | | | 9.0 | 5.9 | | | | | | | |
| Emotional Withdrawal | 9.2 | | | | | 4.1 | | | | | | |
| Motor Retardation | | | | 3.9 | 7.1 | | | | | | | |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

The BPRS Negative Symptom Factor was the only BPRS symptom variable that was not significantly associated with later medication nonadherence at any time interval (see Appendix T). Additionally, although there were significant associations at one or two time points, there was no notable pattern of significant associations of BPRS negative symptoms preceding later medication nonadherence. BPRS Self-Neglect was significantly associated with medication nonadherence four months, $F(1,770) = 13.8$, $p = .000$; and seven months, $F(1,476) = 8.0$, $p = .005$ later (see Appendix U). Medication nonadherence was significantly associated with BPRS Blunted Affect four months, $F(1,781) = 9.0$, $p = .003$; and five months, $F(1,684) = 5.9$, $p = .016$ earlier (see Appendix V). There were also significant associations with BPRS Emotional Withdrawal and medication nonadherence one month later, $F(1,1073) = 9.2$, $p = .003$; and also six months later, $F(1,528) = 4.1$, $p = .042$ (see Appendix W). BPRS Motor Retardation was only significantly associated with later medication nonadherence when it preceded medication

nonadherence by four months, $F(1,769) = 3.9$, $p = .050$; and five months, $F(1,675) = 7.1$, $p = .008$ (see Appendix X).

**GLMM with Test of Mediation**

A GLMM was conducted in order to examine the relationships between medication adherence and negative symptoms while controlling for reality distortion (see Table 11). Reality distortion was controlled because it was suspected to be a third variable that may mediate the significant relationship between negative symptoms and medication adherence. The Reality Distortion variable was comprised of the means of the BPRS variables Hallucinations and Unusual Thought Content. By controlling the variation caused by Reality Distortion, it increased the likelihood of observing the actual relationship between medication adherence and negative symptoms. The negative symptoms that were significantly associated with medication adherence (as the independent variable) were the BPRS Negative Symptom Factor, $F(1,1214) = 5.1$, $p = .024$; BPRS Blunted Affect, $F(1,1205) = 4.6$, $p = .032$; BPRS Emotional Withdrawal, $F(1,1223) = 8.9$, $p = .003$; SANS Affective Flattening, $F(1,1201) = 4.1$, $p = .044$; and SANS Alogia, $F(1,1218) = 4.4$, $p = .035$. BPRS Motor Retardation, SANS Avolition-Apathy, and SANS Anhedonia over the 12 time intervals were not associated with levels of medication adherence over the 12 rating periods. However, when the BPRS Reality Distortion was controlled for as a covariate, the amount of correspondence between adherence and negative symptoms significantly lessened. When controlling for Reality Distortion, the only variables in which the significant associations with medication adherence remained were the BPRS Negative Symptom Factor, $F(1,1213) = 4.1$, $p = .024$; BPRS Emotional Withdrawal, $F(1,1223) = 7.6$, $p = .006$; and BPRS Self-Neglect, $F(1,1222) = 10.6$, $p = .001$. BPRS Blunted Affect, SANS Affective Flattening, SANS Alogia and SANS Attention were no longer significantly associated with

medication adherence when Reality Distortion was controlled. Overall, once Reality Distortion was controlled for as a mediating variable, the significant association between negative symptoms and medication adherence weakened, indicating that Reality Distortion is in fact a variable mediating the relationship between the two variables.

Table 11

*GLMM with Medication Adherence as the Independent Variable Controlling for Reality Distortion*

| Dependent Variable | | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (p) |
|---|---|---|---|---|---|---|
| BPRS | | | | | | |
| Negative Symptom Factor* | *c*** | .051 | .023 | (1,1214) | 5.1 | .024 |
| | *c'**** | .046 | .023 | (1,1213) | 4.1 | .042 |
| Blunted Affect | *c* | .066 | .031 | (1,1205) | 4.6 | .032 |
| | *c'* | .059 | .031 | (1,1204) | 3.7 | .053 |
| Emotional Withdrawal | *c* | .085 | .029 | (1,1223) | 8.9 | .003 |
| | *c'* | .079 | .029 | (1,1223) | 7.6 | .006 |
| Motor Retardation | *c* | .005 | .027 | (1,1224) | 0.0 | .847 |
| | *c'* | .002 | .027 | (1,1222) | 0.0 | .953 |
| Self-Neglect | *c* | .080 | .021 | (1,1222) | 14.7 | .000 |
| | *c'* | .067 | .021 | (1,1222) | 10.6 | .001 |
| *SANS* | | | | | | |
| Affective Flattening | *c* | .063 | .031 | (1,1201) | 4.1 | .044 |
| | *c'* | .051 | .031 | (1,1202) | 2.7 | .098 |
| Alogia | *c* | .064 | .031 | (1,1218) | 4.4 | .035 |
| | *c'* | .059 | .031 | (1,1217) | 3.7 | .056 |
| Avolition-Apathy | *c* | .039 | .039 | (1,1214) | 1.0 | .313 |
| | *c'* | .024 | .039 | (1,1218) | 0.4 | .534 |
| Anhedonia | *c* | .038 | .032 | (1,1202) | 1.4 | .231 |
| | *c'* | .026 | .031 | (1,1206) | 0.7 | .409 |
| Attention | *c* | .074 | .035 | (1,1217) | 4.5 | .035 |
| | *c'* | .064 | .035 | (1,1216) | 3.3 | .069 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$
* Mean of BPRS Withdrawal and Motor Retardation variables
** Without covariate
*** Controlling for covariate of Reality Distortion

## Chapter 4: Discussion

This chapter presents a summary of this study, including a summary of the results presented in Chapter 3. A discussion of the implications of this study, this study's limitations, and potential directions for future research will be provided.

This study explored the relationship between the negative symptoms and medication nonadherence in individuals who (at the onset of the study) were within two years of their first psychotic episode. It is important to learn more about this relationship because research suggests that the severity of negative symptoms is a main factor impacting the outcome of treatment for schizophrenia (Brier & Berg, 1999; Ventura et al., 2009). The presence of negative symptoms in schizophrenia is associated with poor prognosis and functional outcome because they impair motivation and interests (Makinen et al., 2008; Ventura et al., 2009; Woo & Keatinge, 2008). Further, negative symptoms tend to be stable and enduring throughout the course of the illness in part because they are resistant to medication and psychosocial interventions (Hanson et al., 2010; Rollins et al, 2010). The evidence for whether negative symptoms are responsive to medication adherence is mixed, and this author is only aware of five studies prior to this study that have explored a potential relationship between negative symptoms and medication nonadherence (Erhart et al., 2006).

The sample for this study was comprised of individuals who upon study entry were in the midst of their first psychotic episode. Over the course of 12 months, symptom ratings were established from SANS and BPRS ratings and medication adherences ratings were created based on pill counts, plasma concentrations of risperidone and 9-hydroxyrisperidone, self-report of nonadherence to a treatment team member, clinician assessment and Medication Event Monitoring System (for Sample 4, only). Ratings were consolidated into one-month means for

data analysis and analysis consisted of bivariate correlations to examine the relationship between negative symptoms and medication adherence. Data analysis also consisted of generalized linear mixed models.

