# Clinical Characteristics of People in Randomized Clinical Trials of First Episode Schizophrenia Spectrum Disorders: Attrition versus Non-Attrition Groups

Author: Joanne D. Wojcik

Boston College

William F. Connell School of Nursing

# CLINICAL CHARACTERISTICS OF PEOPLE IN RANDOMIZED CLINICAL TRIALS OF FIRST EPISODE SCHIZOPHRENIA SPECTRUM DISORDERS: ATTRITION VERSUS NON-ATTRITION GROUPS

a dissertation

by

JOANNE D. WOJCIK

submitted in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

December 2009

# Clinical Characteristics Of People In Randomized Clinical Trials Of First Episode Schizophrenia Spectrum Disorders: Attrition Versus Non-Attrition Groups

Submitted by Joanne D. Wojcik PhD, RN

Dissertation Advisor Judith Shindul-Rothschild, PhD, RN

## Abstract

*Background:* Early identification of psychosis and intensive treatment has been the focus of the treatment of people with a first episode (FE) schizophrenia spectrum disorder (SSD). Attrition rates in studies of people in the first episode are high, which makes it difficult to understand the meaning of the study outcomes. High attrition rates affect the validity of a study by decreasing its power and the study's ability to detect differences between treatment groups. Additionally, the people who leave a study may be different from those who stay in demographic, illness and treatment characteristics.

*Method:* This study is a secondary analysis of a group of FE SSD participants enrolled in one of three separate double-blind, randomized, drug trials. The variables were first analyzed across the three drug study data sets to determine if the patient populations are comparable across the three studies to allow for the merging of the data. Exploratory and descriptive statistics of study participants were conducted in a comparison of the three studies, for the merged group, and for the attrition and non-attrition groups. Effect sizes (Cohen's d) were calculated for each variable in the individual studies and in the merged dataset for the magnitude of difference between the attrition and non-attrition groups.

*Results:* The three studies were merged after analysis found no consistent difference in demographic and illness characteristics between the three studies. There was no significant difference between the attrition and non-attrition groups in the merged data in

demographic and illness characteristics. Treatment characteristics consistently found lack of efficacy and patient withdrawal of consent to be the two most frequent reasons for attrition from the studies. In addition, participants receiving a typical agent were less likely to complete the study. Effect size calculations found attrition group to more likely be Caucasian, with a lower median income. The attrition group had more years of education, but was not in school in the year previous to hospitalization.

*Conclusion:* Historically, attrition is a major problem in clinical trials of people in a first episode of schizophrenia spectrum disorders. People receiving typical antipsychotic medication are more likely to leave a study. Most common reasons for attrition include lack of efficacy and withdrawal of consent.

Acknowledgement

There are so many people to thank for their assistance and support in completing this dissertation. There have been two chairs for this dissertation committee. Anne Norris is my advisor and original committee chair. It is with much appreciation that I thank you for all of your wisdom and assistance in helping me narrow my area of interest, define the problem, and develop the research questions, along with the many hours of reading and editing. Judith Shindul-Rothschild became the committee chair after the proposal defense. I am deeply appreciative of your expertise and countless hours of editing, guidance and support. Barbara Wolfe was instrumental in providing conceptual guidance in the early phases of the dissertation. I truly appreciate and thank you for your support, encouragement and detailed editing skills. William Stone, I am greatly appreciative of your guidance, support and insight providing a deeper understanding of the neurocognitive deficits in schizophrenia. I want to give a warm thank you to each of you.

I would like to thank the Boston College Connell School of Nursing for providing me with a fellowship, without which I could not have attended this program. June Horowitz provided me with a wonderful and supportive experience while working on her NIMH treatment intervention, the CARE project. I have learned a great deal from Kate Gregory and Christine Murphy, the project directors. In particular, I would like to thank Christine Murphy for all her support and patience. I learned a great deal about developing and implementing a data analytic plan along with the subsequent analysis of the CARE data.

I would like to thank all of my professors and classmates who made our classes incredibly interesting and a wonderful learning environment. In particular, Sr. Callista Roy, Dorothy Jones and Pamela Grace opened my eyes to different ways of viewing the world and providing much support during this time.

I could not have completed this dissertation without the tremendous amount of support I received from colleagues and friends. Raquelle Mesholam-Gately provided ongoing support and taught me so much about the details of neuropsychological testing and statistics. I could not have done this without you. Tony Giuliano also provided a huge amount of editorial support and encouragement. A heart felt thank you to you both. I want to also thank Larry Seidman and Matcheri Keshavan for their understanding and encouragement as I worked on this dissertation.

Last but definitely not least, I would like to thank my family and friends. Without your support and encouragement I could not have completed this dissertation. Your patience and understanding, as I struggled to balance home, school and work, is truly appreciated. Amanda, you married the same month I started school and now you are a nurse and the mother of twins. Chris, you have grown into a fine young man during these years. I am very proud of you both. Finally, I wish to dedicate this dissertation to my mother who taught me to embrace learning, and how to be resilient when overwhelmed. I know you are proud of me and I can see you smiling in my heart.

## TABLE OF CONTENTS

List of Tables



List of Figure

# CHAPTER 1

## First Episode Schizophrenia Spectrum Disorders

### *Statement of the Problem*

In the past fifteen to twenty years there has been a refocus in the treatment of first episode (FE) schizophrenia spectrum disorders (SSD) to early identification of psychosis and intensive treatment in the hopes of sustaining remission and preventing relapse. This effort has lead to pre- and post-marketing clinical trials conducted with a specific focus on FE SSD. Attrition rates in these studies are high which makes it difficult to understand the meaning of the study outcomes and to generalize the results (Kane, 2005). High attrition rates affect the validity of a study by decreasing its power and the study's ability to detect differences between study groups. Additionally, the people who leave a study may be different than those who stay (Streiner, 2002).

One statistical method for handling missing data created by attrition, commonly used in pharmaceutical studies and accepted by the FDA, is Last Observation Carried Forward (LOCF). LOCF allows all participants who completed a baseline and at least one post randomization visit to be included in the data analysis. In this method, the participants' last assessment score is entered into all missing visits. LOCF has been a key data analysis tool in FE SSD clinical trials where attrition rates do not allow for dropping cases as the cost of replacing participants is prohibitive (Leon et al., 2006). More recently, questions have been raised in the literature about the lack of theoretical underpinnings for this statistical method. Authors wonder if this method results in bias and potentially contributes to a distortion of the findings (Barnes, Lindborg, & Seaman, 2006a; Mazumdar, Liu, Houck, & Reynolds, 1999; Streiner, 2008; Wood, White, &

Thompson, 2004). The results from these clinical trials are used to guide practice but the findings, based on both a high attrition rate as well as a potentially biased statistical method, may be difficult to accurately interpret.

This chapter introduces the concept of first episode schizophrenia and describes the importance of early diagnosis and intervention. A review of the available literature regarding the clinical presentation, neurocognition, epidemiology, risk factors, treatment goals, and barriers to effective treatment of individuals experiencing a FE SSD is presented in order to lay the groundwork for a proposed study of attrition of subjects from clinical trials of medications used to treat FE SSD.

## *Background and Significance*

First episode SSD represents a heterogeneous collection of illnesses that includes schizotypal personality disorder, schizophrenia, schizoaffective disorder, and schizophreniform disorder. For the purpose of this study schizotypal personality disorder will not be discussed because it is a non-psychotic schizophrenia spectrum disorder. The SSDs in the psychotic end of the spectrum are defined by a period of psychosis, but onset, course and degree of impairment vary markedly. SSDs are characterized by delusional and hallucinatory symptoms and decreased levels of psychosocial functioning. The psychotic symptoms of SSDs often have an episodic course, with periods of symptomatic remission but often without attainment of functional remission. While the first episode may vary widely in terms of duration and illness severity, a first episode is typically defined as the time period beginning with the initial onset of psychosis and ending with the onset of a new or second psychotic episode. The first episode also

includes the period of symptom remission prior to the onset of a new, second episode of illness.

Psychosis onset most often exerts a disruptive impact on afflicted individuals' psychosocial and adaptive functioning, and enhances risk for a variety of negative outcomes, including suicide and long term disability (Perkins, Lieberman, & Lewis, 2006a). As recognition of the functional impact of SSDs matured over the past 20 years, burgeoning research and clinical interest in this period of illness development resulted in calls for intensive early intervention to reduce disability. A commonly accepted maxim is that early identification and treatment of FE SSD is critical to maximize an individual's level of psychosocial functioning and prevent further deterioration in functioning (Perkins et al., 2006a).

This viewpoint has lead to pre and post marketing clinical trials conducted with a specific focus on FE SSD in the hope of sustaining remission and preventing relapse. Attrition rates in these studies are high. What is not clear is the effect of high attrition rates on the results of these studies. This is unfortunate because the findings from these clinical trials are used to guide practice.

### *Clinical Presentation*

Schizophrenia Spectrum Disorders (SSD) is a term used to describe a heterogeneous disorder with marked variation in onset, course and symptom severity. This variability in illness onset (rapid versus slow), course (single episode to multiple episodes) and severity (good outcome and recovery to poor outcome with poor recovery) means that clinical presentation varies, but all individuals present with positive symptoms (psychosis) and many with negative symptoms (impaired social functioning and

anhedonia). Additionally, the clinical presentation can be complicated by comorbid substance abuse and symptoms of other Axis I disorders including depression, mania, post traumatic stress disorder and obsessive compulsive disorder.

People receive a diagnosis of schizophrenia after having had two or more of the following symptoms, delusions, hallucinations, disorganized speech, grossly disorganized behavior, and negative symptoms. There must be significant social and occupational disability for at least six months, this may include prodromal and residual symptoms. When the symptoms have been evident for at least one month but no more than six months, then schizophreniform disorder is diagnosed. The diagnosis of schizoaffective disorder is given when the psychotic symptoms are prominent, but there is also a significant period of time when an episode of major depression or mania has occurred after the onset of the psychosis (American Psychiatric Association, 2000). Participants in two of the three studies meet DSM-IV diagnostic criteria and the participants in the third study meet DSM-III-R diagnostic criteria. The differences between the DSM-III-R (American Psychiatric Association, 1987) and DSM-IV (American Psychiatric Association, 1994) diagnosis of schizophrenia are minor; the duration of psychosis was increased from one week to one month and negative symptoms were added to the symptoms listed in criterion A (American Psychiatric Association, 1994).

Positive symptoms, such as hallucinations and delusions, are perceptual abnormalities of the senses and are a hallmark symptom of psychosis (see Table 1) (Lindenmayer & Khan, 2006). Most common are auditory hallucinations of one or more voices that often make comments about the individual or keep up a running commentary (American Psychiatric Association, 2000). Delusional beliefs are another hallmark

symptom of SSD (American Psychiatric Association, 2000). There are many different types of delusions, such as delusions of being under the control or influence of another person or force and paranoid delusions to name two. For example, a person has the belief of being controlled by radio waves coming thru the windows caused by a specific group of people. Moreover, hallucinations and delusions can be dangerous for the individual and others if an individual acts on these altered perceptions and beliefs. Positive symptoms and cognitive dysfunction can cause severe disruption in behavior and attention resulting in disorganization. This disorganization may be behavioral in nature and/or include grossly disorganized speech such as derailment or loose associations. Other criteria for schizophrenia include a significant disruption in psychosocial and occupational functioning (American Psychiatric Association, 2000).

Negative symptoms (see Table 1) are another common characteristic of SSD and are a distinct construct found to be separate from social cognition and neurocognitive deficits (Andreasen, 1982; Andreasen, Flaum, Swayze, Tyrrell, & Arndt, 1990; Carpenter, Heinrichs, & Wagman, 1988; Sergi et al., 2007; Stahl & Buckley, 2007). Alogia, affective flattening, anhedonia and avolition are the most common negative symptoms (Malla et al., 2002). People with negative symptoms are often quiet, non-talkative and often keep to themselves. Family members and caregivers may see these behaviors as less troublesome than positive symptoms, but fail to appreciate how much they may interfere with social and occupational functioning (Stahl & Buckley, 2007). Additionally, depression, anxiety, and side effects of antipsychotic medications can serve as secondary causes of negative symptoms (Lindenmayer & Khan, 2006). Hence, treatment of these secondary influences is critical. Moreover, unlike chronic

schizophrenia, first episode negative symptoms may change over time suggesting they may be more malleable to treatment interventions (Edwards, McGorry, Waddell, & Harrigan, 1999; Stahl & Buckley, 2007; Subotnik, Nuechterlein, Ventura, Green, & Hwang, 1998). Therefore, early identification and treatment are critical for negative symptoms as well.

Table 1.
*Positive and Negative Symptoms*

| Symptom | Results in: |
|---|---|
| Positive | |
| Hallucinations | Distorted or altered perceptions |
| Delusions | Inferential thinking |
| Disorganized speech | Difficulty in communication with disordered thoughts and language |
| Bizarre behavior | Dysinhibition of self monitoring of behavior |
| Negative | |
| Affective flattening or blunting | Decreased range of affect, facial expression, eye contact and gestures<br>Reduced experience and perception of emotions |
| Alogia | Poverty of speech and thought content<br>Increased latency of response |
| Avolition and Apathy | Decreased energy, interest, desire, motivation and drive in activities of daily living and occupational functioning |
| Anhedonia | Decreased ability to experience pleasure in previously enjoyed activities |
| Asociality | Decreased interest in recreational, social and sexual activities |

*Early Course*

The early course of SSD can be divided into three time periods or phases: premorbid functioning, prodrome, and the onset of psychotic (i.e., positive) symptoms (Perkins, Miller-Anderson, & Lieberman, 2006b). Premorbid functioning is the time that the individual is engaged in usual psychosocial and academic functioning prior to prodrome but with a range of functioning from good to poor (Addington, van Mastrigt, & Addington, 2003; Lieberman et al., 2001). However, subtle motor and cognitive deficits, as well as difficulties in academic and social functioning, have been noted in individuals during their childhood prior to the onset of prodrome (Gold, 2004). Adding to the heterogeneity of the illness presentation is the heterogeneity associated with this premorbid period. In retrospective studies of those individuals with established SSDs, approximately 47.5% show relatively normative early levels and patterns of development, while 37.3% show subtle and 15.2% significant premorbid difficulties (Malla & Payne, 2005).

Prodrome has been defined as the time period when there is a change from premorbid level of functioning to the earliest signs and symptoms of the emerging disorder, and most often includes increasing social withdrawal, changes in or worsening of mood, impairment in role functioning (a decrease in school grades is common), blunted or inappropriate affect, poor hygiene, peculiar or odd thoughts and beliefs, and a decrease in interest, motivation, energy, and concentration (Tully & McGlashan, 2006). These changes in behavior and functioning may be non-specific and can be associated with a variety of other problems such as stress, depression, substance use, and post traumatic stress disorder (Larsen, McGlashen, & Moe, 1996). The most common co-

morbid diagnoses for individuals in the prodrome are mood disorders, alcohol and drug abuse/dependence, especially cannabis, and anxiety disorders (Addington et al., 2007; Meyer et al., 2005; Rosen, Miller, D'Andrea, McGlashan, & Woods, 2006).