In the sample used for this study, bivariate correlations revealed a significant relationship between higher levels of negative symptoms and higher levels of medication nonadherence. Specifically, greater nonadherence to the second-generation oral antipsychotic medication risperidone was associated with higher levels of affective flattening (and blunted affect), alogia, avolition-apathy, anhedonia-asociality, self-neglect, and emotional withdrawal, in bivariate correlations. Of the negative symptoms examined, the BPRS variable Emotional Withdrawal had the strongest association with medication nonadherence and SANS Affective Flattening had the weakest association. BPRS Motor Retardation and SANS Attention were the only variables not significantly correlated with medication nonadherence. It is possible that the lack of significance between medication nonadherence and SANS Attention may relate to the common view that this variable is more of a cognitive symptom than a negative symptom.

The results of bivariate correlations also indicate that there appears to be a temporal relationship between negative symptoms and medication nonadherence. Specifically, medication nonadherence predicted the presence of negative symptoms at a later time. There was not a significant pattern of association when exploring the temporal relationship of negative symptoms preceding medication nonadherence. Interestingly, bivariate correlations revealed that the more time that passed after medication nonadherence, the stronger the relationship between negative symptoms and earlier medication nonadherence. Medication nonadherence most strongly preceded later increases in SANS Alogia, SANS Avolition-Apathy, and BPRS Affective

Flattening. The weakest association between medication nonadherence and later negative symptom levels was between SANS Anhedonia-Asociality and BPRS Self-Neglect.

GLMM analysis examined the relationship between medication adherence and negative symptoms while controlling for repeated observations within subjects. Similar to the bivariate correlations, the mixed model analyses revealed that overall there was a significant relationship between negative symptoms and medication nonadherence. Also similar to the bivariate correlations, GLMM analysis was completed to explore the temporal relationship of negative symptoms and medication adherence with time lags. However, unlike the bivariate correlations examining time lags, much of the significant association disappeared when time lags were explored with GLMM, which controlled for the repeated observations within subjects. There may have been a few subjects for whom the temporal lag pattern was most apparent, and consequently, it is possible that once repeated observations within subjects was controlled much of the significant association disappeared.

Although much of the temporal relationship with medication nonadherence preceding negative symptoms dissipated once repeated observations within subjects was controlled, there was still an observable temporal pattern in which initial medication nonadherence was significantly associated with an increase in negative symptoms in short intervals of time (e.g., approximately one – three months later) and then again with much longer lags of time (e.g., eleven or twelve months later). This pattern of temporal relationships was evident with SANS Affective Flattening, SANS Alogia, SANS Avolition-Apathy, SANS Anhedonia-Asociality, BPRS Negative Symptom Factor, BPRS Self-Neglect, and BPRS Blunted Affect. SANS Attention, BPRS Emotional Withdrawal, and BPRS Motor Retardation were also significantly associated with preceding medication nonadherence, although the pattern of association with

shorter and then much longer intervals was not present, it was either one or the other, or both short and long time lags in addition to other intervals of significant associations.

However, there was also very little variation in symptom ratings and medication nonadherence ratings over the 12 month rating period. There may have been little variation in symptom ratings since negative symptoms are typically stable over the course of the illness and are also are minimally responsive to antipsychotic medication (Subotnik, Nuechterlein, Ventura, Green, & Hwang, 1998). The level of negative symptoms was also mild in this sample. Regarding the low levels of medication nonadherence, it is possible that this is because some of the factors related to medication nonadherence previously discussed were controlled or decreased in this study. For example, cost of care and ease of access to health care providers were controlled by providing free services and also providing transportation to and from the UCLA Aftercare Clinic for individuals in this study. The impact of substance use also was reduced in this study because of the exclusion criterion for significant substance abuse. It is possible that high levels of stability in medication adherence and symptoms over the 12 time intervals limited possible relationships between adherence and changes in these symptoms.

One possible explanation for the temporal relationship of early medication nonadherence and later levels in negative symptoms is that there could be a third variable mediating the relationship between the two. This is a consideration given that there is little evidence that antipsychotic medications improve negative symptoms so it is curious as to why medication nonadherence in this study led to an increase in negative symptoms at a later time. Therefore it is possible that this significant association does not mean that medication is treating negative symptoms per se but rather that the negative symptoms are improving secondary to the improvement in positive symptoms. For example, a period of nonadherence to antipsychotic

medication might lead to an increase in positive symptoms such as hallucinations or delusions, which consequently also leads to higher levels of negative symptoms. This is consistent with the findings of Subotnik et al. (2014) indicating that when positive symptoms were controlled for, there was no longer a significant relationship between medication adherence and negative symptoms. This is also supported by this study's GLMM analyses in which the significant association between negative symptoms and medication adherence was greatly reduced once the impact of reality distortion was controlled. The only symptoms in which the significant association remained once reality distortion was controlled were the BPRS Negative Symptom Factor, BPRS Emotional Withdrawal, and BPRS Self-Neglect.

The finding that the strong association between negative symptoms and medication nonadherence greatly dissipates once the impact of reality distortion is controlled suggests that positive and negative symptoms of psychosis are strongly related, and not independent of one another. Further, the relationship between positive and negative symptoms in this study was stronger than the relationship between negative symptoms and medication adherence. This supports Ventura et al.'s 2003 findings that negative symptom exacerbations occurred simultaneously with positive symptom exacerbations to an extent significantly greater than chance, suggesting that positive and negative symptom exacerbations are linked to one another.

It is possible that negative symptoms are a response to positive symptoms, such as hallucinations and delusions. For example, a person may socially withdraw (asociality) or minimize their speech (alogia) due to paranoia or auditory hallucinations. Or, an individual may be preoccupied with internal stimuli (e.g., hearing voices) and consequently no longer have interest in activities (anhedonia) or motivation to complete tasks (avolition). If an individual with intense auditory hallucinations shuts down by not being willing to make eye contact or converse

with others, it likely would be interpreted as negative symptoms. This aligns with recent diagnostic changes from the *Diagnostic Statistical Manual, 4th Edition, TR* to the *Diagnostic Statistical Manual, 5th Edition*. Specifically, subtypes (e.g., Catatonic, Paranoid, etc.) were removed from the Schizophrenia diagnosis. The American Psychiatric Association reportedly made this change for a few reasons, one of which was to create a dimensional approach to rating severity for the core symptoms of schizophrenia in order to capture heterogeneity in symptom type, and severity expressed across individuals with psychotic disorders (APA, 2013). This change appears to reflect the findings of this dissertation study, that positive and negative symptoms are not orthogonal but rather related to one another.

It is possible that the strong relationship between negative and positive symptoms relates to electrodermal activity (EDA). Prior research has demonstrated that heightened autonomic responsivity is associated with negative symptoms (Subotnik et al., 2012). Specifically, it appears that behaviors similar to negative symptoms (e.g., emotional restriction and social withdrawal) may be an attempt to reduce the body's autonomic over-responsiveness that occurs as a response to environmental stress such as expressed emotion (Schell et al., 2005; Subotnik et al., 2012). For example, the relationship between negative symptoms and electrodermal activity may relate to individuals withdrawing from social interactions and attempting to suppress visible reactions and cope with overstimulating environments (Schell et al., 2005). Therefore, high expressed emotion predicts both positive and negative symptoms, and both positive and negative symptoms are concurrently associated with electrodermal activity. However, if the negative symptoms which are associated with increased electrodermal activity are a result of environmental stress, they would be secondary rather than primary negative symptoms (Schell et al., 2005).

Although this dissertation study suggested that positive symptoms are a mediating variable in the relationship between medication nonadherence and negative symptoms, even when controlling for reality distortion, there was still a significant relationship between the two variables. This suggests that positive symptoms only partially mediate the relationship between medication adherence and negative symptoms. It is possible that while both positive and negative symptoms relate to electrodermal activity, negative symptoms are significantly associated with electrodermal activity independent of positive symptoms. Elecrodermal activity and responsivity are indicators of sympathetic nervous system (SNS) functioning (Dawson et al., 2010; Subotnik et al., 2012). As mentioned, heightened EDA levels, as opposed to reduced EDA levels, are present in a subset of schizophrenia patients who have prominent negative symptoms. Electrodermal activity has also been shown to be heightened in the weeks preceding a psychotic relapse or exacerbation, supporting the idea that electrodermal activity changes in anticipation of symptomatic changes (Dawson & Schell, 2002). EDA is a physiological indicator of stress since it is controlled by the sympathetic nervous system and consequently, when individuals experience psychosocial/environmental stressors, their EDA increases, which then appears to contribute to the return of symptoms (Dawson & Schell, 2002; Dawson et al., 2010). One possibility for the present study's findings that medication nonadherence leads to greater negative symptoms is that second-generation antipsychotic medication controls electrodermal activity. Consequently, once someone is less adherent to psychotropic medication, electrodermal activity might increase, leading to a compensatory increase in negative symptoms. This compensatory increase is an attempt to regulate the electrodermal activity and the subsequent brewing incipient psychosis by withdrawing from environmental stimulation. Thus, antipsychotic medications may allow individuals to tolerate their environment better, thereby

lessening the effects of environmental stressors such as high expressed emotion within families. This is supported by Subotnik et al's 2012 finding that the highest levels of negative symptoms were observed in individuals who exhibited greater electrodermal activity and also lived in high expressed emotion environments. Specifically, negative symptoms were predicted by the interaction of high expressed emotion and EDA. Such a finding is also understandable given the well-replicated findings that high expressed emotion environments predict psychotic relapse (Subotnik et al., 2012).

As mentioned in Chapter 1, the research exploring a possible relationship between negative symptoms and medication nonadherence is mixed and limited. To this author's knowledge, there have only been five studies exploring this relationship prior to this dissertation. Additionally, while Subotnik et al. (2014) also explored whether there is a potential temporal relationship between medication nonadherence and negative symptoms, it appears that the present study is the first to examine this question with fine-grained temporal analyses (specifically, one month intervals instead of Subotnik et al.'s [2014] three month intervals). Also different from Subotnik et al.'s 2014 study was the method of data analysis and the symptom measures used. Subotnik et al. utilized cross-lag panel analyses and the Sobel Test to determine causality between medication nonadherence and negative symptoms whereas this study utilized GLIMM. This study also utilized the BPRS in addition to the SANS, and was able to compare similarities and differences by using both instruments, while Subotnik et al. (2014) measured symptoms with the SANS and SAPS. Therefore, by using different data analyses and symptom measures, this dissertation study was able to see if Subotnik et al.'s findings could be replicated with new measures and with a more detailed analysis of the temporal relationship (as mentioned due to the smaller time intervals).

Tattan and Creed's 2001 study exploring this relationship also used the SANS. Consistent with the findings of this study, Tattan and Creed found that individuals with lower adherence to medication had significantly higher SANS Avolition, Apathy, and Alogia scores. Of interest, Tattan and Creed's findings are consistent with the present study's findings even though the samples were at different stages in the course of their illness. Specifically, this study focused on individuals who were early in the course of their psychosis (within two years of their first psychotic episode) whereas the duration of illness in Tattan and Creed's sample ranged from 9 – 22 years. This suggests that the finding that there is a significant relationship between medication adherence and negative symptoms may generalize to the entire course of illness, and not just shortly after a first episode of psychosis.

Kao and Liu (2010) used the PANSS instead of the SANS or BPRS to assess a relationship between symptoms and medication nonadherence, yet they also found a significant relationship between the negative symptoms and medication nonadherence. Since they used different measures, it is unclear if there were similar findings regarding which negative symptoms were more significantly associated with medication nonadherence.

Similar to the present study, Steger et al. (2012) explored the relationship between negative symptoms and medication adherence using the SANS with the first episode psychosis population. Consistent with the present study, Steger et al. found greater alogia and affective flattening in medication nonadherent individuals. They also found that the individuals whose negative symptoms resolved at the three-month mark also had lower levels of positive symptoms. This may support the idea that there is a significant relationship between positive and negative symptoms.

A few of the five studies explored the role of insight as a mediator in the relationship between negative symptoms and medication nonadherence since there is known relationship between poor insight and nonadherence, and insight is negatively correlated with the presence of negative symptoms (Chang et al., 2011; Mintz et al., 2003). For example, Baloush-Kleinman et al. (2011) identified that the presence of negative symptoms predicted attitudes (including insight) towards medication, which in turn predicted adherence. It appears that this dissertation is the second study (Subotnik et al., 2014 was the first) to explore the role of positive symptoms (e.g., Reality Distortion) as a variable mediating the relationship between negative symptoms and medication nonadherence. However, this dissertation appears to be the first study examining the presence of a mediator in such a fine-grained temporal analyses, with one-month intervals as opposed to three-month intervals.

**Limitations**

This dissertation supports the limited prior research indicating that there is a significant relationship between negative symptoms and medication nonadherence. Although there have been a few studies which have previously explored this relationship, the current research in this area is still very limited and much needed. The results of this study have significant implications for treatment and mitigating risk factors for medication nonadherence. However, since the mean level of negative symptoms was mild for this study's sample, it may have limited the ability to assess the strength of the relationship between negative symptoms and medication nonadherence. It is possible that had higher levels of negative symptoms been present, or if there had been more variation in negative symptom levels, the association between negative symptoms and medication nonadherence may have been more robust.

It is likely that the mild level of negative symptoms is in part attributable to the highly controlled and comprehensive level of treatment provided by the UCLA Aftercare Research Program. The sample used in this study was controlled in many ways (as mentioned previously regarding excluding substance use, etcetera), which is a strength in that it eliminates confounding variables in the relationships explored in this study; however, the limitation is that it also impacts the ability of these results to be generalized to individuals typically seen in community treatment programs. Specifically, common factors contributing to nonadherence (e.g., cost of care and ease of access to treatment) were controlled in this study, thus limiting the generalizability of this study to community treatment providers. As mentioned above, another limitation related to the generalizability of this study is that the sample used for this dissertation had very minimal substance use. Because substance abuse is a predictor of medication nonadherence and is also commonly comorbid with psychotic disorders, it would be worthwhile for future studies to explore the role of negative symptoms in medication non-adherence in this population (Kamali et al., 2006; Saddichha, Sur, Sinha, & Khess, 2010).