During the prodrome phase of illness, non-specific negative symptoms also have been noted retrospectively to occur in up to 78% of people with a FE SSD (Rakfeldt & McGlashan, 2004). The prodrome phase can last from a period of weeks to 2 – 5 years and ends with the emergence of frank psychotic symptoms meeting criteria for a SSD. During the prodrome phase, individuals may experience either attenuated or brief intermittent psychotic symptoms that are infrequent and short lived, lasting a matter of minutes. These attenuated or brief psychotic symptoms lack a psychotic level of conviction and belief and do not cause associated avoidance or other psychotically-motivated behavior (Addington et al., 2007).

The prodrome phase ends when the frank psychotic symptoms emerge. This first episode of psychosis continues until the resolution or remission of the psychotic symptoms. However, the course varies markedly. A minority of people will have one episode of psychosis with full recovery, while others will experience a more chronic illness with repeated episodes without full recovery (Perkins et al., 2006b). The worst outcomes occur for those individuals who have a severe form of this illness and do not achieve symptom remission.

*Gender Differences*

There are a number of gender differences in the occurrence, course and the type of symptom expression of the illness found during the time of the first episode and first hospital admission (Goldstein, Tsuang, & Faraone, 1989). The belief that schizophrenia

occurs equally between men and women has been disputed more recently, as approximately 65% of the first episode population is male (Bromet & Fennig, 1999) and data suggest males may have a 30-40% higher risk of developing schizophrenia than females (Eaton & Chen, 2006). On average men have an earlier onset of psychotic symptoms (18-25) than do women (25-35) and women have a second peak onset of the illness around menopause (ages 45-55) in studies of the first episode and chronic schizophrenia, (Eaton & Chen, 2006; Gelber et al., 2004; Shtasel, Gur, Gallacher, Heimberg, & Gur, 1992; Szymanski et al., 1995). However, this age at onset difference is not always statistically significant (Eaton & Chen, 2006; Ganguli & Brar, 1992).

In first episode studies, men have a lower premorbid level of functioning than do women, especially during late adolescence (Gelber et al., 2004; Preston, Orr, Date, Nolan, & Castle, 2002). Males with schizophrenia are more apt to have developmental problems such as learning disabilities and delays in starting school. Those with developmental problems have significantly more deficits in neuropsychological functioning (Goldstein, Seidman, Santangelo, Knapp, & Tsuang, 1994). Women tend to be more impulsive, with inappropriate sexual behavior and paranoid and depressive symptoms (Goldstein & Link, 1988). Men have more negative symptoms, with more isolation and withdrawal, and with lower levels of psychosocial functioning (Goldstein & Link, 1988; Goldstein et al., 1989; Roy, Maziade, Labbe, & Merette, 2001; Shtasel et al., 1992).

In general, males with schizophrenia have more neurocognitive deficits than do male healthy controls and female patients on tests of attention, verbal memory and executive functioning. Goldstein et al. (1998) reported that women with schizophrenia

are less impaired in verbal processing, but are still impaired in tests of attention, executive functioning, visual memory, and motor functions relative to female control subjects. The reason for these gender differences is poorly understood but may be related to normal sex differences in brain physiology and cognition (Goldstein et al., 1998). Additionally, Hoff et al. (1998) found no gender difference in neurocognitive functioning in men and women experiencing a first episode SSD as compared to those with chronic schizophrenia. Szymanski et al. (1995) observed that women in a first episode of SSD had a better pharmacological treatment response with greater symptomatic improvement than men.

### *Neurocognition*

Although the diagnosis of schizophrenia is based on the duration and severity of positive and negative symptoms, cognitive deficits have been recognized as a core feature of schizophrenia (Keefe & Eesley, 2006). Cognitive deficits remain fairly stable over the years from first episode on (Gold, 2004; Heaton et al., 2001; Hoff et al., 1999; Rund et al., 2007), and are found in a milder form in first degree relatives of people with schizophrenia (Green, 2006). In general, people who develop SSD score 1 to 2 standard deviations below normal on many tests of neurocognition (Gold, 2004; Hoff et al., 1999). However, there is a broad range of function in individuals with SSD as compared to normal control groups (Gold, 2004; Heinrichs & Zakzanis, 1998).

In a meta-analysis of neurocognitive deficits in schizophrenia, Heinrichs and Zakzanis (1998) described core deficits in seven neurocognitive domains including memory, motor, attention, general intelligence, spatial ability, executive function, and language function. These core deficits are characterized by problems with abstraction,

problem solving and reasoning, working memory, verbal and visual learning, spatial memory, attention and vigilance, speed of processing, motor speed, and social cognition (Green, 2006; Green, Kern, Braff, & Mintz, 2000). The areas with the largest effect sizes on functioning are verbal memory, performance and full scale IQ, attention as measured by the continuous performance tests, and word fluency. This study will focus on general intelligence, attention, learning, language, memory, executive function, and motor functioning. However, many of these domains are interrelated and deficits in one area are associated with deficits in another area.

Individuals with schizophrenia have full scale estimated IQ scores 0.5 standard deviations, a medium effect size, below normal control scores (Woodberry, Giuliano, & Seidman, 2008). Impairment in full scale IQ is associated with deficits in working memory, processing speed, and memory as compared to healthy controls (Dickinson, Iannone, Wilk, & Gold, 2004). This impairment is correlated with poor insight in particular, but also with negative symptoms such as affective flattening, alogia, and social withdrawal (Sharma & Antonova, 2003).

Attention and information processing reflects the ability of the brain to identify relevant information or stimuli in the environment, and to sustain that focus as it is transferred for other levels of processing. In schizophrenia, difficulty with attention and information processing contributes to the executive functioning and working memory deficits and, therefore, the ability of the brain to think through problems (Sharma & Antonova, 2003).

Working memory is the short term, temporary memory system we use to do many tasks over the day. The information in working memory is either used and then discarded,

or integrated into longer-term memory. Working memory is critically important in holding the information, and in the short term, understanding the meaning of that information. It may include active rehearsal and processing of the information to guide our immediate behavior (Sharma & Antonova, 2003). Working memory deficits are significantly correlated with formal thought disorder, an inability to stay on target when speaking and include loose associations, tangential and circumstantial speech in people with schizophrenia (Spitzer, 1993). People with SSD who have the worst learning and memory deficits also exhibited the largest deficits in executive functioning, and attention (Bilder et al., 2000) and greater global impairment in other domains as compared to normal controls (Fitzgerald et al., 2004).

Executive functioning is impaired in all people with schizophrenia but the degree of impairment varies greatly and is found to be associated with IQ score (Heinrichs & Zakzanis, 1998). Executive function includes the abilities to organize, problem solve, develop a plan of action and then carry out that plan, along with an ongoing assessment of the self and how that plan is working. This includes the ability to reassess and revise the problem solving strategy and plan of action. An adequate level of executive functioning requires the use of abstract reasoning to develop different options, to anticipate potential outcomes and then to choose the best plan of action. This impairment is significantly correlated with poor insight in particular, but also with negative symptoms such as affective flattening, alogia, and social withdrawal (Horan & Blanchard, 2003; Sharma & Antonova, 2003).

The language domain includes both expressive and receptive elements and has large effect sizes in people with schizophrenia as compared to normal controls. This

includes tests of vocabulary and word fluency. Word fluency may be influenced by high doses of antipsychotic medications resulting in lower scores as compared to healthy controls (Heinrichs & Zakzanis, 1998).

Learning deficits, ranging from medium to large effect sizes, are found in people with a first episode SSD (Heinrichs & Zakzanis, 1998). The learning system of the brain is very complicated and all parts of the system are not equally affected. Heinrichs and Zakzanis (1998) found more consistent deficits in verbal learning than in non-verbal learning in people with schizophrenia. Learning deficits are based on the ability to store the learning in memory and then to be able to retrieve that information. Sharma and Antonova (2003) describe two types of memory, declarative and procedural. Declarative memory is the ability to learn from experience and then recall that learning. This deficit in declarative memory in people with schizophrenia is not due to forgetting, but to errors in encoding, retrieval, and impairments in working memory. This longer term memory is known as declarative memory and reflects the ability to learn information and be able to remember or recall it at a later time. On the other hand, the ability to learn new skills and motor activities, called procedural learning, is characterized by only mild deficits.

Motor performance is often included under executive functioning since it is the end stage of processing and planning behavior. Motor function is assessed by tests of finger tapping or grooved pegboard (Spreen & Strauss, 1998b). Effects sizes of these deficits in people with schizophrenia are moderately large and males are less affected than females (Heinrichs & Zakzanis, 1998).

Cognitive deficits are thought to be relatively independent of clinical symptoms in SSD (Gold, 2004; Nieuwenstein, 2001; Velligan et al., 1997), particularly positive

symptoms (Keefe et al., 2006b; Stirling et al., 2003) but the data regarding this relationship are mixed. Bilder and colleagues (2000) reported that the severity of generalized cognitive deficits was weakly associated with severity of psychotic symptoms, but only after patients were clinically stable (6 months after hospitalization and either in remission or with stable residual symptoms) after a first episode of SSD. Stirling et al. (2003) found poor performance on neurocognitive tests predicted higher levels of negative symptoms at follow-up in first episode patients. Better premorbid functioning has been associated with milder working memory deficits, while the worst working memory deficits have been associated with more relapses in the first year (Rund et al., 2007). Neurocognitive deficits, particularly the worst attention and executive function deficits are associated with more severe psychosocial and functional (work related behavior) impairment of people with schizophrenia (Bilder et al., 2000). Stirling et al. (2000; Stirling et al., 2003) found treatment outcome to not be associated with baseline deficits but instead associated with a decline in neurocognitive functioning from baseline to follow-up (on average 10 years later).

Disentangling the association between cognitive impairment and social functioning is complicated, and is influenced by negative symptoms (Keefe & Eesley, 2006). The association between negative symptoms and neurocognitive deficits in learning and memory may represent a common set of symptoms that is assessed by two different methods (e.g., neurocognitive testing and clinical rating of symptoms) (Fitzgerald et al., 2004; Keefe & Eesley, 2006). The type of antipsychotic medication may also play a role in cognitive and social functioning impairments. Patients switched from typical to atypical antipsychotic medications tend to show improved cognition, quality of life and

social problem solving (Keefe & Eesley, 2006). Social functioning deficits (e.g., poor social problem solving) have been shown to be most highly associated with poor verbal ability and poor verbal memory (Addington & Addington, 2000).

Overall, executive function deficits along with problems in attention, memory, and learning cause the most impairment in individuals with a FE SSD. These deficits contribute to increased difficulty in solving problems, expressing and evaluating thoughts, integrating information, detecting inconsistencies between verbal and perceptual information, paying attention, and learning new information, along with a decrease in mental flexibility (Hoff et al., 1999).

### *Epidemiology*

Currently, researchers have focused only on SSDs in general, and there are no published epidemiological studies of first episodes of psychosis. Jablensky (1997) emphasized that incidence rates of SSDs vary based on country, region of birth and gender in contrast to prior assertions that the incidence rates were homogeneous. McGrath (2006) in a review of the literature noted different incidence patterns in the Northern Hemisphere as compared to the Southern Hemisphere. For example, the Northern Hemisphere has higher incidence rates in urban areas and among migrant workers, and higher latitudes are often associated with season of birth and males (McGrath, 2006; Saha, Chant, Welham, & McGrath, 2006), but this is not true in the Southern Hemisphere (McGrath & Welham, 1999). Most researchers have focused on the incidence and point and lifetime prevalence of these disorders in different countries. Incidence (0.11 to 0.70 per 1,000) and lifetime prevalence (2.7 to 8.3 per 1,000) vary depending on the country (Eaton & Chen, 2006). McGrath also noted variance in

incidence for different countries depending on which diagnostic criteria were used. For example, cities in countries that use the World Health Association CATEGO S+ computer generated diagnosis based on a psychiatric rating scale, a narrow diagnostic criteria (Aarhus, Denmark to Nottingham, England) reported incidences that range from 7 to 14 per 100,000 while those that use the ICD-10, a broader criteria (Honolulu, Hawaii to Chandigarh, India) reported incidences that range from 16 to 42 per 100,000 (McGrath, 2005). Even within the US, the prevalence ranged from 6 to 11 per 1,000 (Faraone, Glatt, & Taylor, 2004).

At the individual level, recent data support the notion that there are gender differences in rates of SSD (McGrath, 2005). As previously described, males have a higher risk (Eaton & Chen, 2006) and an earlier age of onset (Bromet & Fennig, 1999) than females as demonstrated by several investigators (Eaton & Chen, 2006; Gelber et al., 2004; Shtasel et al., 1992; Szymanski et al., 1995). However, gender differences in age at onset were not always statistically significant (Eaton & Chen, 2006; Ganguli & Brar, 1992).

## *Risk Factors*

The risk factors associated with vulnerability to SSDs is complicated and likely additive. The range of factors broadly implicated in illness development includes genetic risk factors/family history, gestational and obstetric-perinatal complications, substance abuse and stressful events. Each of these will be reviewed in turn.

### *Genetic Risk*

A family history of schizophrenia is one of several risk factors that can result in an increased vulnerability to a SSD. The risk of developing schizophrenia varies with the

relationship when a relative has a diagnosis of schizophrenia. The lifetime risk for first-degree family members of people with schizophrenia is 9% for a sibling, 13% for children with one parent with schizophrenia, and 46% if both parents have a diagnosis of schizophrenia (Tsuang, Stone, & Faraone, 1999). Faraone and colleagues (2004) in twin studies showed that the rate of concordance for schizophrenia in monozygotic twins was approximately 45% - 75%, while it was 4 - 15% for dizygotic twins and varied depending on the specific diagnostic criteria used.

Researchers studying non-psychotic first-degree relatives of people with schizophrenia demonstrated a genetic linkage. Abnormalities similar to those observed in individuals with schizophrenia, have been observed to be less severe in the non-psychotic first-degree relatives. These non-psychotic first-degree relatives do not have any of the clinical symptoms of schizophrenia (Turetsky et al., 2007). These abnormalities have been found in brain functioning through magnetic resonance imaging (MRI) (Seidman et al., 2007; Seidman et al., 2006; Thermenos et al., 2007), in electrophysiology through the use of a specialized functional electroencephalogram (Turetsky et al., 2008) and in neurocognition through the use of cognitive test batteries (Bove, 2008; Horan et al., 2008; Tsuang et al., 2006). In addition, the degree of abnormality in structural MRI increases in the non-psychotic relative as the number of relatives with schizophrenia increases (Faraone et al., 2003; Faraone et al., 2000; Seidman et al., 2002). These findings have led to a change in the focus of genetic studies from attempts to identify genes associated with schizophrenia (phenotypes) to identifying markers of vulnerability (endophenotypes). Given that the abnormalities exist, current efforts are focused on identifying the endophenotypal genes that control the neurodevelopment of brain structure, function,

electrophysiology and cognition found in both affected and non affected family members (Seidman & Wencel, 2003; Turetsky et al., 2007). The hope is that identification of endophenotypes and phenotype will allow us to better understand the genetic basis of schizophrenia (Braff, Freedman, Schork, & Gottesman, 2007). It is important to note these markers are not sufficient to cause schizophrenia (Kremen & Hoff, 2004). Clinically, identification of the genetic basis of schizophrenia may lead to better ways to identify young people at genetic high risk and to provide treatment at the earliest signs and symptoms of psychosis.