Another limitation for this particular study's exploration of correlates of negative symptoms is that it focused on recent first-episode schizophrenia patients. It is unknown whether the findings of this study would generalize to individuals at different stages of the course of psychosis. Also, the sample included very few individuals with deficit syndrome, which may be an ideal subgroup to look at to explore whether there is such a relationship between negative symptoms and medication adherence. However, given that severe negative symptoms are often debilitating, it may likely be very difficult to recruit and retain individuals with such severe negative symptoms in intervention studies.

A final limitation of this study relates to the data set construction. Symptom ratings and medication adherence ratings that exceeded four weeks were divided and included in multiple consecutive monthly means. This limited the chance of finding a temporal trend with the data. Specifically, this contributed to there being less within-subject change over time and therefore the overall range of ratings was truncated. Consequently, the possibility of identifying the true effect size was reduced.

**Future Directions**

The extant literature on this topic is sparse and the present findings require replication. Future research should address whether the relationships between negative symptoms and medication adherence, and between negative and positive symptoms can be replicated in samples of individuals at other stages of the illness (other than first episode), and with other symptom measures assessing the presence and level of negative symptoms. Additionally, as mentioned, given that there is little evidence that antipsychotic medications address/reduce negative symptoms, it is surprising that there was a strong association between earlier medication nonadherence and later negative symptoms. The findings of this dissertation suggest that there is a significant relationship between positive and negative symptoms, a relationship that appears to be more strongly associated than the relationship between negative symptoms and medication adherence. Consequently, further research should explore the significant interaction between negative and positive symptoms and whether this relationship helps to explain other generally understood relationships within psychosis, such as the relationship between negative symptoms and poor insight, or the relationship between poor insight and medication nonadherence. It would also be beneficial to explore whether there are mediating variables (other than positive

symptoms) that contribute to the significant relationship between negative symptoms and medication adherence.

As mentioned, the sample for the current study had well-controlled symptoms, which likely contributed to the mild level of negative symptoms, and limited generalizability to individuals seen and treated at community treatment centers. Therefore, future research should explore whether the relationship between medication nonadherence and negative symptoms remains in samples of individuals with a higher level of negative symptoms, and in environments that have less control over confounding variables (e.g., access to treatment), so as to see the real-world applicability of this study's findings.

In order to determine whether the significant relationship between medication nonadherence and negative symptoms occurs in samples with higher levels of negative symptoms, research should be conducted exploring this relationship in individuals with deficit syndrome. As a means of learning more about treatment implications of the relationship between negative symptoms and medication adherence, future research should explore whether the significant temporal relationship between negative symptoms and medication adherence is also present in individuals experiencing disorders comorbid with psychosis, such as substance use.

It is also unclear why the relationship between negative symptoms and medication adherence was stronger the more time that passed between evaluation points. Future research should explore potential reasons why this relationship became stronger as more time passed between the two points in time. Research should also examine why medication adherence was significantly associated with later negative symptoms at smaller intervals of time (e.g., a couple months) and then again at longer gaps of time (e.g., 12 months later). Additionally, future

research should explore which variables (other than positive symptoms) might serve as mediators between negative symptoms and medication nonadherence.

The results of this study have the potential to greatly contribute to the clinical treatment for first episode schizophrenia since a significant relationship was found between negative symptoms and medication adherence. Currently, there are minimal interventions for the treatment of negative symptoms, and given the relationships found in this study, further research involving negative symptoms as an intervention target should be conducted.

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# APPENDIX A

## GPS IRB Exemption Notice Approval

# PEPPERDINE UNIVERSITY

Graduate & Professional Schools Institutional Review Board

June 10, 2014

Elisha Agee
[redacted]

**Protocol #:** P0614D01
Project Title: The relationship between second-generation antipsychotic medication adherence and negative symptoms in first episode schizophrenia

Dear Ms. Agee:

Thank you for submitting your application, *The relationship between second-generation antipsychotic medication adherence and negative symptoms in first episode schizophrenia,* for exempt review to Pepperdine University's Graduate and Professional Schools Institutional Review Board (GPS IRB). The IRB appreciates the work you and your faculty advisor, Dr. Woo, have done on the proposal. The IRB has reviewed your submitted IRB application and all ancillary materials. Upon review, the IRB has determined that the above entitled project meets the requirements for exemption under the federal regulations (45 CFR 46 - http://www.nihtraining.com/ohsrsite/guidelines/45cfr46.html) that govern the protections of human subjects. Specifically, section 45 CFR 46.101(b)(2) states:

> (b) Unless otherwise required by Department or Agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:
>
> **Category (2) of 45 CFR 46.101**, research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: a) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and b) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

Your research must be conducted according to the proposal that was submitted to the IRB. If changes to the approved protocol occur, a revised protocol must be reviewed and approved by the IRB before implementation. For any proposed changes in your research protocol, please submit a **Request for Modification Form** to the GPS IRB. Because your study falls under exemption, there is no requirement for continuing IRB review of your project. Please be aware that changes to your protocol may prevent the research from qualifying for exemption from 45 CFR 46.101 and require submission of a new IRB application or other materials to the GPS IRB.

A goal of the IRB is to prevent negative occurrences during any research study. However, despite our best intent, unforeseen circumstances or events may arise during the research. If an unexpected situation or adverse event happens during your investigation, please notify the GPS IRB as soon as possible. We will ask for a complete explanation of the event and your response. Other actions also may be required depending on the nature of the event. Details regarding the timeframe in which adverse events must be reported to the GPS IRB and the appropriate form to be used to report this information can be found in the *Pepperdine University Protection of Human Participants in Research: Policies and Procedures Manual* (see link to "policy material" at http://www.pepperdine.edu/irb/graduate/).

Please refer to the protocol number denoted above in all further communication or correspondence related to this approval. Should you have additional questions, please contact Kevin Collins, Manager of the

Institutional Review Board (IRB) at gpsirb@peppderdine.edu. On behalf of the GPS IRB, I wish you success in this scholarly pursuit.

Sincerely,

Thema Bryant-Davis, Ph.D.
Chair, Graduate and Professional Schools IRB

cc: Dr. Lee Kats, Vice Provost for Research and Strategic Initiatives
Mr. Brett Leach, Compliance Attorney
Dr. Stephanie Woo, Faculty Advisor

# APPENDIX B

## UCLA Archival Dataset Permission

**UNIVERSITY OF CALIFORNIA, LOS ANGELES**

**UCLA**

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO

SANTA BARBARA • SANTA CRUZ

DEPARTMENT OF PSYCHIATRY AND
BIOBEHAVIORAL SCIENCES
DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA
300 UCLA MEDICAL PLAZA
LOS ANGELES, CALIFORNIA 90095-6968

May 23, 2014

Thema Bryant-Davis, Ph.D, Chairperson
Graduate and Professional School Institutional Review Board
Pepperdine University
Graduate School of Education & Psychology
6100 Center Drive 5th Floor
Los Angeles, CA 90045

Dr. Bryant-Davis,

This letter is to certify that I have given Elisha Agee permission to use a UCLA Aftercare Research Program archival data set for her Psy.D. dissertation. The data set is comprised of clinical symptom ratings from two longitudinal studies of patients with a recent first episode of schizophrenia that were conducted at the UCLA Aftercare Research Program. Both research protocols were conducted under full approval of the UCLA Institutional Review Board.