*Gestational and Perinatal Complications*

Gestational and perinatal events, such as maternal influenza, starvation, pre-eclampsia, pregnancy induced hypertension, anoxic birth injuries, prematurity and other obstetric complications increase the risk of schizophrenia, with an overall odds ratio of 2.0 (Clarke, Harley, & Cannon, 2006; Gilmore & Murray, 2006; McClure & Lieberman, 2003). Other factors include exposure to genital and reproductive tract infections (Babulas, Factor-Litvak, Goetz, Schaefer, & Brown, 2006) and other perinatal infections such as toxoplasmosis (Dickerson, Boronow, Stallings, Origoni, & Yolken, 2007; Mortensen et al., 2007) and meningitis, as well as advanced paternal age (Eaton & Chen, 2006). These obstetric and perinatal complications do not cause schizophrenia, but comprise another set of factors contributing to a vulnerability to SSDs.

The genetic and perinatal factors may give rise to both structural and functional brain and developmental abnormalities in vulnerable individuals. The presence of neurological abnormalities contributes another set of factors that lead to a vulnerability to SSDs. Neurological abnormalities include hard and soft signs of impairment in sensory

functioning, motor coordination (such as difficulty in balance and coordination), reflexes, language and cognition, and sequencing problems including difficulty with rhythmic behaviors such as finger and toe tapping (Rosso et al., 2000). Children may exhibit right left confusion, and difficulty in audiovisual integration (Bachmann, Bottmer, & Schroder, 2005). Signs of neurological dysfunction are found in 50 – 65% of individuals with schizophrenia as compared to 5% of normal controls (Heinrichs & Buchanan, 1988) with individuals with other psychiatric disorders having fewer of these signs, but more than a normal control group (Bombin, Arango, & Buchanan, 2005).

In schizophrenia, these neurological abnormalities are associated with negative symptoms (decreased affect, interest and motivation) and cognitive deficits (impairment in memory, attention, reasoning, and problem solving) (Bombin et al., 2005; McClure & Lieberman, 2003). Many of these impairments, tied to developmental stages, first arise in early childhood through adolescence (Niemi, Suvisaari, Tuulio-Henriksson, & Lonnqvist, 2003). Several researchers and clinicians have suggested that cognitive deficits, delays in speech and motor milestones, and poor academic and social adjustment found in childhood may be markers for risk and, as such, contribute or indicate vulnerability to later development of schizophrenia (Gold, 2004; Niemi et al., 2003). For example, in a follow-back study of individuals with a first episode of schizophrenia, Bilder and colleagues (2006) found these patients had significantly lower scores on academic achievement tests as compared to matched controls as early as first grade. The gap between the two groups (those with schizophrenia and those without) continued to grow through 12$^{th}$ grade (Bilder et al., 2006).

*Substance Abuse*

Substance use and abuse is both a risk factor and an important barrier to effective treatment (the latter will be discussed in a subsequent section of this chapter). In a review of substance abuse in FE SSD, Larsen and colleagues (2006) found prevalence rates of 6% to 44% for those who abused drugs and 3% to 35% for those who abused alcohol. Across studies, cannabis appears to be the most commonly used drug, followed by alcohol (Buhler, Hambrecht, Loffler, Van der Heiden, & Hafner, 2002; Cantwell et al., 1999; Green et al., 2004). Substance abuse, in particular cannabis, has been found to increase the risk of developing schizophrenia by up to 6 times (Andreasson, Allebeck, & Rydberg, 1989). In two recent reviews of large population-based, longitudinal studies, cannabis use was noted to double the risk of developing schizophrenia, with the risk increasing in proportion to amount of use (Odds Ratio 2.1-21.7) (Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002), particularly in vulnerable individuals, such as those with a family history of psychosis (Henquet, Murray, Linszen, & van Os, 2005; Smit, Bolier, & Cuijpers, 2004). A number of investigators have postulated that use for several years before the onset of schizophrenia may result in cannabis-induced neurobiological changes and an increased vulnerability to schizophrenia. Meanwhile, cannabis use may trigger or precipitate illness onset in people who have a preexisting vulnerability from genetic, perinatal and environmental factors (Hambrecht & Hafner, 2000; Henquet et al., 2005).

Individuals with SSD who use drugs have been characterized as male and younger as compared to those who do not use drugs (Cantwell et al., 1999; Hambrecht & Hafner, 2000; Larsen et al., 2006; Linszen, Dingemans, & Lenior, 1994), and in particular, those

with a premorbid cannabis use disorder have a lower age at onset of SSD (Addington & Addington, 1998; Buhler et al., 2002; Green et al., 2004; Linszen et al., 1994). However, not all studies have found an association of substance abuse with a younger age at onset (Green et al., 2004; Wade, Harrigan, McGorry, Burgess, & Whelan, 2007).

*Stressful Events*

At the individual level, a sensitivity or vulnerability to stress is often regarded as an important risk factor, one that is at the intersection of biological and social influences on the disorder onset and/or progression. Stress vulnerability has been documented prior to illness onset, during relapse, and in the context of normative daily life events or hassles (Goldman & Mitchell, 2004). Goldstein's (2006) review of the affective arousal system in schizophrenia implicates structural and functional neural abnormalities that are exacerbated by specific endocrine dysfunction, namely, overactivity of the hypothalamic pituitary adrenal (HPA) axis. HPA axis dysfunction may result in neuronal dysfunction and hypersensitivity to stress, as seen in schizophrenia.

Adolescence is a time of endocrine changes and other developmental as well as environmental stresses, (e.g. increased social demands, and the use of alcohol and drugs of abuse). Taken together, an interaction among genetic, developmental and environment risk factors during the perinatal and peri-adolescent period may result in a vulnerability to psychosis and the actual development of psychosis in some individuals (Csernansky & Bardgett, 1998; Keshavan, 1999; Keshavan, Gilbert, & Diwadkar, 2006; McClure & Lieberman, 2003; O'Donnell & Grace, 1998). This model of vulnerability to psychosis suggests that it may be possible to intervene during these early phases to prevent the

progression to psychosis as well as the progression and downward course of the illness (Keshavan, 1999).

### *Goals of Treatment*

The treatment of people in a first episode of schizophrenia is multifaceted and complex, requiring an understanding of many different factors that may influence treatment outcomes. The hope of intensive early treatment in the FE is to increase the number of people who have only one psychotic episode and achieve both symptomatic and functional recovery (about 12%) and decrease relapse rates in those who have multiple episodes (Perkins et al., 2006a). First episode SSD has high rates (approximately 85%) of symptom recovery during the first year after the psychotic episode, but of these patients only 56.7% achieve a second year of symptomatic recovery (Lieberman et al., 1993; Robinson et al., 1999b). This means almost half of the individuals with SSD continue to be afflicted with significant symptoms. Moreover, the functional recovery rate is much lower (37.9%) in the first episode (Robinson, Woerner, McMeniman, Mendelowitz, & Bilder, 2004), with only 10% - 20% of people returning to a level of work at which they can support themselves (McGlashen, 1988). Goals essential to effective, early treatment include reduction of duration of untreated psychosis, maximization of symptomatic and functional recovery through effective treatment, and prevention of relapse (Spencer, Birchwood, & McGovern, 2001). Investigators have demonstrated better outcomes for people in a first episode SSD when treatment is provided within specialized, intensive, treatment programs.

The President's New Freedom Commission on Mental Health (New Freedom Commission on Mental Health, 2003) emphasized the importance of recovery and the

development of resilience as the goal of treatment. Canada, England, Australia and parts of Europe have intensive psychosocial treatment in specialized or integrated clinics for teens and young adults in the FE (Addington & Gleeson, 2005; Lewis, Tarrier, & Drake, 2005; Mullen, Murray, & Happell, 2002; Spencer et al., 2001). Thus far, positive outcomes at these comprehensive specialized clinics have included better medication adherence and increased satisfaction with treatment, and less substance misuse (Penn, Waldheter, Perkins, Mueser, & Lieberman, 2005; Petersen et al., 2005), fewer inpatient days (Cullberg, Levander, Holmqvist, Mattsson, & Wieselgren, 2002), a decrease in the frequency of psychotic episodes (Falloon et al., 1998b) and a decrease in positive and negative symptoms (Sanbrook, Harris, Parada, & Young, 2003). It is clear that specialized treatment programs can improve treatment outcome, but there remain many barriers to effective treatment.

*Barriers to Effective Treatment*

Clinicians and researchers have identified and discussed numerous barriers to effective treatment in the literature. However, the scope of this review will be limited to those that have received the most attention and appear to have the greatest impact. Thus, this review will exclude system barriers such as the relative absence of specialized treatment services in most areas of the US, and the inaccessibility of psychosocial treatments such as cognitive behavioral therapy due to lack of trained personnel in mental health clinics.

Barriers to effective treatment can be viewed as falling into one of three categories: (1) those that result in a delay in diagnosis and treatment; (2) those inherent to the illness and its treatment; and (3) those that may be related to psychosocial factors. Taken

together, these three types of barriers affect the ability of people in FE SSD to achieve symptomatic and functional recovery.

*Barrier to Early Diagnosis and Treatment*

Duration of untreated psychosis (DUP) is a concept used to define a time period beginning with the appearance of frank psychotic symptoms and ending with the initiation of antipsychotic medication. DUP itself is not a barrier to early diagnosis and treatment, but constitutes a way of representing a multitude of issues that prevent an individual from seeking treatment, such as delusional beliefs, lack of insight, stigma, and mental health literacy, which are harder to measure. DUP is an important, measurable concept in the field and a shorter DUP is associated with a better response to antipsychotic medication, and improved functional outcome (Perkins, Gu, Boteva, & Lieberman, 2005). The DUP for people with SSD ranges anywhere from 4 weeks to 5 years of untreated psychosis before they start treatment (Eaton & Chen, 2006; Gelber et al., 2004; Perkins et al., 2005). A shorter DUP is associated with an acute onset of psychosis, greater family involvement (Morgan et al., 2006), pre-psychosis employment, and living with a partner (Wunderink, Nienhuis, Sytema, & Wiersma, 2006).

In general, many authors have reported outcomes to be worse (as defined by more symptoms and decreased functioning) in people with a longer DUP (Black et al., 2001; Marshall et al., 2005; Norman, Lewis, & Marshall, 2005). A long DUP has been associated with multiple episodes (Altamura, Bassetti, Sassella, Salvadori, & Mundo, 2001), longer time to remission, poor symptom remission (Loebel et al., 1992; Wunderink et al., 2006), greater severity of negative symptoms (Black et al., 2001; Perkins et al., 2005; Scully, Coakley, Kinsella, & Waddington, 1997), generalized

cognitive impairment (Scully et al., 1997), and severity of positive symptoms (Black et al., 2001). In contrast, investigators have also found that DUP is not associated with remission (Ho, Andreasen, Flaum, Nopoulos, & Miller, 2000), substance abuse (Larsen et al., 2006), neurocognitive functioning (Hoff et al., 2000; Perkins et al., 2005; Rund et al., 2007), or positive symptom severity (Ho et al., 2000; Loebel et al., 1992; Perkins et al., 2005). However, in a critical review, Norman and colleagues (2005) found DUP to be an independent predictor of remission of positive symptoms during the first year of treatment.

Despite all of the studies using DUP as a predictor and a factor associated with treatment response and outcome, very little is known about the actual individual reasons and/or barriers that prevent individuals from seeking treatment at the onset of a first psychotic episode. Psychopathology and psychosocial issues may influence when and how an individual seeks and enters treatment and are issues requiring further study.

*Barriers Inherent to Illness and Its Treatment*

Barriers inherent to the illness and its treatment include individual differences in positive and negative symptoms, the phenomenon of relapse, and medication side effects. Severe positive symptoms are associated with a decrease in treatment response (Robinson et al., 1999b) and a significant correlation between negative symptoms and impaired occupational and social functioning, increased financial dependence, and decreased global level of functioning in FE SSD (Ho, Nopoulos, Flaum, Arndt, & Andreasen, 1998). Meanwhile, each relapse episode requires a longer time to recovery (Lieberman et al., 1993; Szymanski et al., 1995), and higher doses of antipsychotic medication than the previous episode (Lieberman et al., 1993). Moreover, despite the good symptomatic

recovery rates, relapse rates are high in people who have recovered from a first episode of SSD. Robinson and colleagues (1999a) reported a cumulative 5 year first relapse rate of 81.9% and for those who recovered from this first relapse, 78% went on to a second relapse.

Intolerability of antipsychotic medications due to side effects can lead to medication non-adherence (Hudson et al., 2004; Perkins, 2002), particularly with respect to side effects that mimic Parkinsonian symptoms (Robinson et al., 2002), akathisia (Hudson et al., 2004), or cause weight gain, dyslipidemia or diabetes secondary to metabolic syndrome (Lieberman et al., 2005a). Other side effects, such as antipsychotic drug induced dysphoria, sedation, and sexual side effects also play a role in patients choosing to stop their medications (Perkins, 1999, 2002).

*Psychosocial Barriers to Treatment*

In FE SSD barriers to effective treatment and medication adherence includes a lack of insight and understanding of the risks of this chronic illness, difficulty getting to appointments, and a lack of family support (Perkins, 1999, 2002). Patient self-reports of barriers to medication adherence include the stigma of taking medication, forgetfulness, and a lack of social supports (Hudson et al., 2004).

*Negative Attitudes Toward Medication*

Medication non-adherence has also been associated with a negative attitude toward taking medication. For example, Lacro and colleagues (2002) found in their review of studies on medication adherence, that a negative attitude toward medication did predict non-adherence. Predictors of a negative attitude toward medication include less insight about symptoms, primary negative symptoms, and employment (Freudenreich,

Cather, Evins, Henderson, & Goff, 2004). Freudenreich et al. (2004) theorize that the relationship between employment and negative attitude reflects either an increased awareness of side effects and their effect on functioning, or an awareness of the stigma associated with antipsychotic medication as the cause for this negative attitude. Similarly, Hudson et al. (2004) found patients identified the stigma of taking medication as a barrier to medication adherence.

*Other Barriers*

*Substance abuse.* The use of alcohol and drugs in the time period before and after the onset of psychosis presents major challenges to treatment of the first episode. Several investigators who collected follow-up data of first episode substance abusers at the beginning of the psychotic illness found a significant association with poor medication adherence (Buhler et al., 2002; Green et al., 2004; Wade et al., 2007), more severe positive symptoms and poorer social functioning (Hambrecht & Hafner, 2000; Wade et al., 2007). The ongoing use of cannabis is a barrier to effective treatment because it is associated with significantly more relapses (Linszen et al., 1994) and with more re-hospitalizations, inpatient days, and psychopathology (Caspari, 1999). Moreover, medication non-adherence and co-morbid substance abuse caused the highest rates of readmission (57%) over a 4 year period (Hunt, Bergen, & Bashir, 2002).

## *The Problem of Medication and Treatment Non-Adherence*

Medication adherence sets the stage for a return to age appropriate tasks, and an improvement in psychosocial and occupational functioning. Hence, reducing medication non-adherence is an essential treatment goal. Medication non-adherence causes disruption in the process of symptomatic and functional recovery because after a first

episode, each subsequent relapse has been found to require a longer time to recovery than the previous episode (Lieberman et al., 1993; Szymanski et al., 1995), and to require higher doses of antipsychotic medication in subsequent episodes (Lieberman et al., 1993).

During the first year of treatment there is a high rate of medication non-adherence (39%) and inadequate (irregular use of medication) adherence (20%), with only 41% of this population medication-and treatment-adherent (Coldham, Addington, & Addington, 2002). One study of FE SSD and atypical antipsychotic medications found people who stopped antipsychotic medication against medical advice were more likely to be depressed, with ongoing substance abuse and a poor treatment response (Perkins et al., 2008). Additionally, in studies of the typical antipsychotic medications, approximately 40% of patients have stopped taking medication by the end of the first year, and this proportion increases to 75% by two years. However, it is important to note that there is wide variation in how adherence is defined and measured in the literature, from missing one dose to stopping antipsychotic medication (Gray, Wykes, & Gournay, 2002; Lacro et al., 2002; Velligan et al., 2006; Zygmunt, Offson, Boyer, & Mechanic, 2002). Additionally, self report, with questionable reliability, is the most commonly used method to determine adherence as reported in the literature (Velligan et al., 2006). Moreover, the lack of consistent definition and data collection methods are methodological problems that limit generalization across studies of non-adherence.

After stopping medication, approximately 75% of individuals will relapse over one year as compared to a 25% relapse rate for those who continue their medication (Perkins, 1999). The high relapse rates highlight the critical importance of medication adherence. One year later those with non-adherence had significantly more positive

symptoms, higher rates of relapse, more alcohol and cannabis use, less insight into illness/symptoms, and a poorer quality of life (Coldham et al., 2002). Low levels of cognitive functioning during the pre-morbid phase (Robinson et al., 2002) and high levels cognitive disorganization (Perkins, 1999, 2002) may also contribute to failure to take medication as scheduled in the first episode. People with medication non-adherence had an earlier age of onset, poorer pre-morbid functioning, and less family involvement. Compounding the problem of non-adherence, co-morbid substance abuse causes the highest rates of readmission (57%) over a 4 year period (Hunt et al., 2002).

Frequently, individuals in a FE view psychosis as an acute illness and want to stop medication once they have achieved remission of positive symptoms. However, discontinuing antipsychotic medication is not always a realistic or desirable goal even when medication discontinuation is a treatment goal. Wunderink and colleagues (2007) compared two groups (i.e., gradual medication discontinuation versus maintenance treatment) in first-episode patients in remission and found that 43% of the people in the discontinuation group relapsed as compared to 21% of those who received maintenance medication. Overall, only 20% were able to successfully discontinue their medication during the follow-up period of 2 years.

A related barrier is treatment non-adherence such as missed office visits, and failure to follow through with referrals to psychosocial treatment and substance abuse programs. The range of treatment non-adherence varies from refusal to engage in treatment to missed visits resulting in premature termination of treatment (Perkins, 2002). As with medication non-adherence, treatment non-adherence is associated with relapse and re-hospitalization (Perkins, 2002).

Overall, individuals in a FE SSD fail to seek and/or remain in treatment. Regardless of the cause, such as paranoia or other symptom-motivated avoidant behavior, the result is often medication non-adherence and potential relapse. Clearly, adherence to medication is critical for treatment and relapse prevention.

*Clinical Trials: Relevance to Problem of Medication and Treatment Non-Adherence*

What happens in a clinical trial has relevance to the problem of medication and treatment non-adherence in four respects. First, the goal of clinical trials of individuals in a FE SSD has been to identify a more effective antipsychotic medication with fewer side effects. Second, clinical trials of antipsychotic medication provide the knowledge upon which clinicians base their medication and treatment decisions. Third, non-adherence in clinical trials is an under-investigated phenomenon. For example, understanding why patients decide to stop medications is important in preventing medication non-adherence, but understanding the patient's point of view has not traditionally been a clinical priority.

In the largest study to date of the effectiveness of post marketed antipsychotic medications, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, investigators found at the end of the 18 month treatment period that 74% of patients were no longer taking the antipsychotic medication assigned at the start of the study (Lieberman et al., 2005a). The reasons for discontinuation were only collected when the patient and clinician agreed on the reason, but not when the clinician and patient disagreed on the reason. When the clinician and patient disagreed, no reasons were listed other than "patient decision." This is unfortunate as patient decision is by far the most common reason for drug discontinuation (Weiden, 2007).

What happened in the CATIE study is all too common: complete data on reasons

for discontinuation are not collected in clinical trials. Thus, clinical trials drive treatment decisions but provide few or no insights into reasons for non-adherence to these recommendations. Attrition rates from randomized controlled trials (RCT) of antipsychotic medication in young people in a first episode of SSD range from 4% at 6 weeks to 87.9% at 2 years (Crespo-Facorro et al., 2006; Green et al., 2006). These high attrition rates occur despite more frequent study visits than found in usual care, and a proactive approach to the follow-up of missed visits and missed doses of medication. Most commonly, the statistical method of Last Observation Carried Forward (LOCF) is used to replace missing data related to attrition (Leon et al., 2006; Mazumdar et al., 2007; Streiner, 2002; Streiner, 2008; Wood et al., 2004). Attrition rates in clinical trials can be high and the use of statistical methods to replace missing data related to this attrition can create bias in the results (Barnes et al., 2006a).

Investigators have often described the treatment groups in a study as equivalent based on a comparison of baseline scores of severity of psychosis and demographic characteristics. However, we do not know very much about two different groups, those who remained in a study and those who either withdrew or were withdrawn. Thus, it is unclear whether the results of clinical trials are generalizable to all patients with SSD, or only to those who remain in the clinical trial.

### *Conclusions*

In the past fifteen to twenty years, a new focus on the treatment of first episode schizophrenia spectrum disorders has emerged to include an emphasis on early identification of psychosis and intensive treatment in the hope of preventing symptom exacerbation, chronicity and a downward course in psychosocial functioning. The goal of

FE treatment is to decrease the number and frequency of relapses from those rates exhibited by persons diagnosed with chronic schizophrenia, in which 60% of patients have an episodic relapsing course with a decrease in functioning, and 30% have a severe chronic course with unremitting psychosis (Bromet & Fennig, 1999; Huber, Gross, & Schutter, 1975).

The International Early Psychosis Association Writing Group (2005) and Spencer et al (2005; Spencer et al., 2001) identify achieving and maintaining the highest possible level of symptomatic remission and functional recovery as the goal of treatment. In addition to psychosocial treatment strategies, antipsychotic medication use during an acute episode of psychosis as well as during remission to prevent relapse is essential. As such, medication remains the cornerstone of treatment. Symptomatic and functional recovery requires an understanding of the many factors that influence the willingness of a person in a FE SSD to take antipsychotic medication and remain in treatment. Without ongoing effective antipsychotic drug treatment, individuals are often unable to engage in the intensive psychosocial rehabilitation necessary for functional recovery.

One strategy of researchers has been to compare currently available antipsychotic medications in the hope that one will be better tolerated, have fewer side effects and be more efficacious. Moreover, pre-and post-marketing studies attempt to influence the view of which antipsychotic medications are considered first line or the advantages of one medication over another (Green et al., 2006; Lieberman et al., 2003b; Robinson et al., 2006; Sanger et al., 1999; Schooler et al., 2005; Tollefson et al., 1997). However, these studies have high rates of patient attrition and do not identify the differences between those who stay in the clinical trial and those who leave. It is important to move beyond

baseline demographic and psychosis severity and explore the ways that patients who remain in clinical trials differ from those who leave in regards to clinical presentation, risk factors, and barriers to effective treatment.

# CHAPTER 2

## Attrition and its Significance to FE SSD Treatment and Adherence

In the past fifteen to twenty years there has been a refocus in the treatment of first episode (FE) schizophrenia spectrum disorders (SSD) to early identification of psychosis and intensive treatment in the hopes of sustaining remission and preventing relapse. This effort has lead to pre-and post-marketing clinical trials conducted with a specific focus on FE SSD. Attrition rates in these studies are high which makes it difficult to understand the meaning of the study outcomes and to generalize the results (Kane, 2005). This is unfortunate because the results from these clinical trials are used to guide practice.

### *Attrition*

Attrition has been defined as a reduction in numbers (Berube, 1985). In the context of clinical trials, the term attrition has been used to refer to a reduction in numbers due to participant drops outs, including side effects, lack of efficacy, administrative withdrawal, discontinuation, and all cause discontinuation (Holroyd, Powers, & Andrasik, 2005; Leon et al., 2006; Perkins et al., 2008). These descriptors represent the various reasons that researchers might give for participants leaving a clinical trial. Many, but not all, researchers describe the reasons for attrition in their reports, some in detail, some only in broad categories. For example, for the CATIE study, the investigators collected information on all causes of discontinuation, but did not collect the patient's reason for discontinuation if the physician disagreed with patient's reason for stopping medication (Weiden, 2007).

Attrition from a clinical trial can happen at any time during the study, from screening to the double blind treatment phase (see Figure 1). Attrition during screening

can result from poor medication adherence, an inability to comply with study procedures (e.g., too psychotic to follow directions or procedures), or a withdrawal of consent to participate. Some studies include a washout phase that may also result in attrition. Post-randomization attrition may be due to adverse events or a failure to improve (lack of efficacy), medication non-adherence and consent withdrawal. Another form of attrition includes participants who are lost to follow-up, such as those who fail to keep clinic appointments and are non-responsive to phone calls and letters.

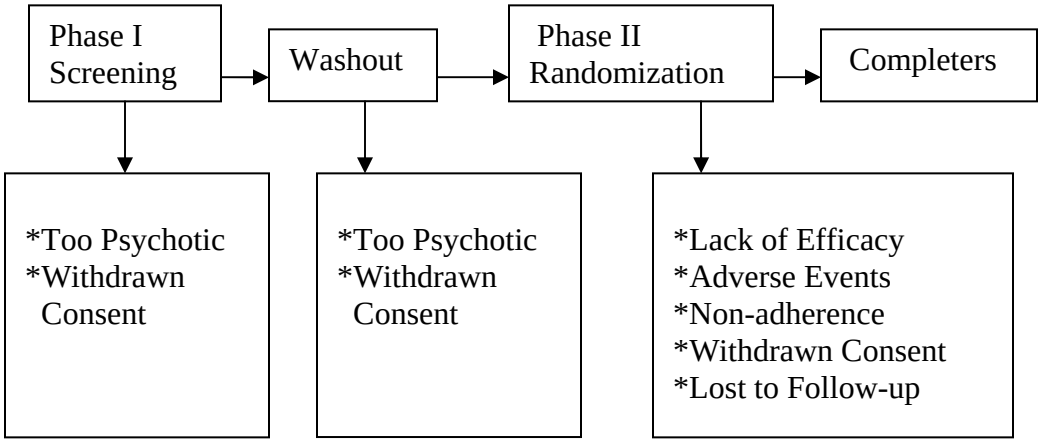



*Figure 1.* Common Causes of Attrition from Clinical Trials at Different Phases

---

*Attrition and Randomized Clinical Trials*

There are multiple factors that might contribute to high attrition rates in clinical trials which can occur at any time during a study (see Figure 1). Additional factors include the length of the clinical trial, variability in protocol design, differences between diagnostic groups, participant characteristics and cultural issues. Attrition rates from

randomized controlled trials (RCT) of antipsychotic medication in young people in a first episode of SSD are high, but vary depending on the length of the clinical trial (see Table 2), ranging from 4% at 6 weeks to 82.3% at 2 years (Crespo-Facorro et al., 2006; Emsley, 1999; Green et al., 2006; Lieberman et al., 2003a; Lieberman et al., 2003b; McEvoy et al., 2007; Robinson et al., 2006; Sanger et al., 1999; Schooler et al., 2005).

The most common reported causes of attrition from these FE studies (see Table 3) is patient withdrawal (mean 18.4%), lack of efficacy (mean 11%), and other causes (mean 9.1%) while the lowest was lost to follow-up (3.7%). However, other causes of attrition are under-reported or rarely addressed. For example, only one study (Lieberman et al., 2003a) reported the number of participants who had signed consent forms as well as those who were randomized to a condition. Most investigators report only the number of participants who are randomized (see Table 4). Consequently, it is not possible to estimate how many individuals signed the consent form but dropped out before they could be randomized. Some of the studies have a washout phase, potentially a time of high risk for attrition, but the researchers do not report on the number of patients who left the study during either the screening or washout phases. The lack of information about attrition rate during washout is unfortunate. This information is important for patient safety among other reasons.

A high attrition rate is not unique to clinical trials involving individuals diagnosed with FE SSD. Other randomized trials of antipsychotic medications for the treatment of schizophrenia also have high attrition rates. Wahlbeck, Tuunainen, Ahokas, and Leucht (2001) examined the dropout rates from 163 drug trials for the treatment of schizophrenia from 1955 to 2000 and found a pooled dropout rate of 33%, with a range of 18.6%

(chlorpromazine) to 44.3% (haloperidol). As in the trials for FE SSD, the dropout rate increased as the length of the trial increased. Investigators have reported similar rates for both typical (41.2% range 9.7% - 65.4%) and atypical antipsychotics (35.5% range 0% - 69.1%) in clinical trials of antipsychotic medications lasting 12 weeks or fewer (Kemmler, Hummer, Widschwendter, & Fleischhacker, 2005).

Attrition rates for schizophrenia treatment trials are generally higher than those observed for trials of other Axis I psychiatric disorders. Khan, Schwartz, Redding, Kolts, and Brown (2007) found the schizophrenia group had the largest attrition rate (51%) of five diagnostic groups (see Table 5). They identified lack of efficacy, adverse events, and loss to follow-up and other causes as the three main reasons for termination for all diagnostic groups. Attrition in the schizophrenia group was more likely due to a lack of efficacy (29%), loss to follow-up and other reasons (21.8%) than it was for the other disorders, but less likely due to adverse events (5.7%). Consistent with the Wahlbeck et al. (2001) analysis, Khan et al. (2007) found a significant ($p<.001$) relationship between the length of the clinical trial and completion rates for the schizophrenia group only, but not the other psychiatric diagnostic groups. Thus, the literature regarding attrition in clinical trials involving patients with schizophrenia argues for length of clinical trial, lack of efficacy, and loss to follow-up being critical factors for attrition in FE SSD.

Table 2.