Respectfully,

Kenneth L. Subotnik, Ph.D.
Associate Director, UCLA Aftercare Research Program
Research Psychologist and Adjunct Professor
300 UCLA Medical Plaza, Rm. 2240
Los Angeles, CA 90095-6968
(310) 825-0334 (voice)
ksubotnik@mednet.ucla.edu

# APPENDIX C

## Brief Psychiatric Rating Scale, Version 4.0, Record Form

# Brief Psychiatric Rating Scale (Version 4.0)

Patient Name/ID # _____ Date _____ Rater _____

Hospital/Location _____ Period of Assessment_____

| NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Not Assessed | Not Present | Very Mild | Mild | Moderate | Moderately Severe | Severe | Extremely Severe |

*Rate items 1-14 on the basis of patient's self-report during interview. Note items 7, 12, and 13 are also rated on observed behavior during the interview. Mark "NA" for symptoms not assessed.*

***PROVIDE EXAMPLES:***

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1. | Somatic Concern | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 2. | Anxiety | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 3. | Depression | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 4. | Suicidality | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 5. | Guilt | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 6. | Hostility | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 7. | Elevated Mood | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 8. | Grandiosity | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 9. | Suspiciousness | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 10. | Hallucinations | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 11. | Unusual Thought Content | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 12. | Bizarre Behavior | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 13. | Self-neglect | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 14. | Disorientation | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

Rate items 15-24 on the basis of observed behavior or speech of the patient during the interview.

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 15. | Conceptual Disorganization | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 16. | Blunted Affect | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 17. | Emotional Withdrawal | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 18. | Motor Retardation | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 19. | Tension | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 20. | Uncooperativeness | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 21. | Excitement | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 22. | Distractibility | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 23. | Motor Hyperactivity | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 24. | Mannerisms and Posturing | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

Sources of information (check all applicable):

_____ Patient

_____ Parents/Relatives

Explain here if validity of assessment is questionable:

_____ Symptoms possibly substance-induced

_____ Under reported due to lack of rapport

_____ Mental health professionals
_____ Chart
_____ Other (e.g., police report)

_____ Patient uncooperative
_____ Difficult to assess due to formal thought disorder
_____ Other

Confidence in assessment

_____ 1 = not at all - 5 = very confident

Record information:

# APPENDIX D

## Scale for the Assessment of Negative Symptoms (SANS) Record Form, Modified by the UCLA Center for Research on Treatment and Rehabilitation of Psychosis

# Scale for the Assessment of Negative Symptoms (SANS)* **

Date: _____ Patient name/ID: _____
Rating Period: _____ Interviewer: _____

*0=None 1=Questionable 2=Mild 3=Moderate 4=Marked 5=Severe*

**AFFECTIVE_FLATTENING_OR_BLUNTING** **(Provide Examples)**

1. **Unchanging Facial Expression** **0 1 2 3 4 5**
   The patient's face appears wooden, changes less than expected as emotional content of discourse changes.

2. **Decreased Spontaneous Movements** **0 1 2 3 4 5**
   The patient shows few or no spontaneous movements, does not shift position, move extremities, etc.

3. **Paucity of Expressive Gestures** **0 1 2 3 4 5**
   The patient does not use hand gestures, body position, etc., as an aid to expressing his ideas.

4. **Poor Eye Contact** **0 1 2 3 4 5**
   The patient avoids eye contact or "stares through" interviewer even when speaking.

5. **Affective Nonresponsivity** **0 1 2 3 4 5**
   The patient fails to smile or laugh when prompted.

6. **Lack of Vocal Inflections** **0 1 2 3 4 5**
   The patient fails to show normal vocal emphasis patterns, is often monotonic.

7. **Global Rating of Affective Flattening** **0 1 2 3 4 5**
   This rating should focus on overall severity of symptoms, especially unresponsiveness, eye contact, facial expression, and vocal inflections.

**ALOGIA**

8. **Poverty of Speech** **0 1 2 3 4 5**
   The patient's replies to questions are restricted in the amount, tend to be brief, concrete, and unelaborated.

9. **Blocking** **0 1 2 3 4 5**
   The patient indicates, either spontaneously or with prompting, that his or her train of thought was interrupted.

10. **Increased Latency of Response** **0 1 2 3 4 5**
    The patient takes a long time to reply to questions; prompting indicates the patient is aware of the question.

11. **Global Rating of Alogia** **0 1 2 3 4 5**
    The core feature of alogia is poverty of speech.

**AVOLITION-APATHY** **(Provide Examples)**

12. **Grooming and Hygiene** **0 1 2 3 4 5**

The patient's clothes may be sloppy or soiled, and he or she may have greasy hair, body odor, etc.

**13a. Impersistence at Work or School** *(relative to general population)* **0 1 2 3 4 5**
Based on the patient's age and sex, rate the degree to which the patient has difficultyin seeking or maintaining employment, attending school, keeping house, or engaging in volunteer work.

**13b. Impersistence at Work or School** *(relative to selected sample)* **0 1 2 3 4 5**
Rate the patient's impersistence relative to a patient sample chosen by the project principal investigator. DO NOT include 13b in the Global rating of Avolition-Apathy.

.

**14. Physical Anergia** **0 1 2 3 4 5**
The patient tends to be physically inert. He or she may sit for hours and does not initiate spontaneous activity.

**15. Global Rating of Avolition-Apathy** **0 1 2 3 4 5**
Strong weight may be given to one or two prominent symptoms if particularly striking.

## ANHEDONIA-ASOCIALITY

**16. Recreational Interests and Activities** **0 1 2 3 4 5**
The patient may have few or no interests. Both the quality and quantity of interests should be taken into account.

**17. Sexual Activity** **0 1 2 3 4 5**
The patient may show a decrease in sexual interest and activity, or enjoyment when active.

**18. Ability to Feel Intimacy and Closeness** **0 1 2 3 4 5**
The patient may display an inability to form close or intimate relationships, especially with the opposite sex and family.

**19. Relationships with Friends and Peers** **0 1 2 3 4 5**
The patient may have few or no friends and may prefer to spend all of his or her time isolated.

**20. Global Rating of Anhedonia-Asociality** **0 1 2 3 4 5**
This rating should reflect overall severity, taking into account the patient's age,family status, etc.

## ATTENTION

**21. Social Inattentiveness** **0 1 2 3 4 5**
The patient appears uninvolved or unengaged. He may seem "spacy."

**22. Inattentiveness During Mental Status Training** **0 1 2 3 4 5**
Tests of "serial 7s" (at least five subtractions) and spelling "world" backwards. Score: 2=1 error; 3=2 errors; 4=3 errors

**23. Global Rating of Attention** **0 1 2 3 4 5**
This rating should assess the patient's overall concentration, clinically and on tests.