*Attrition Rates for First Episode SSD Clinical Trials*

| Author | Study Site | Study Design | Time | Discontinued (Range) | Imputation Method |
|---|---|---|---|---|---|
| Crespo-Facorro et al., 2006 | Spain | Randomized | 6 weeks | 4.0% (1.8 - 6.6%) | LOCF |
| Emsley, 1999 | International | Double-Blind, Randomized | 6 weeks | 25.6% (20.2 - 30.9%)* | not reported |
| Lieberman et al., 2003a | China | Double-Blind, Randomized | 12 weeks | 10.5% (10 - 11%) | |
| | | | 52 weeks | 18.75% (15 - 22.5%) | LOCF |
| Lieberman et al., 2003b[1] | International | Double-Blind, Randomized | 12 weeks | 39.0% (32 - 46%)* | LOCF |
| Green et al., 2006[1] | | | 26 weeks | 47.5% (40.5 - 54.5%)* | |
| | | | 2 years | 82.3% (76.6 - 87.9%)* | LOCF |
| McEvoy et al., 2007 | US & Canada | Double-Blind, Randomized | 52 weeks | 70.3% (68.4 – 71.4%) | LOCF and Mixed Models |
| Robinson et al., 2006 | United States | Open-label Randomized | 4 months | 28.0% | Survival analysis and ANCOVA |
| Sanger et al., 1999 | International | Double-Blind, Randomized | 6 weeks | 44.8% (27.1 - 62.5%)** | LOCF |
| Schooler et al., 2005 | International | Double-Blind, Randomized | 2 years | 39.3% (36.5 - 42.1%) | not reported |

[1] These two reports are based on the same subsample at different time periods *p<.05, **p<.001

Table 3.

*Reasons Reported for Attrition from First Episode SSD Clinical Trials*

| | | | Reason Reported for Discontinuation | | | | | |
|---|---|---|---|---|---|---|---|---|
| Author | Weeks | Discontinued (%) | Lack of efficacy | Adverse events | Non-adherence | Patient withdrawal | Lost to follow-up | Other* |
| Crespo-Facorro et al., 2006 | 6 | 4.0% | | | | 2.0% | 1.0% | 1.0% |
| Emsley, 1999 | 6 | 25.6% | | 14.5% | | | | 11.1% |
| Lieberman et al., 2003a | 12 | 10.5% | | | | | | |
| | 52 | 18.8% | 1.9% | 5.0% | | 11.9% | | |
| Lieberman et al., 2003b[1] | 12 | 39.0% | 9.1% | 4.5% | | 8.7% | | 16.7% |
| Green et al., 2006[1] | 26 | 47.5% | | | | | | |
| | 104 | 82.2% | 18.3% | 9.9% | 12.6% | 22.8% | 5.3% | 13.3% |
| McEvoy et al., 2007 | 52 | 70.3% | 10.8% | 10.0% | | 41.5% | | 8.0% |
| Robinson et al., 2006 | 17 | 28.0% | 6.0% | | 8.0% | 4.0% | 2.0% | 8.0% |
| Sanger et al., 1999 | 6 | 44.8% | 23.5% | 9.4% | | | | |
| Schooler et al., 2005 | 104 | 39.3% | 7.4% | 5.8% | 2.3% | 11.9% | 6.5% | 5.4% |

[1] These two reports are based on the same sample at different time periods * Ineligible to continue, other causes, or not reported

Table 4.

*Study Methods for First Episode SSD*

| Author | Consented (N) | Randomized (N) | Washout Phase | Study Phases |
|---|---|---|---|---|
| Crespo-Facorro et al., 2006 | | 172 | 3-5 days (for 3 subjects) | Screening, DB* randomization |
| Emsley, 1999 | | 183 | No | Screening, DB randomization |
| Lieberman et al., 2003a | 164 | 160 | No | Screening, DB randomization |
| Lieberman et al., 2003b[1] | | 263 | 2 -14 days | Screening, DB randomization |
| Green et al., 2006[1] | | | | |
| McEvoy et al., 2007 | | 400 | No | Screening, DB randomization |
| Robinson et al., 2006 | | 120 | No | Screening, Open-Label randomization |
| Sanger et al., 1999 | | 83 | 2 - 9 days | Screening, DB randomization |
| Schooler et al., 2005 | | 555 | 3 - 7 days | Screening, DB randomization |

* Double-Blind

[1] These two reports are based on the same sample at different time periods

Table 5.

*Reasons Reported for Attrition from Other Psychiatric Studies*[1]

| | Reason Reported for Discontinuation | | | | | |
|---|---|---|---|---|---|---|
| | Lack of efficacy | | Adverse events | | Lost to follow-up and other reasons | |
| | Placebo | Drug | Placebo | Drug | Placebo | Drug |
| Schizophrenia | 35.0% | 23.0%*** | 5.7% | 5.7% | 19.1% | 21.8% |
| Depression | 14.4% | 6.8%*** | 4.5% | 11.8%*** | 17.5% | 16.2% |
| Generalized Anxiety Disorder | 7.5% | 3.7%* | 8.5% | 19.9%*** | 11.4% | 10.6% |
| Obsessive-Compulsive Disorder | 7.4% | 3.7%*** | 2.5% | 9.0%*** | 8.1% | 9.3% |
| Panic Disorder | 16.5% | 3.9%*** | 6.3% | 12.9%** | 7.7% | 7.2% |

[1]Table adapted from Kahn et al., (2007)
*p=<.05 **p=<.01 ***p=<.001

*Attrition from Non-Psychiatric Clinical Trials*

Six pharmacology clinical trials (see Table 6) (Arnold et al., 2005; Brili et al., 2008; Leung et al., 2007; Mark et al., 2007; Retsch-Bogart et al., 2008; Schreiber et al., 2007) were selected for a comparison with the psychiatric clinical trials because the participants in these trials have a chronic illness that may cause a decrease in level of functioning. Attrition rates from the randomized controlled trials of non-psychiatric medications are lower (22.9%) than from the FE SSD clinical trials (39.1%). The most common cause of attrition from the non-psychiatric studies (see Table 7) is adverse events (mean 12.9%), other causes (mean 10.3%), and patient withdrawal (mean 6.9%), while the lowest was non adherence (2.0%). However, the mean rate for attrition for other causes was inflated by one study in which the study sponsor terminated the study early due to lack of efficacy.

Unfortunately, it is difficult to use information regarding these non-psychiatric clinical trials to inform understanding of attrition in FE SSD group for at least two reasons. First, the FE SSD group and the non-psychiatric group participants differ with respect to mean age (27.4 versus 35.7 respectively). Second, the drug side effect profiles and nature of the illnesses are quite different. Ideally, one would like to compare similar age groups that vary in nature of illness such as participants in clinical trials of medication for Type II diabetes treatment, but such trials have not been conducted. Consequently, it is not possible to disentangle the influences of development and illness characteristics. Thus without additional research, it remains important to consider both age of participant and nature and severity of illness symptoms as potential contributors to the high attrition rates observed in FE SSD.

Table 6.

*Attrition Rates for Non-Psychiatric Clinical Trials*

| Author | Illness | Mean Age | Study Design | Time | Discontinued (Range) | Imputation Method |
|---|---|---|---|---|---|---|
| Arnold et al., 2005 | Fibromyalgia | 46.9 | DB[1], Randomized | 12 weeks | 38.9% (35 - 43%) | LOCF |
| Brili et al., 2008 | Inflammatory process s/p repair coarctation of aorta | 27.3 | Randomized, Crossover with 4 week washout | 12 weeks | 0% | None |
| Leung et al., 2007 | Dyspepsia | 30.8 | DB, Randomized | 12 weeks | 19.7% (19.2 - 20.3%) | Intent to Treat |
| Mark et al., 2007 | Genital Herpes Simplex Virus Type 2 | 39.0 | DB, Randomized | 65 weeks<br>2 years | SP1* 14.9% (10.3 - 19.4%)<br>SP2* 61.3% (58.3 - 64.1%) | Left missing<br>Left missing |
| Retsch-Bogart et al., 2008 | Cystic Fibrosis Pseudomonas | 26.0 | DB, Randomized | 4 weeks | 6.7% | Not included in efficacy data |
| Schreiber et al., 2007 | Ulcerative Colitis | 43.9 | DB, Randomized | 8 weeks | 34.4% (22.6%-43.5%) | LOCF |

* SP1 = Sampling Period 1, SP2 = Sampling Period 2

Table 7.

*Reasons Reported for Attrition from Non-Psychiatric Clinical Trials*

| | | | Reason Reported for Discontinuation | | | | | |
|---|---|---|---|---|---|---|---|---|
| Author | Weeks | Discontinued (%) | Lack of efficacy | Adverse events | Non-adherence | Patient withdrawal | Lost to follow-up | Other |
| Arnold et al., 2005 | 12 | 38.9% | 8.2% | 18.6% | 1.4% | 7.3% | 2.8% | 0.6%* |
| Brili et al., 2008 | 12 | 0% | | | | | | |
| Leung et al., 2007 | 12 | 19.7% | | | | 8.9% | 10.8% | |
| Mark et al., 2007 | 65 | 13.3% | 5.3% | | 1.3% | 4.0% | 2.7% | |
| | 104 | 47.1% | 2.7% | | | 3.0% | 2.7% | 34.7%** |
| Retsch-Bogart et al., 2008 | 4 | 6.7% | | 2.9% | | | | 3.8%*** |
| Schreiber et al., 2007 | 8 | 34.4% | | 17.2% | 3.2% | 11.3% | 0.5% | 2.2%* |

*Protocol Violation **Early termination of study by sponsor ***Reason not report

*Handling Missing Data --Last Observation Carried Forward*

Last Observation Carried Forward (LOCF) is a statistical method commonly used in pharmaceutical studies and accepted by the FDA as a method for handling missing data created by attrition. LOCF allows all participants who completed a baseline and at least one post randomization visit to be included in the data analysis (Barnes et al., 2006a; Mazumdar et al., 2007; Streiner, 2002; Streiner, 2008; Wood et al., 2004). In this method, the participants' last assessment score is entered into all missing visits. LOCF has been a key data analysis tool in FE SSD clinical trials where attrition rates are too high to allow for dropping cases and the cost of replacing participants is prohibitive.

LOCF assumes that no further change in a participant's response will take place once they have dropped from a study, regardless of when they drop. However, this assumption is hard to defend because in real life change is to be expected (Mazumdar et al., 2007; Streiner, 2008; Wood et al., 2004). Moreover, using the last data point fails to make use of all prior data points that could be used to show the direction of change (getting better, worse or no change; (Streiner, 2002).

Most importantly, Barnes, Lindborg and Seaman (2006a) argue that LOCF's use should be limited because its initial intent was meant to introduce bias in the analysis of safety data. When LOCF is used in the analysis of safety data, early drops due to adverse events bias statistical results against a drug, creating a bias in the direction toward safety. Applying this same technique to efficacy data analysis can introduce bias in an unknown direction, affecting validity of study findings (Barnes et al., 2006a). This bias is more pronounced if the attrition rates are different for each drug treatment group and if the drops occur at different times during the study (Mazumdar et al., 1999). In FE SSD

clinical trials there can be significant differences in post randomization attrition rates for each drug treatment group. For example, Sanger (1999) and Emsley (1999) found a statistically significant difference in attrition rates between the study drugs. Lieberman et al. (2003b) report a statistically significant difference in attrition between the two study drugs at 12 weeks. In the long- term continuation phase of that study, Green et al. (2006) report the differences in attrition rates due to adverse events and lost to follow-up. It should be noted here that two researchers (Green et al., 2006; McEvoy et al., 2007) used observed case analysis, a mixed models technique, and LOCF. Green et al., (2006) only reported the results from the mixed models because the results were not "substantially different" from the LOCF analysis. McEvoy et al., (2007) report comparing the results of mixed models and LOCF methods but the results of this comparison are not noted. Finally, most FE SSD clinical trials do not provide data as to the attrition rate prior to randomization creating the possibility of undetectable differences in attrition rates (see Table 3).

It is important to note attrition from psychiatric studies is usually not random but related to the medication, such as side effects and lack of efficacy, or to the study procedures such as subject burden (Mazumdar et al., 2007). Non-random missing data, often referred to as 'nonignorable missingness', differs from data missing at random in that the latter can be ignored whereas the former cannot (Mazumdar et al., 2007; Streiner, 2008). Imputation of missing data using LOCF implies that all data are missing at random regardless of whether or not such data meet the criteria for being missing at random (Leon et al., 2006; Mazumdar et al., 2007; Sheiner, 2002).

In the literature, there are different models for operationalizing LOCF. In a

reanalysis of several large clinical trials of atypical antipsychotic medication as compared to a typical antipsychotic, Leucht, Engel, Bauml, and Davis (2007) compared three different models of LOCF, and a fourth non LOCF method which analyzed only those participants who had completed the study. The first LOCF method included all randomized participants in the data analysis. This model is the closest to the more common practice of including only those participants who completed at least one post randomization visit, a method thought to bias against a drug with very early attrition due to early onset side effects. Haloperidol is one example of an antipsychotic with early onset side effects where this bias could be seen. The second LOCF model excluded only the adverse events attrition group from the data analysis. The third LOCF model excluded the whole attrition group except for those with a lack of efficacy.

Leucht et al. (2007) compared results for their four models for handling missing data under two different conditions: (a) data pooled across multiple studies; and (b) data analyzed separately for each study. When data were pooled across studies, the researchers did not find a difference in effect size between the various models. However, when they analyzed the data separately, the use of the first LOCF model (similar to the approach most frequently used in FE SSD research) resulted in higher effect sizes in favor of the atypical antipsychotic medications in 50% of the study data sets. The authors concluded further study comparing results using other statistical methods was needed.

In summary, although LOCF has been a key data analysis tool in FE SSD clinical trials where attrition rates are high, its use may result in biased results where the direction of the bias is variable (Leon et al., 2006). Potentially more problematic is that LOCF ignores other variables that may impact attrition. Furthermore LOCF keeps the

focus on the potentially biased outcome rather than on the individuals in the completion and attrition groups of clinical trials. Changing the focus to understanding the differences between those participants who stay and those who leave the study may help to inform clinicians of the demographic, illness and treatment characteristics of persons most likely to tolerate and perhaps benefit from an antipsychotic medication.

### *Overview of Proposed Study*

The aim of this study is to: (1) evaluate the differences between those FE SSD participants who remain in a study and those who leave with respect to their demographic, illness and treatment characteristics; (2) evaluate the effect size for all of the variables and independently for each of the three studies. The attrition and non-attrition groups will be evaluated for differences in factors that effect outcomes such as cognitive deficits, substance use, and severity of positive and negative symptoms.

This study is a secondary analysis of a group of FE SSD participants enrolled in one of three separate double-blind, randomized, drug trials. These studies are typical and representative of other studies of FE SSD found in the literature. Two of the studies used in this analysis were investigator-initiated pharmaceutical-sponsored (Eli Lilly and AstraZeneca) multi-site studies of people in a first episode of SSD. The third study, funded by the National Institute of Mental Health (RO1 MH52376), studied the efficacy and safety of clozapine versus haloperidol in first episode schizophrenia.