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*Modified 10-2-00 by the UCLA Center for Research on Treatment and Rehabilitation of Psychosis

# APPENDIX E

## GLMM with Medication Adherence Ratings Preceding SANS Affective Flattening Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months prior | .201 | .078 | (1,159) | 6.7 | .011 |
| 11 months prior | .050 | .068 | (1,266) | 0.6 | .459 |
| 10 months prior | .092 | .061 | (1,353) | 2.3 | .131 |
| 9 months prior | -.029 | .052 | (1,429) | 0.3 | .583 |
| 8 months prior | .022 | .045 | (1,509) | 0.2 | .624 |
| 7 months prior | -.000 | .040 | (1,593) | 0.0 | .996 |
| 6 months prior | .006 | .037 | (1,682) | 0.0 | .868 |
| 5 months prior | .048 | .035 | (1,780) | 1.9 | .172 |
| 4 months prior | .074 | .034 | (1,878) | 4.7 | .031 |
| 3 months prior | .036 | .033 | (1,973) | 1.2 | .271 |
| 2 months prior | .060 | .033 | (1,1073) | 3.4 | .068 |
| 1 month prior | .076 | .032 | (1,1168) | 5.6 | .018 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX F

## GLMM with Medication Adherence Ratings Preceding SANS Alogia Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months prior | .176 | .066 | (1,141) | 7.3 | .008 |
| 11 months prior | .136 | .060 | (1,253) | 5.1 | .024 |
| 10 months prior | .072 | .057 | (1,346) | 1.6 | .211 |
| 9 months prior | .005 | .048 | (1,420) | 0.0 | .923 |
| 8 months prior | .036 | .042 | (1,512) | 0.7 | .399 |
| 7 months prior | .017 | .040 | (1,605) | 0.2 | .678 |
| 6 months prior | .056 | .036 | (1,695) | 2.4 | .124 |
| 5 months prior | .043 | .035 | (1,792) | 1.5 | .216 |
| 4 months prior | .089 | .034 | (1,893) | 6.9 | .009 |
| 3 months prior | .075 | .033 | (1,985) | 5.3 | .022 |
| 2 months prior | .110 | .032 | (1,1086) | 12.0 | .001 |
| 1 month prior | .103 | .031 | (1,1183) | 11.0 | .001 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX G

## GLMM with Medication Adherence Ratings Preceding SANS Avolition-Apathy Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months prior | .342 | .100 | (1,157) | 11.8 | .001 |
| 11 months prior | .078 | .085 | (1,257) | 0.8 | .359 |
| 10 months prior | .192 | .074 | (1,341) | 6.7 | .010 |
| 9 months prior | .173 | .066 | (1,427) | 6.8 | .010 |
| 8 months prior | .017 | .059 | (1,509) | 0.1 | .767 |
| 7 months prior | -.033 | .054 | (1,596) | 0.4 | .545 |
| 6 months prior | .014 | .049 | (1,685) | 0.1 | .777 |
| 5 months prior | -.020 | .046 | (1,782) | 0.2 | .670 |
| 4 months prior | -.038 | .044 | (1,883) | 0.7 | .397 |
| 3 months prior | .003 | .043 | (1,980) | 0.0 | .947 |
| 2 months prior | .059 | .042 | (1,1083) | 2.0 | .157 |
| 1 month prior | .096 | .040 | (1,1178) | 5.9 | .015 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX H

## GLMM with Medication Adherence Ratings Preceding SANS Anhedonia-Asociality Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months prior | .284 | .094 | (1,180) | 9.1 | .003 |
| 11 months prior | .037 | .077 | (1,267) | 0.2 | .633 |
| 10 months prior | .119 | .068 | (1,350) | 3.1 | .080 |
| 9 months prior | -.036 | .058 | (1,425) | 0.4 | .532 |
| 8 months prior | .000 | .050 | (1,507) | 0.0 | .999 |
| 7 months prior | .063 | .045 | (1,594) | 2.0 | .159 |
| 6 months prior | .042 | .041 | (1,680) | 1.1 | .300 |
| 5 months prior | .032 | .040 | (1,783) | 0.7 | .419 |
| 4 months prior | .043 | .037 | (1,877) | 1.3 | .252 |
| 3 months prior | .063 | .035 | (1,970) | 3.2 | 074 |
| 2 months prior | .067 | .034 | (1,1067) | 3.9 | .047 |
| 1 month prior | .080 | .032 | (1,1162) | 6.2 | .013 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX I

## GLMM with Medication Adherence Ratings Preceding SANS Attention Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months prior | .091 | .100 | (1,195) | 0.8 | .365 |
| 11 months prior | .126 | .082 | (1,282) | 2.4 | .127 |
| 10 months prior | .050 | .075 | (1,367) | 0.4 | .506 |
| 9 months prior | .012 | .068 | (1,455) | 0.0 | .862 |
| 8 months prior | -.013 | .060 | (1,541) | 0.1 | .825 |
| 7 months prior | .019 | .053 | (1,624) | 0.1 | .721 |
| 6 months prior | .021 | .047 | (1,707) | 0.2 | .194 |
| 5 months prior | .031 | .044 | (1,806) | 0.5 | .485 |
| 4 months prior | -.002 | .042 | (1,900) | 0.0 | .972 |
| 3 months prior | .081 | .039 | (1,990) | 4.2 | .041 |
| 2 months prior | .107 | .038 | (1,1088) | 8.2 | .004 |
| 1 month prior | .080 | .036 | (1,1181) | 5.0 | .026 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX J

## GLMM with Medication Adherence Ratings Preceding BPRS Negative Symptom Factor Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months prior | .187 | .054 | (1,164) | 12.1 | .001 |
| 11 months prior | .011 | .052 | (1,280) | 0.0 | .840 |
| 10 months prior | .052 | .045 | (1,360) | 1.3 | .253 |
| 9 months prior | -.043 | .038 | (1,437) | 1.3 | .259 |
| 8 months prior | -.008 | .034 | (1,525) | 0.1 | .823 |
| 7 months prior | .032 | .031 | (1,616) | 1.1 | .299 |
| 6 months prior | .009 | .028 | (1,704) | 0.1 | .750 |
| 5 months prior | -.006 | .026 | (1,800) | 0.0 | .834 |
| 4 months prior | .011 | .025 | (1,894) | 0.2 | .649 |
| 3 months prior | .023 | .024 | (1,988) | 0.9 | .341 |
| 2 months prior | .031 | .024 | (1,1086) | 1.7 | .197 |
| 1 month prior | .049 | .023 | (1,1182) | 4.5 | .033 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX K

## GLMM with Medication Adherence Ratings Preceding BPRS Self-Neglect Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months prior | .129 | .050 | (1,201) | 6.7 | .011 |
| 11 months prior | -.015 | .038 | (1,285) | 0.2 | .690 |
| 10 months prior | .068 | .037 | (1,364) | 3.5 | .062 |
| 9 months prior | .073 | .032 | (1,450) | 5.1 | .025 |
| 8 months prior | .035 | .030 | (1,538) | 1.3 | .247 |
| 7 months prior | .056 | .029 | (1,631) | 3.6 | .057 |
| 6 months prior | .009 | .027 | (1,719) | 0.1 | .733 |
| 5 months prior | -.010 | .025 | (1,814) | 0.2 | .702 |
| 4 months prior | .021 | .025 | (1,908) | 0.7 | .409 |
| 3 months prior | .076 | .024 | (1,998) | 10.4 | .001 |
| 2 months prior | .076 | .022 | (1,1097) | 11.7 | .001 |
| 1 month prior | .042 | .021 | (1,1190) | 3.8 | .052 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX L

## GLMM with Medication Adherence Ratings Preceding BPRS Blunted Affect Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months prior | .171 | .072 | (1,152) | 5.7 | .018 |
| 11 months prior | .003 | .069 | (1,268) | 0.0 | .964 |
| 10 months prior | .132 | .062 | (1,356) | 4.6 | .033 |
| 9 months prior | -.078 | .052 | (1,432) | 2.2 | .137 |
| 8 months prior | .010 | .046 | (1,520) | 0.0 | .838 |
| 7 months prior | .028 | .043 | (1,608) | 0.4 | .509 |
| 6 months prior | -.012 | .038 | (1,690) | 0.2 | .675 |
| 5 months prior | .002 | .035 | (1,786) | 0.0 | .949 |
| 4 months prior | .023 | .034 | (1,885) | 0.5 | .495 |
| 3 months prior | -.004 | .033 | (1,978) | 0.0 | .905 |
| 2 months prior | .018 | .032 | (1,1077) | 0.3 | .576 |
| 1 month prior | .066 | .032 | (1,1172) | 4.4 | .037 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX M

## GLMM with Medication Adherence Ratings Preceding BPRS Emotional Withdrawal Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months prior | .165 | .071 | (1,199) | 5.4 | .021 |
| 11 months prior | .044 | .064 | (1,284) | 0.5 | .491 |
| 10 months prior | .002 | .057 | (1,373) | 0.0 | .979 |
| 9 months prior | .011 | .049 | (1,457) | 0.1 | .817 |
| 8 months prior | .018 | .043 | (1,547) | 0.2 | .677 |
| 7 months prior | .097 | .039 | (1,635) | 6.1 | .014 |
| 6 months prior | .057 | .036 | (1,723) | 2.5 | .113 |
| 5 months prior | .024 | .035 | (1,814) | 0.5 | .482 |
| 4 months prior | .038 | .033 | (1,905) | 1.4 | .242 |
| 3 months prior | .050 | .032 | (1,998) | 2.5 | .112 |
| 2 months prior | .072 | .030 | (1,1097) | 5.7 | .017 |
| 1 month prior | .073 | .029 | (1,1191) | 6.3 | .013 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX N

## GLMM with Medication Adherence Ratings Preceding BPRS Motor Retardation Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months prior | .195 | .065 | (1,182) | 8.9 | .003 |
| 11 months prior | .002 | .057 | (1,88) | 0.0 | .977 |
| 10 months prior | .058 | .052 | (1,374) | 1.3 | .259 |
| 9 months prior | -.035 | .046 | (1,459) | 0.6 | .447 |
| 8 months prior | -.027 | .040 | (1,546) | 0.5 | .494 |
| 7 months prior | -.018 | .037 | (1,637) | 0.2 | .624 |
| 6 months prior | -.007 | .034 | (1,724) | 0.0 | .838 |
| 5 months prior | -.035 | .031 | (1,816) | 1.3 | .263 |
| 4 months prior | -.020 | .029 | (1,908) | 0.5 | .497 |
| 3 months prior | .028 | .028 | (1,999) | 1.0 | .318 |
| 2 months prior | .007 | .028 | (1,1097) | 1.1 | .800 |
| 1 month prior | .013 | .028 | (1,1192) | 0.2 | .646 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX O

GLMM of SANS Affective Flattening Ratings with Subsequent Medication Adherence Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months later | .078 | .134 | (1,69) | 0.3 | .561 |
| 11 months later | -.118 | .084 | (1,149) | 2.0 | .158 |
| 10 months later | .040 | .069 | (1,231) | 0.3 | .566 |
| 9 months later | -.095 | .058 | (1,315) | 2.7 | .100 |
| 8 months later | -.088 | .052 | (1,404) | 2.8 | .095 |
| 7 months later | -.042 | .052 | (1,492) | 0.7 | .419 |
| 6 months later | -.060 | .050 | (1,582) | 1.4 | .232 |
| 5 months later | -.108 | .044 | (1,681) | 6.0 | .015 |
| 4 months later | -.093 | .039 | (1,779) | 5.9 | .015 |
| 3 months later | -.039 | .035 | (1,877) | 1.2 | .268 |
| 2 months later | -.009 | .034 | (1,984) | 0.1 | .778 |
| 1 month later | .031 | .032 | (1,1099) | 0.9 | .340 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX P

## GLMM of SANS Attention Ratings with Subsequent Medication Adherence Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months later | -.022 | .125 | (1,69) | 0.0 | .862 |
| 11 months later | -.041 | .079 | (1,150) | 0.3 | .605 |
| 10 months later | -.034 | .068 | (1,234) | 0.3 | .568 |
| 9 months later | -.045 | .064 | (1,313) | 0.5 | .485 |
| 8 months later | .050 | .060 | (1,391) | 0.7 | .402 |
| 7 months later | -.033 | .055 | (1,478) | 0.4 | .548 |
| 6 months later | -.007 | .053 | (1,565) | 0.0 | .892 |
| 5 months later | -.025 | .048 | (1,658) | 0.3 | .611 |
| 4 months later | -.036 | .042 | (1,749) | 0.7 | .400 |
| 3 months later | -.030 | .0393 | (1,847) | 0.6 | .454 |
| 2 months later | .037 | .038 | (1,972) | 1.0 | .326 |
| 1 month later | .077 | .036 | (1,1092) | 4.5 | .034 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX Q

## GLMM of SANS Alogia Ratings with Subsequent Medication Adherence Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months later | -.055 | .122 | (1,69) | 0.2 | .662 |
| 11 months later | -.069 | .084 | (1,149) | 0.7 | .416 |
| 10 months later | .067 | .070 | (1,235) | 0.9 | .342 |
| 9 months later | -.060 | .059 | (1,319) | 1.0 | .311 |
| 8 months later | -.143 | .052 | (1,404) | 7.6 | .006 |
| 7 months later | -.048 | .049 | (1,490) | 1.0 | .328 |
| 6 months later | -.033 | .048 | (1,572) | 0.5 | .489 |
| 5 months later | -.044 | .043 | (1,669) | 1.1 | .306 |
| 4 months later | -.026 | .037 | (1,765) | 0.5 | .478 |
| 3 months later | -.027 | .034 | (1,860) | 0.6 | .430 |
| 2 months later | -.011 | .032 | (1,981) | 0.1 | .735 |
| 1 month later | .058 | .031 | (1,1094) | 3.4 | .067 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX R

GLMM of SANS Avolition-Apathy Ratings with Subsequent Medication Adherence Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months later | .174 | .134 | (1,69) | 1.7 | .199 |
| 11 months later | .095 | .092 | (1,151) | 1.1 | .308 |
| 10 months later | .134 | .080 | (1,235) | 2.8 | .095 |
| 9 months later | .111 | .071 | (1,318) | 2.4 | .121 |
| 8 months later | .040 | .065 | (1,400) | 0.4 | .539 |
| 7 months later | -.045 | .060 | (1,488) | 0.6 | .455 |
| 6 months later | -.083 | .057 | (1,577) | 2.2 | .144 |
| 5 months later | -.052 | .050 | (1,678) | 1.1 | .301 |
| 4 months later | -.018 | .045 | (1,773) | 0.2 | .687 |
| 3 months later | -.027 | .042 | (1,871) | 0.4 | .512 |
| 2 months later | -.076 | .041 | (1,984) | 3.5 | .061 |
| 1 month later | -.034 | .040 | (1,1099) | 0.7 | .392 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX S