### *Research Questions*

The following research questions will be addressed:

1. What are the demographic profiles, illness and treatment characteristics of the participants in the three double-blind randomized drug trials?

2. To what extent do patients' demographic profiles, illness and treatment characteristics differ in those who withdraw for any reason and those who remain in the three double-blind randomized drug trials?
3. What is the effect size in analyses comparing those who withdraw and those who remain in terms of their demographic profiles, illness and treatment characteristics in: (a) each of the three double-blind randomized drug trials; and, (b) a merged data set combining all three double-blind randomized drug trials?

For the purposes of this study, demographic characteristics are defined as age, gender, race, marital status, education, employment, median household income and functional health. Illness characteristics are defined as diagnosis, severity of psychiatric symptoms, severity of positive and negative symptoms, substance use, duration of untreated psychosis, number of previous hospitalizations, and cognitive functioning. Treatment characteristics are defined as medication, number of days in a washout phase, and medication adherence.

### *Summary*

Historically, the problem of attrition from clinical trials has not received much, if any attention. There has been a tendency to use LOCF to compensate for the phenomenon of attrition, but questions about the limitations of LOCF have been raised in the statistics literature suggesting its use can be problematic. A secondary data analysis of data from three separate double-blind, randomized drug trials for FE SSD is proposed as a means to shift the focus to the differences between participants who complete a clinical trial and those in the attrition group. A better understanding of the demographic, illness,

and treatment characteristics related to attrition is critical for clinicians and researchers to understand which treatment works best for which people and may lead to more effective early intervention for patients in first episode schizophrenia spectrum disorders.

# CHAPTER 3

## Methods

### *Study Design and Procedures*

#### *Sample*

For this secondary analysis, data will be integrated from three different randomized, double-blind treatment studies of first episode schizophrenia spectrum disorders (FE SSD) and analyzed using SPSS 16 (Statistical Programs for Social Science) (SPSS, 2008). The studies took place at an academic clinical research unit based in a community mental health center. Studies with an inpatient component occurred on a dedicated inpatient research unit and outpatient visits at offices in the same facility. Appendix A contains written documentation of permission to work with study data and institutional review board approvals. Appendix B contains a description of the study phases and attrition rates for all three studies. For the purpose of this study consented includes everyone who signed a consent form and evaluable refers to people who completed diagnostic workup and were included in this analysis if they met criteria for FE SSD. Between screening and randomization two studies had a taper and washout phase (see description of each individual study).

Participants in all three studies met criteria for DSM-III-R (American Psychiatric Association, 1987) or DSM-IV (American Psychiatric Association, 1994) diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder, and were comprised of men and women between the ages 18 and 45. All participants had psychotic symptoms that had persisted for at least one month and no longer than five years without entering a second psychotic episode. Women of childbearing potential

agreed to the use of a medically accepted means of contraception. All participants were able to give written informed consent or assent in the case of a legal guardian who then gave the written informed consent.

Exclusion criteria included: (a) past history of psychosis with recovery; (b) substance induced psychotic disorder; (c) non-English speaking; (d) serious and unstable medical illness; and (e) serious suicide risk. The lower age restriction of 18 was, on a case-by-case basis, waived by the Massachusetts Department of Mental Health, and the upper age limit of 45 was designed to exclude the confounding effects of age on the neurocognitive tests. Participants who did not meet inclusion criteria (a) no longer in a first episode, (b) diagnosed with a brief reactive psychosis, an affective psychosis or substance induced psychosis or (c) at randomization did not met severity criteria were not randomized to study medication. Participants were removed from the study by the principal investigator if found to be too psychotic to follow study procedures, and were then treated clinically and discharged to standard clinical care when appropriate.

*Clozapine or Haloperidol in first episode schizophrenia (ClozHal)* Funded by the National Institute of Mental Health (NIMH) (Grant No. R01 MH52376), the “Clozapine and Haloperidol in First Episode Schizophrenia” (no publications as currently in data analysis) is a double-blind, randomized controlled trial of Clozapine and Haloperidol in people with a first episode of schizophrenia. Entry criteria included less than twelve weeks of prior antipsychotic drug exposure and a DSM-III-R (American Psychiatric Association, 1987) diagnosis of schizophrenia. Participants were admitted to an inpatient research unit, gave written informed consent, and entered the screening phase for evaluation of inclusion and exclusion criteria. Once participants met all inclusion and

exclusion criteria, they entered an antipsychotic drug-free washout period for up to two weeks after a taper and discontinuation of antipsychotic medication. Participants were randomized to either clozapine or haloperidol if they met minimal severity criteria. The study medication was started at a cardiac telemetry unit (for 48 hours) to observe for any untoward cardiac effects. Participants were then followed for an acute, double-blind, twelve week treatment phase followed by a two to five year long-term double-blind treatment phase.

*The acute and long-term efficacy of Olanzapine in first episode psychotic disorders: A randomized double-blind comparison with haloperidol (OlzHal)*. Funded by Eli Lilly, "The Acute and Long-term Efficacy of Olanzapine in First Episode Psychotic Disorders" (Green et al., 2006; Keefe et al., 2006a; Lieberman et al., 2003b) is a double-blind, randomized controlled trial conducted at fourteen academic medical centers in the United States and Western Europe for up to two years. Olanzapine was compared with haloperidol in people with a first episode of schizophrenia, schizoaffective disorder or schizophreniform disorder (American Psychiatric Association, 1994) with less than sixteen weeks of prior antipsychotic drug exposure. Participants were admitted to the inpatient research unit, gave informed consent, and entered the screening phase. If screening criteria were met, antipsychotic medication was tapered and discontinued for a drug-free washout period of two days to two weeks. Only those persons who met a minimum severity score at baseline were randomized to study drug (olanzapine or haloperidol). A twelve week acute treatment phase was followed by a long-term, double-blind treatment phase for a total of two years. Participants could be followed on an open label medication phase for up to six months if their symptoms met the severity criteria

(greater than or equal to their baseline score at two consecutive visits at visit 11 (week 12) or anytime in the long term phase.

*Efficacy and tolerability of Olanzapine, Quetiapine and Risperidone in the treatment of first episode psychosis: A randomized double blind 52-week comparison (OlzQueRis)*. Funded by AstraZeneca, this investigator-initiated study entitled "Efficacy and tolerability of Olanzapine, Quetiapine and Risperidone in the treatment of first episode psychosis: A randomized double-blind 52-week comparison" (Keefe et al., 2007; McEvoy et al., 2007; Perkins et al., 2008) was designed for people in a first episode of schizophrenia, schizoaffective disorder or schizophreniform disorder (American Psychiatric Association, 1994), with less than 26 weeks of prior antipsychotic drug exposure. This study had twenty six sites in the US and Canada with a double-blind assessment period of one year. Participants giving informed consent entered the screening phase. This study did not have a drug taper or washout period because it was conducted on an outpatient basis. Baseline evaluations were completed and participants were randomized to study drug (quetiapine, olanzapine or risperidone) for a 52-weeks double-blind, treatment phase.

*Protection of Human Subjects*

All data to be used in this secondary analysis came from patients who signed a written informed consent form for one of the three studies. If found to be incompetent and their inpatient treatment team agreed to the need for a guardian, then legal guardianship was obtained with approval to treat with the study medications. Patients between the ages of 17 to 18 provided written assent and their parents/guardians signed the written consent form. All staff have received training and are in compliance with

good clinical practices as described by the United States Food and Drug Administration (FDA). Approval was obtained by the Boston College and Beth Israel Deaconess Medical Center institutional review boards for protection of human subjects for this secondary analysis of previously collected data (see Appendix A).

*Data Protection*

The research records used in this study are the property of Alan I. Green, MD of the Commonwealth Research Center of Beth Israel Deaconess Medical Center and kept in secure, limited access offices. The database for this analysis is deidentified, does not contain date of birth or zip code information, and is maintained on a password protected computer (PC). The database will be kept on a password protected computer at the Commonwealth Research Center of Beth Israel Deaconess Medical Center at the completion of this dissertation.

*Study Variables*

Appendices C, D and E describe how each variable was measured in the three data sets, and how each is defined for the proposed analyses. If a particular variable was not entered into the data file, it was constructed through a review of the research source documents (e.g., admission and discharge summaries and progress notes) and a data collection form was developed by the researcher to facilitate chart review for, and construction of, these variables (see Appendix F).

Operational Definitions (see Appendices C, D, and E for coding)

*Independent (or Grouping) Variables*

*Attrition* was defined as those who left or did not complete the study for any reason (0 or No), and those who completed 24 weeks of the double-blind phase (1 or

Yes). It was a dichotomous grouping variable for questions 2 and 3.

*Research studies* are defined as the three double-blind randomized studies that were combined for this study ClozHal (1), OlzHal (2), OlzQueRis (3) and were used as a grouping variable for questions 1 and 3.

*Dependent Variables*

A. *Demographic characteristics.* (see Appendix C for demographics form)

Demographic information was reported by participant and documented in the study records. Categories were collapsed as appropriate to the data. The name of the variable used in the tables is noted in parentheses. For purposes of this study, the following operational definitions and/or measures of the demographic variables of interest were used:

*Age* (Age) is the number of years living.

*Gender* (Gender) is the sex of the participant. It is coded as 0 for male and 1 for female.

*Race and/or ethnicity* (Race) is based on the participant's self report and uses the following categories: Caucasian (1), African American (2), Asian (3), or Hispanic (4).

*Marital Status* (Marital Status) is the participants' self-reported current marital status. It is coded as single/never married (1), married/common law (2), separated (3), divorced (4). In study analyses used to address the study questions, these categories are collapsed into (0) never married and (1) ever married.

*Education* is measured in three ways. First, an ordinal measure for school attendance (School Attendance) is used for the 12 months prior to baseline. Values are assigned as follows: not in school (0); in GED/HS classes (1); in college/graduate school

(2). Second, a continuous measure, the total number of years of education completed (Education [years]). The third measure of education, left school, is dichotomous (Left School). Participants are coded as a 1 if they left school due to symptoms under study and a 0 if they did not.

*Living situation* (Living Situation [past year]) is defined as the place where a person is living. It is measured on an ordinal scale. Values are assigned as follows: independent living (1); dormitory (2); family (3); homeless living in a shelter or on the street (4) as the highest level in the year prior to baseline and in the month prior to baseline.

*Employment* is defined as the type of work (including working for wages, or as a volunteer, or attending school) and measured in two different ways. Data for both measures were collected from demographic, admission history forms and weekly assessments. Two levels of employment, first a dichotomous measure (Employment Status [past year]), unemployed due to study disease disability (0) or working for pay/student (1) was collected for the year prior to baseline and one month prior to baseline. The second variable for employment is measured as a continuous variable in terms of the number of hours worked (Hours Employed) for the highest level in the year prior to baseline.

*Functional Level* (Functional Level [past year]) is defined as the percentage of time spent in any educational, occupational, social or productive activity and is measured at the highest level during the year prior to baseline and one month prior to baseline. Educational, occupational, and social activities include time spent working, going to school, housekeeping/activities of daily living and volunteer work. Data for this measure

are obtained from the demographic and history forms. These data are recorded on an ordinal scale as: no useful functioning (1); >0 to ≤25% of time (2); >25% to ≤50% (3); >50% to ≤75% (4); >75% to 100% (5).

*Median Household Income* (Median Household Income) is identified based on US government census data on zip code and street name (United States Census Bureau, 2000). If a street crosses several income categories the average of those income categories were used. The actual zip code number was not entered into the data base. The median income level, associated with the zip code was entered.

B. *Illness Characteristics* (see Appendix D). For purposes of this study, the following definitions were used to describe participants' in relation to the characteristics of their psychiatric illnesses:

*Psychiatric Axis I Diagnosis* is defined as a DSM-III-R (American Psychiatric Association, 1987) or DSM-IV (American Psychiatric Association, 1994) diagnosis of Schizophrenia, Schizophreniform, or Schizoaffective Disorder. This diagnosis was determined by the use of the Structured Clinical Interview for DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 1997), a semi-structured clinical interview for Axis I disorders in all of the studies except for the ClozHal, for which investigators used the Schedule of Affective and Schizophrenia Disorders (SADS) (Spitzer, Endicott, & Robins, 1975). The SADS resulted in a DSM-III-R (American Psychiatric Association, 1987) diagnosis of schizophrenia.

*Age at onset of psychosis* (Age at Onset) is the number of years living at onset of psychosis.

*Severity of Psychiatric Symptoms* is measured by one continuous variable at two

time points: screening and baseline by the Clinical Global Impression – Severity for all three studies (Clinical Global Impression - Screening) (Clinical Global Impression - Baseline).

*The Clinical Global Impression* (CGI) (Guy, 1976) is a single rating of severity of illness coded on a 7-point scale (1 = normal, not at all ill to 7 = among the most extremely ill patients) where the overall severity of symptoms is measured within the context of other people with a diagnosis of a SSD during the previous week. The CGI is completed during the clinical rater's interview. The CGI severity, a single item scale, is reliably correlated with the BPRS and the PANSS (Leucht et al., 2006; Leucht et al., 2005; Mortimer, 2007), frequently used measures of severity. Validity was .71 and the CGI has been shown to be a valid measure of clinical effectiveness and appropriate for clinical use (Berk et al., 2008).

*Duration of Untreated Psychosis (DUP*) (Duration of Untreated Psychosis) is measured in weeks based on the difference in dates between the onset of the first psychotic symptom and the first use of an antipsychotic medication in all three studies. DUP was identified using a consensus rating by senior clinical staff members of the Commonwealth Research Center based on definitions of illness onset as defined by Keshavan and Schooler (1992) and Larsen, McGlashen and Moe (1996). Information was obtained from clinical interviews, medical record review, and interviews with parents and family members whenever possible. DUP is an interval level variable coded from 0 to 208 weeks.

*Number of previous psychiatric hospitalizations* (Psychiatric Hospitalizations) is defined as the number of inpatient psychiatric hospitalizations prior to entry into the

study. It is collected from a review of research records.

*Substance Use* is assessed separately for alcohol, marijuana, cocaine, opiates, PCP, LSD and amphetamines. Use of each substance was measured in three different ways. First, lifetime use coded as absent (0), use (1), abuse (2), or dependence (3) was determined using information from the SCID in the OlzHal and OlzQueRis studies and the SADS in the ClozHal. Both the SCID and SADS have comparable substance use sections that allow collection of lifetime substance use (Lifetime Alcohol) (Lifetime Marijuana) (Lifetime Other Drugs). Second, the Alcohol Use Scale/Drug Use Scale (AUS/DUS) (Drake et al., 1990) was used to retrospectively measure substance use in the month prior to study and during the double-blind phase. The AUS/DUS consists of one-item using a five-item response scale ranging from and coded as 1 (abstinent) to 5 (dependence with hospitalization). The AUS/DUS was only used in the OlzQueRis study. However, it can be used to generate a rating from the participant's research records for the month prior to baseline. Third, two continuous variables, age at first alcohol use (Age Alcohol) and age at first marijuana use (Age Marijuana) will be measured in years. The drug groups (other than alcohol and marijuana) may be combined if use frequencies are too low (e.g. less than 10%) for any individual drug. Inter-rater reliability was .85 for current and .72 for lifetime substance use disorders (Drake et al., 1990).