GLMM of SANS Anhedonia-Asociality Ratings with Subsequent Medication Adherence Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months later | -.105 | .141 | (1,69) | 0.6 | .461 |
| 11 months later | .119 | .088 | (1,149) | 1.8 | .178 |
| 10 months later | -.019 | .075 | (1,235) | 0.1 | .801 |
| 9 months later | .104 | .065 | (1,319) | 2.6 | .107 |
| 8 months later | .004 | .057 | (1,405) | 0.0 | .945 |
| 7 months later | -.045 | .053 | (1,492) | 0.6 | .427 |
| 6 months later | -.092 | .050 | (1,584) | 3.4 | .066 |
| 5 months later | -.002 | .044 | (1,682) | 0.0 | .966 |
| 4 months later | .064 | .039 | (1,779) | 2.8 | .097 |
| 3 months later | -.004 | .035 | (1,878) | 0.0 | .908 |
| 2 months later | -.025 | .033 | (1,983) | 0.6 | .453 |
| 1 month later | -.001 | .032 | (1,1099) | 0.0 | .981 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX T

## GLMM of BPRS Negative Symptom Factor Ratings with Subsequent Medication Adherence Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months later | -.001 | .096 | (1,69) | 0.0 | .991 |
| 11 months later | -.045 | .061 | (1,151) | 0.6 | .462 |
| 10 months later | -.002 | .051 | (1,236) | 0.0 | .974 |
| 9 months later | -.030 | .043 | (1,320) | 0.5 | .485 |
| 8 months later | -.071 | .038 | (1,406) | 3.5 | .063 |
| 7 months later | -.047 | .037 | (1,493) | 1.6 | .212 |
| 6 months later | -.011 | .036 | (1,580) | 0.1 | .772 |
| 5 months later | -.049 | .032 | (1,679) | 2.3 | .127 |
| 4 months later | -.054 | .028 | (1,776) | 3.8 | .052 |
| 3 months later | -.026 | .025 | (1,871) | 1.0 | .306 |
| 2 months later | -.009 | .024 | (1,987) | 0.2 | .702 |
| 1 month later | .023 | .023 | (1,1102) | 1.0 | .329 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX U

## GLMM of BPRS Self-Neglect Ratings with Subsequent Medication Adherence Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months later | -.012 | .063 | (1,69) | 0.0 | .847 |
| 11 months later | .003 | .042 | (1,151) | 0.0 | .936 |
| 10 months later | .015 | .035 | (1,236) | 0.2 | .661 |
| 9 months later | .014 | .036 | (1,303) | 0.2 | .699 |
| 8 months later | -.058 | .034 | (1,380) | 2.8 | .093 |
| 7 months later | -.093 | .033 | (1,476) | 8.0 | .005 |
| 6 months later | -.016 | .032 | (1,561) | 0.3 | .605 |
| 5 months later | .022 | .028 | (1,664) | 0.6 | .438 |
| 4 months later | .090 | .024 | (1,770) | 13.8 | .000 |
| 3 months later | .029 | .023 | (1,854) | 1.6 | .205 |
| 2 months later | .007 | .021 | (1,973) | 0.1 | .744 |
| 1 month later | .035 | .021 | (1,1084) | 2.9 | .090 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX V

GLMM of BPRS Blunted Affect Ratings with Subsequent Medication Adherence Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months later | .022 | .131 | (1,69) | 0.0 | .866 |
| 11 months later | -.031 | .081 | (1,150) | 0.2 | .701 |
| 10 months later | -.056 | .068 | (1,233) | 0.7 | .408 |
| 9 months later | -.053 | .057 | (1,317) | 0.9 | .352 |
| 8 months later | -.101 | .052 | (1,405) | 3.7 | .055 |
| 7 months later | -.065 | .052 | (1,494) | 1.6 | .206 |
| 6 months later | -.052 | .049 | (1,585) | 1.2 | .284 |
| 5 months later | -.105 | .043 | (1,684) | 5.9 | .016 |
| 4 months later | -.133 | .038 | (1,781) | 9.0 | .003 |
| 3 months later | -.067 | .035 | (1,880) | 3.7 | .054 |
| 2 months later | -.023 | .033 | (1,987) | 0.5 | .486 |
| 1 month later | .003 | .032 | (1,1102) | 0.0 | .931 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX W

## GLMM of BPRS Emotional Withdrawal Ratings with Subsequent Medication Adherence Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months later | -.011 | .100 | (1,69) | 0.0 | .916 |
| 11 months later | -.018 | .072 | (1,138) | 0.1 | .807 |
| 10 months later | .044 | .060 | (1,216) | 0.5 | .467 |
| 9 months later | -.033 | .054 | (1,301) | 0.4 | .541 |
| 8 months later | -.065 | .049 | (1,381) | 1.8 | .179 |
| 7 months later | .013 | .046 | (1,468) | 0.1 | .774 |
| 6 months later | .093 | .046 | (1,528) | 4.1 | .042 |
| 5 months later | .067 | .041 | (1,635) | 2.7 | .099 |
| 4 months later | .029 | .035 | (1,736) | 0.7 | .408 |
| 3 months later | .015 | .032 | (1,834) | 0.2 | .649 |
| 2 months later | .023 | .030 | (1,964) | 0.6 | .441 |
| 1 month later | .088 | .029 | (1,1073) | 9.2 | .003 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$

# APPENDIX X

## GLMM of BPRS Motor Retardation Ratings with Subsequent Medication Adherence Ratings

| Time Lag | Estimate | Standard Error of Estimate | df (Numerator, Denominator) | F | Significance (*p*) |
|---|---|---|---|---|---|
| 12 months later | -.015 | .117 | (1,69) | 0.0 | .899 |
| 11 months later | -.033 | .077 | (1,152) | 0.2 | .669 |
| 10 months later | .014 | .066 | (1,235) | 0.1 | .829 |
| 9 months later | .014 | .056 | (1,317) | 0.1 | .807 |
| 8 months later | -.026 | .049 | (1,401) | 0.3 | .595 |
| 7 months later | -.077 | .045 | (1,489) | 2.9 | .088 |
| 6 months later | -.064 | .042 | (1,579) | 2.3 | .130 |
| 5 months later | -.100 | .037 | (1,675) | 7.1 | .008 |
| 4 months later | -.065 | .033 | (1,769) | 3.9 | .050 |
| 3 months later | -.018 | .030 | (1,862) | 0.3 | .561 |
| 2 months later | -.021 | .029 | (1,982) | 0.5 | .470 |
| 1 month later | -.020 | .028 | (1,1096) | 0.5 | .481 |

*Note*. Light gray shading = $p < 0.05$, Dark gray shading = $p < 0.01$