*Cognitive Functioning* is defined by the domains of intellectual, attention, executive, language, memory, and motor functioning and was measured using standard neuropsychological tests. All tests were conducted prior to baseline and start of randomized medication. These tests provide/generate a composite score for each domain. In two of the domains (executive functioning and language) each study used the same

neuropsychological test, but in each of the remaining domains two different tests were used. In neuropsychological testing there are many different tests to measure individual domain functioning and it is not unusual for different tests to be combined under a domain. Between the three studies, there was no more than two tests used within a domain. The two tests, within a domain, are considered comparable because they measure the same domain functioning and results are coded as standardized scores and percentile rank which are comparable across studies (Lezak, 1995; Spreen & Strauss, 1998d). The neuropsychological tests used in each domain are described below and the individual study noted.

*Intellectual Functioning* (Intellectual Functioning) is based on an estimated premorbid IQ obtained using two different neuropsychological tests:

1. Wide Range Achievement Test, Third Edition (WRAT 3) (Spreen & Strauss, 1998e) reading subscale, standardized scores and percentile rank (ClozHal, OlzQueRis). The test-retest reliability of the WRAT 3 was .97 and construct validity for WRAT 3 total reading score was .69 (Wilkinson, 1993).
2. North American Adult Reading Test (NAART) Second Edition (Spreen & Strauss, 1998c), number of errors was used to derive a Wechsler Adult Intelligence Test - Revised (WAIS-R) estimated premorbid IQ score (OlzHal) (Nelson & Willison, 1991) using standardized scores and percentile rank. Test-retest reliability was above .98 (Crawford, Stewart, Besson, Parker, & De Lacey, 1989) and validity (.85) was high for general intelligence (Crawford, Stewart, Cochrane, Parker, & Besson, 1989). The WRAT-R and the NAART estimated premorbid IQ is highly correlated (.80) (Johnstone, Callahan, Kapila, & Bouman, 1996).

*Executive Functioning* is based on the Wisconsin Card Sort, 64 card version (WCST- 64) (Heaton, Chelune, Talley, Key, & Curtiss, 1993; Lezak, 1995) using percentile rank of perseverative responses (Executive Functioning – Perseverative) and total number of categories completed (Executive Functioning – Total Categories) in all three studies (ClozHal, OlzHal, OlzQueRis). Test re-test reliability was .94 (Heaton, 1981) and found the WCST to be a valid measure of executive functioning in schizophrenia (.70) (Sullivan et al., 1993).

*Language Functioning* (Language Functioning) is based on the Controlled Word Association Test (COWAT - FAS) the total number of correct words and percentile score for the letters F, A, S using education, age and gender adjusted norms (Spreen & Strauss, 1998a) in all three studies (ClozHal, OlzHal, OlzQueRis). Test-retest reliability was .74 (Ruff, Light, Parker, & Levin, 1996) and .84 (Ross et al., 2007) with construct validity.

*Memory Functioning* (Memory Functioning) is based on two different neuropsychological tests that have been found to be highly correlated:

1. Wechsler Memory Scale – Revised (WMS-R) (Wechsler, 1987) Logical Memory (LM1) subtest standardized scores and percentile rank of immediate recall (ClozHal, OlzHal). Immediate recall was used from the LM1 test because the Hopkins Verbal Learning Test (HVLT) only involved immediate recall. Additionally, only the A (1) form of LM was used at baseline so the immediate recall score was prorated by multiplying by two and then standardized scores and percentile rank were obtained from the WMS-R manual (Wechsler, 1987). Inter-rater reliability for LM1 are .74 and .99 (Wechsler, 1987). Validity for a standardization sample was .52 and .76 for a mixed clinical sample (Russell, 1982).

2. Hopkins Verbal Learning Test (Brandt & Benedict, 2001), sum of the number of items recalled on each trial (OlzQueRis) using standardized T-scores and percentile rank score. The T- score was obtained from the raw score using the manual (Brandt & Benedict, 2001). The T-scores were converted to percentile rank (Spreen & Strauss, 1998d). Validity between the HVLT-R and LM1 immediate total recall found significant correlations (Pearson .75 $p<.001$) (Shapiro, Benedict, Schretlen, & Brandt, 1999) and test-retest reliability for total recall at .74, $p<.001$ (Benedict, Schretlen, Groninger, & Brandt, 1998).

*Motor Functioning* (Motor Functioning) is based on two highly correlated measures of motor speed for the dominant hand in the three studies:

1. Finger Tapping (Heaton, Grant, & Matthews, 1992), standardized T scores and percentile rank for dominant hand only (ClozHal, OlzHal). Test-retest evaluation found reliability coefficients for dominant hand .64 and non-dominant hand .87 (Goldstein & Watson, 1989). Finger tapping test has been shown to be correlated (.78) with a pegboard task (Triggs, Calvanio, Levin, Heaton, & Heilman, 2000) even though they load on different dimensions of manual proficiency (Stanford & Barratt, 1996).

2. Grooved Pegboard version used in the OlzQueRis study involved inserting pegs for two minutes using the dominant hand only. The resultant score is based on the average number of pegs inserted in two minutes for two trials for dominant hand (OlzQueRis). Z-scores were calculated based on data for patients with schizophrenia and normative data (patient score minus the control mean/control standard deviation) (Keefe et al., 2006b). The calculated Z-scores were converted to percentile rank (Spreen & Strauss, 1998d). Test-retest reliability was .82 (Kelland, Lewis, & Gurevitch, 1992). Schear &

Sato (1989) found a modest relationship (-.35) with finger tapping. It has been found to be more closely related to finger tapping than to grip strength (Corey, Hurley, & Foundas, 2001).

*Visual Attention Functioning* (Visual Attention Functioning) is based on two different neuropsychological tests:

1. Cancellation Test (Mesulam, 1985) (ClozHal) does not have standardized normative data. Instead the scoring is based on two components of the test, the organization score and the time it takes to complete the task. There are standardized rules for scoring the organization of the search on two different forms (letters or symbols). A normal search organization is systematic and mostly systematic, and an abnormal search organization is mostly unsystematic and unsystematic. A normal time to completion should be $\leq$ 120 seconds, scores above that are labeled as abnormal (Weintraub, 2000). This result in four scores, two for organization (one for letter cancellation and one for symbol cancellation) and the time to completion for each of the forms of the test. The following rule was applied, any abnormal score or time resulted in a final score of abnormal and no abnormal score or time was rated as normal. Reliability and validity data are not available for this test of spatial scanning ability but it has been widely used in neurology (Mesulam, 1985).

2. The Visual Continuous Performance Test (CPT), identical pairs (IP) version, d' prime (CPT-IP response sensitivity) for each of three conditions (2, 3 and 4 digit numbers) (OlzHal, OlzQueRis) (Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988) does not have published normative data. Instead, normative guidelines for people in a FE SSD were provided by Dr. Cornblatt (personal communication November 24, 2008). Dr

Cornblatt did not report reliability and validity data for this earlier version of the test. The average d'prime score was rated as normal (≥2.5), and mild to moderate impairment (1.8-2.4) and severe impairment (<1.7) as abnormal.

C. *Treatment Characteristics* for the participants are based on the following: (see Appendix E)

*Participation* is defined as the length of time participants remained in the study and is measured by one dichotomous variable and one continuous variable. The dichotomous variable (Termination Phase) describes the phase when participant left the study: early withdrawal (1) and double-blind (2). Early withdrawal is defined as occurring during the screening, washout and baseline study visit prior to taking the first dose of study medication. Double-blind withdrawal is defined as leaving the study during the 24 weeks of double blind medication treatment excluding the baseline visit. The second measure, completion weeks creates a continuous variable. It measures the number of weeks the participant completed in the double-blind phase (Double-Blind [weeks]).

*Study termination* is defined as the reason for leaving a study and is measured as a categorical variable (Termination Reason). The value labels for this variable are: 0 = completed study; 1 = adverse event; 2 = lack of efficacy (LOE) - MD perception; 3 = LOE patient & MD agree; 4 = patient withdrew consent; 5 = lost to follow-up; 6 = patient moved; 7 = inclusion/exclusion criteria not met; 8 = too psychotic for study procedures; 9 = requires disallowed medication; 10 = patient stopped study medication; 11 = severity criteria not met. Study termination (Termination [collapsed]) was collapsed into three groups: (1) patient related issues (e.g. patient withdrew consent, lost to follow-up and patient moved), (2) medication related issues (e.g. adverse events, lack of

efficacy), and (3) research design related issues (e.g. inclusion criteria, requires disallowed medication, severity criteria not met).

*Washout* is defined as a period of time during which the patient is taken off of his/her antipsychotic medication. Washout was dichotomized as either having experienced a washout (1) or not having this (0). The continuous variable, number of days without antipsychotic drug treatment, was used to describe the sample (Washout [days]).

*Antipsychotic medication* is defined as two categorical variables. The categories coded for the first variable include not randomized (0), clozapine (1), olanzapine (2), haloperidol (3), quetiapine (4), or risperidone (5). Second, the medication was dichotomized into typical (0 - haloperidol) or atypical (1 - clozapine, olanzapine, quetiapine, and risperidone) medication (Randomized Medication).

*Data Analysis*

Prior to answering the research questions frequencies and percents were calculated for all categorical study variables and mean, standard deviation, median and range for continuous variables. Next, variables with continuous data were checked for the presence of skewness using the Pearson's coefficient of skewness with marked skewness identified if the value is $\geq|1.0|$. Two methods of handling skewed continuous data include the use of a median split or dividing the data into three categories (low, medium and high). The categorical variables were checked to ensure there is a minimum of 10% of the data within a category (Burns & Grove 2001). If there was less than 10% in any category, then categories were collapsed in a manner consistent with and appropriate to the variable.

The variables were first analyzed across the three drug study data sets to determine if the patient populations are comparable across the three studies. If minor or non-statistically significant differences are found, dummy variables were created to capture the effect of variable differences and these variables were entered into all major study analyses. Exploration of the effects of these differences was conducted.

Question 1: "What are the demographic profiles, illness, and treatment characteristics of the participants in the three double-blind randomized drug trials?" and

Question 2: "To what extent do patients' demographic profiles, illness, and treatment characteristics differ in those who withdraw for any reason and those who remain in the three double-blind randomized drug trials?"

Exploratory and descriptive statistics of study participants were conducted in a comparison of the three studies, for the merged group, and for the attrition group and non-attrition group (see Appendix G). For the continuous variables, t-tests (2 groups) or ANOVA (more than 2 groups) were used unless the variables did not meet the assumptions for a t-test. The Welch test was used when the data was not robust to violations of the assumptions (e.g., heterogeneity of variance with unequal group sizes and less than 20 in a group). Mann Whitney U was used when there were small but equal sized groups (less than 20). Levene's statistic was evaluated for unequal variance between the groups. As this is a pilot study there will be some leeway on identifying factors that may be related to attrition. Because this is an exploratory analysis of data a post hoc power analysis was done to evaluate if there is sufficient power to reject the null hypotheses (Huck, 2008).

Question 3: "What is the effect size in analyses comparing those who withdraw and those who remain in terms of their demographic profiles, illness and treatment characteristics in: (a) each of the three double-blind randomized drug trials; and, (b) a merged data set combining all three double-blind randomized drug trials?"

Effect sizes (Cohen's d) were calculated for each variable in the merged data for the attrition and non-attrition groups, and independently for the attrition and non-attrition groups for each of the three double-blind randomized drug trials. Because there were five different drugs under study and the sample size is small differences between the individual drugs and the attrition and non-attrition groups were not done. Instead, effect sizes were used to evaluate the magnitude of change between the two groups and to evaluate for variation in effect size between the three studies as compared to the merged sample. The criteria used for the effect size was small (> .20), medium (> .50), and large (> .80) (Huck, 2008).

The effect size (Cohen's d) for the continuous variables was calculated using an online effect size calculator (see appendix H) (Becker, 2000). The formula $ES = 2\sqrt{\frac{\chi^2}{N - \chi^2}}$ was used for the calculation of Cohen's d from categorical variables (Chi Square 2x2 only and Fisher's Exact) (Lipsey & Wilson, 2001). In this formula ES= effect size; $X^2$=Pearson's Chi Square; and N = the sample size.

It is recommended that Chi Square analysis for > 2 x 2 contingency table not be calculated. Even with two dichotomous variables there is an attenuation of the correlation coefficient. This attenuation is increased when there is increased skew, greater

than a 50/50 split. This attenuation restricts the correlation coefficient (<.80) and the attenuation worsens when the two variables have more than two values (> 2 x 2 contingency table) to the point of being unreliable (Lipsey & Wilson, 2001). Effect size calculation for the variables analyzed using the median (e.g., Mann-Whitney U) will use the mean instead as there is not a formula for effect size with the median (R. Mesholam-Gately, PhD, verbal communication, January 17, 2009).

# CHAPTER 4

## Results

This chapter will first present an explanation of how the data was prepared for analysis. Next is a description of the merged three studies to provide an overview of the study population. Each research question is answered in turn with a presentation of the results for the demographic profiles, and illness and treatment characteristics. For the results of the individual studies each study is presented in turn (ClozHal, OlzHal, OlzQueRis).

### *Data preparation*

In preparation for data analysis, the continuous variables were evaluated for skewness and the categorical variables for cell size. In the merged database marked skewness was found and the use of a median split was employed for: (1) duration of untreated psychosis (skewness = 2.139) divided into $\leq$13 and >13 weeks; (2) number of prior psychiatric hospitalizations (skewness = 1.678) divided into <2 or $\geq$2 hospitalizations; and (3) number of days in washout (skewness = 1.968) divided into $\leq$ 3 and > 3 days.

When small cell size was found the cells were collapsed in a manner consistent with the data. The following demographic categorical variables were collapsed into dichotomous variables. Race/Ethnicity became non-Caucasian (0) or Caucasian (1). School attendance in past year became in school (0) or not in school (1). Highest work level became not working (0) or working/student (1). Highest useful functioning became no useful functioning to 25% (0) or 25 – 100% (1).

In the illness characteristics, the lifetime substance use categorical variables were

collapsed into dichotomous variables, no use and use (0) or abuse and dependence (1) and were used in the analysis. Another set of lifetime substance use categorical variables were developed for descriptive purposes to retain the distinction between those with no use and use: no use (0); use (1); and abuse and dependence (2). For the neuropsychological test scores with percentile rank, the scores were converted into the Barona scale which defines below average as < $25^{th}$ percentile and above average as >$74^{th}$ percentile. (Strauss, Sherman, & Spreen, 2006). This division provides a way to categorize the results as below average, average or above average, a more understandable way to interpret the results.

Reason for termination had three different values to describe who made the decision to terminate the study for a lack of efficacy (by MD, by patient, or by agreement between patient and MD). These were combined into one value, lack of efficacy. This variable was not used in the analysis but was retained for descriptive purposes.

*Independent or Grouping Variables*

The independent variable attrition was used with the merged database and with each of the studies individually. In the merged database there were 54 (65.8%) people in the attrition group and 28 (34.2%) who completed the twenty four weeks of the study. For complete details on the attrition and non-attrition groups in the merged database see Appendix J, Tables 14 – 16.

Each of the three double-blind randomized studies were analyzed separately. There were 36 participants in the ClozHal with 25 (69.4%) in the attrition group; 29 participants in the OlzHal study with 20 (69%) in the attrition group; and 17 participants in the OlzQueRis study with 9 (52.9%) in the attrition group. For details on the attrition

and non-attrition groups for the ClozHal study see Appendix K, Tables 17 – 19; OlzHal study Appendix L Tables 20 – 22; OlzQueRis study Appendix M Tables 23 – 25.

## Description of the Merged Sample

### *Demographic Characteristics*

This section provides a description of the demographic characteristics for the whole or merged database prior to answering the research questions. A total of 82 people in a first episode (FE) of a schizophrenia spectrum disorder (SSD) participated in one of the three clinical trials. On average the participants were 22.8 years old, predominately male (89%), and never married (96%). The majority were Caucasian (52%) followed by African Americans (28%), Hispanic (15%) and Asian (5%). At baseline the majority were not in school (61%), and the whole group had an average of 12.1 years of completed education. The highest level of school completed included high school diploma or GED (35%), some college (30%) and graduate school (7%) but 27% of this sample never completed high school. Of those who attended college (37%) only 7% graduated. In the group of those in school, 40% had to leave school due to psychiatric symptoms. This sample reflects a wide range of socioeconomic groups with a median household income of $41,186 (in 1999 dollars), based on US census zip code track, with a range of $11,400 to $98,000 (homeless were excluded).

Change in the level of functioning is common in the year prior to hospitalization (see Table 8). During the past year the majority (64%) of the participants reported they were living with family, followed by living independently or in a dormitory (30%) and 5 (6%) were homeless due to psychiatric symptoms. However, in the month prior to baseline there was a decrease in the participants ability to maintain functional role

responsibilities with only 18% living independently and the number of homeless people doubled. Likewise, the number of people working and/or students in the prior 12 months (77%) dropped to 43% in the month prior to hospitalization. Consistent with a deterioration in functional roles prior to entering the study, twice as many participants reported no useful functioning (53%), than in the previous year (22%).

Table 8.

*Demographic Characteristics at 1 Year and 1 Month Prior to Entry to Study*

| Functional Role | 1 year prior to study (N) % | 1 month prior to study (N) % |
|---|---|---|
| Living level | | |
| Independent/Dormitory | (23) 30% | (14) 18% |
| Family | (49) 64% | (54) 69% |
| Homeless, shelter | (5) 6% | (10) 13% |
| Occupational | | |
| Student | (23) 30% | (10) 13% |
| Working for pay | (37) 47% | (23) 30% |
| Unemployed | (18) 23% | (44) 57% |
| Overall level of functioning | | |
| No useful functioning to 25% | (16) 22% | (40) 53% |
| 25% to 75% | (9) 12% | (17) 22% |
| 75% to 100% | (48) 66% | (19) 25% |

*Illness Characteristics*

This section provides a detailed description of the illness characteristics for the whole group prior to answering the research questions. At the time of admission to the study 65% were diagnosed with schizophrenia, 20% schizophreniform and 15% with schizoaffective disorder, with the average onset of psychosis at 21 years of age. At both

screening and baseline the participant's severity of illness was between moderately and markedly ill (mean 4.7 and 4.4 respectively) as measured by the Clinical Global Impression – Severity (CGI). The average duration of untreated psychosis (DUP) was 30 weeks but was skewed (range from 0 to 208 weeks) resulting in the use of a median split (13 weeks) for the analysis. The majority of the participants had one (53%) or two (26%) prior psychiatric hospitalizations (mean 1.75, range 0 to 6).

Table 9.

*Lifetime Substance Use*

| Substance | No Use (N) % | Use (N) % | Abuse (N) % | Dependence (N) % |
|---|---|---|---|---|
| Alcohol | (10) 13.2% | (30) 39.5% | (18) 23.7% | (18) 23.7 |
| Marijuana | (17) 22.1% | (17) 22.1% | (23) 29.9% | (20) 26.0% |
| LSD | (43) 57.3% | (28) 37.3% | (4) 5.3% | - |
| Cocaine | (51) 68.0% | (21) 28.0% | (2) 2.7% | (1) 1.3% |
| Opiates | (67) 89.3% | (7) 9.3% | - | (1) 1.3% |
| Amphetamines | (65) 86.7% | (9) 12.0% | (1) 1.3% | - |
| PCP | (66) 88.0% | (8) 10.7% | (1) 1.3% | - |

The analysis of the merged data on substance use found a similar mean age at first use for alcohol and marijuana (14.5 and 15.1 respectively). Rates of lifetime abuse or dependence (see Table 9) were highest for marijuana (56%), followed by alcohol (47%). Substance use at any level found LSD (43%) and cocaine (32%) to also be high, while

use of opiates (11%), amphetamines (13%) and PCP (12%) was low. Only 22% reported no use of marijuana and 13% stated they had never used alcohol. Use of substances sharply declined in the month prior to entering the study with 74% reporting no use of alcohol or marijuana. During the 24 weeks of the double-blind phase of the study twenty-one participants (34%) resumed use of alcohol and fourteen participants (24%) resumed marijuana use. Despite the heavy lifetime use of other drugs (LSD and cocaine) only one person reported using any other drug during the double-blind phase.

Neurocognitive functioning was divided into six domains: estimated premorbid IQ; visual attention (Cancellation Test or Continuous Performance Test – Identical Pairs); executive functioning (Wisconsin Card Sorting Test, perseverative errors and categories achieved); language (Controlled Word Association Test - letters FAS; verbal memory (Wechsler Memory Scale – Revised, Logical Memory I or Hopkins Verbal Learning Test); and motor speed (Finger Tapping or Grooved Pegboard). The average estimated premorbid IQ for the merged data was 102.8, well within the normal range. The tests with percentile rank scores were converted into the Barona scale which defines below average as < $25^{th}$ percentile and above average as >$74^{th}$ percentile (see Table 10). The Wisconsin Card Sorting Test of executive functioning for the whole group averaged 15.94 perseverative errors, over twice as high as the normal mean norm of 6.92 (SD 5.04) . The average number of categories achieved (2.39) was well below the average norm of 5.58 (SD 1.10) (Strauss et al., 2006).

Table 10.

*Selected Neuropsychological Categorical Test Domains*

| Domain | Below Average (N) % | Average (N) % | Above Average (N) % | Between 3 Studies p |
|---|---|---|---|---|
| Executive functioning Perseverative response | (16) 24.6% | (31) 47.7% | (18) 27.7% | ns |
| Language | (20) 31.7% | (33) 52.4% | (10) 15.9% | ns |
| Verbal Memory | (48) 73.8% | (11) 16.9% | (6) 9.2% | ns |
| Motor speed | (36) 55.4% | (24) 36.9% | (5) 7.7% | ns |
| | Abnormal (N) % | Normal (N) % | | |
| Visual Attention | (39) 68.4% | (18) 32.6% | | .007 |

*Treatment Characteristics*

The treatment characteristics are described in this section for the merged group without any comparisons. Of the original 82 participants, 63 were randomized to study medication: 35% haloperidol (n = 22); 27% olanzapine (n = 17); 25% clozapine (n = 16); 8% risperidone (n = 5); and 5% seroquel (n = 3). For data analysis purposes the randomized drugs were divided into atypical (n = 41, 64.5%) and typical (haloperidol n = 22, 35.5%).

A total of 66% (54) did not complete the study, 23% (19) left before randomization to study medication and 43% (35) left during the double-blind phase. The

mean number of weeks completed in the double-blind phase was 15.7 weeks. Lack of efficacy (31.5%) was the most common medication related reason for leaving the study followed by withdrawal of consent by the participant (22.2%).

*Summary of Merged Sample*

Demographic Profiles

- On average 22.8 years old, predominately male and never married
- Wide range of socioeconomic groups
- Decreasing level of role functioning as participants approached study entry

Illness Characteristics

- Average onset of psychosis at 21 years of age
- Severity of illness was rated as moderately to markedly ill
- History of high use of marijuana, alcohol and other drugs which sharply decreased in month prior to study
- Neuropsychological functioning varied widely from well below average to above average

Treatment Characteristics

- The majority of participants were randomized to atypical agents (64%)
- Attrition rates were high (66%)
- Lack of efficacy and withdrawal of consent were the two most common reasons for attrition

*Question 1:* What are the demographic profiles, illness and treatment characteristics of the participants in the three double-blind, randomized drug trials?

Comparison of the three double-blind, randomized drug trials found statistically significant differences between the three studies in demographic characteristics (see Appendix I, Table 11), illness characteristics (see Appendix I, Table 12), and one treatment characteristic (see Appendix I, Table 13). The significant results will be described in this section. Operational definitions and coding criteria are listed in Appendix C for demographic characteristics. Illness characteristics in Appendix D and treatment characteristics in Appendix E. Results with and without Bonferroni correction will be described for continuous variables when findings are statistically significant.

*Statistically Significant Differences Between the Three Studies*

Demographic characteristics

Median income and highest functioning level in the past year were statistically different between the three studies. The median income was highest in the ClozHal group (M = $49,722) and lowest in the OlzHal group (M = $36,362), Welch ($F = 3.838$, $df = 2,35.325$, $p = .031$) without Bonferroni correction. Post hoc tests with Bonferroni correction found the difference between these two groups to be not significant ($p=.055$), but there is a trend.

Two measures of functioning were found to be significantly different between the three studies. First, employment status, “not working due to disease disability” and “working and/or student”, during the year prior to baseline had the vast majority of the OlzHal study participants working or in school (93%) ($X^2$ (2, n = 78) = 9.200, p = .01) as compared to the OlzQueRis study which had the lowest number of people working or a

student (53.3%). Similarly, the second functional measure, the “percent of time spent in useful activities” (0 to 25% or >25 to 100%) ($X^2$ (2, n = 73) = 6.819, p = .033) found the OlzHal participants to be functioning at the higher level (93.1%) as compared to the OlzQueRis study (61.5%).

Illness Characteristics

The significant illness characteristics between the three studies include severity of illness and three of the neurocognitive domains, estimated premorbid IQ, memory functioning and visual attention. There was a significant difference between the three studies in the severity of illness Welch (F = 6.148, df = 2,34.993, p = .005); post hoc tests with Bonferroni correction found the severity of illness at screening was highest (m = 5.36 markedly ill) for the OlzQueRis than in the ClozHal group (M = 4.62 moderately ill) (F = 5.970, df = 2,69, p = .009) and the OlzHal groups (M = 4.39 moderately ill) (F = 5.970, d.f. = 2,69, p = .006). These findings suggest that the OlzQueRis group was more severely ill at screening than the other two studies. Of note, the mean clinical assessment for the baseline CGI was moderately ill and there was no significant difference between the three studies Welch (F = .282, df = 2,65, p = .761).

The significant findings for the neuropsychological tests will describe each domain separately. The first domain, estimated premorbid IQ, was significantly higher in the OlzQueRis group (M = 107) than in the ClozHal group (M = 101.5), Welch (F = 3.878, df = 2,26.345, p = .033) but post hoc tests with Bonferroni correction found no significant difference between the groups (p = .09).

The second domain, memory functioning (Wechsler Memory Scale – Revised, Logical Memory I or Hopkins Verbal Learning Test) results showed the percentile score

to be strikingly lower in the OlzQueRis group (Hopkins Verbal Learning Test) and significantly different from the other two groups (Logical Memory I) Welch ($F = 23.074$, $df = 2,33.398$, $p < .001$). The homogeneity of variance (Levene) was significant at a .000 level. In post hoc tests with Bonferroni correction, the memory functioning score for the OlzQueRis study was lower than the ClozHal study ($p = .004$) but not significantly different from the OlzHal study ($p = .077$). It is unclear why there is such a difference in scores.

The third significant domain was visual attention (Cancellation Test or Continuous Performance Test – Identical Pairs). The OlzHal group had more participants in the abnormal group (94.4%) ($X^2$ (2, n = 57) = 9.922, p =.007), compared to both the ClozHal (62.1%) and the OlzQueRis groups (40%).

The treatment characteristic, number of days in washout, a dichotomous variable due to skewness in the continuous variable, was significantly different between the ClozHal and the OlzHal groups (Fisher's Exact p = .008). The majority of the participants in the ClozHal study (n = 21, 70%) had fewer days in washout ($\leq$3) and the OlzHal study had the highest percentage of participants (n = 18, 66.7%) in the higher washout group ($\geq$4). Prior to the washout period, the current antipsychotic medication was tapered and stopped in a manner consistent with good clinical practices. In all cases, if someone had a rapid increase in symptoms, the washout period was terminated and randomization to study medication occurred.

Summary of significant differences between the three studies:

Demographic Profiles

- The median income was highest in the ClozHal group and lowest in the OlzHal

group

- The OlzHal group had the highest employment status and functional level
- The OlzQueRis group had the lowest employment status and functional level

Illness Characteristics

- The OlzQueRis group had the highest severity of illness at screening
- The OlzQueRis group had the highest premorbid IQ
- Memory functioning was lowest in the OlzQueRis group
- The majority of OlzHal group had abnormal scores in visual attention while the OlzQueRis group had the least number of abnormal scores

Treatment Characteristics

- The ClozHal group had fewer days in washout

*Question 2:* To what extent do patients' demographic profiles, illness, and treatment characteristics differ in those who withdraw for any reason and those who remain in each of the three double-blind randomized drug trials?

Each of the three double-blind, randomized drug trials were analyzed separately for differences in the attrition and non-attrition groups. Findings for the merged sample and then each of the drug trials are described.

*Attrition vs. Non-attrition Groups*

Merged Data (all three studies)

The sample characteristics for the attrition and non-attrition group for demographic, illness and treatment characteristics can be found in Appendix J Tables 14 – 16 respectively. There were no statistically significant differences between the attrition and non-attrition groups in demographic and illness characteristics in the merged data. There was a significant different between the attrition and non-attrition groups in whether the participant was randomized to typical (haloperidol) or atypical (olanzapine, quetiapine, risperidone, clozapine) antipsychotic medication. One study (OlzQueRis) did not contain a typical antipsychotic medication. The data was analyzed for typical and atypical agents without the OlzQueRis study. Significantly fewer participants on typical antipsychotic medication completed the study (25% n = 22), compared to those receiving an atypical medication (75% n = 41) ($p < .05$) (excluding the OlzQueRis study).

*ClozHal*

ClozHal Demographic Profile

In the demographic profile of the ClozHal study (see Appendix K, Table 17), there were two significant findings, age at study entry and years of education. The

attrition group was modestly but significantly older (M = 23.88) than the non-attrition group (M = 20.09), Levene's test was significant (.006), (t = -3.409, df = 33.307, p = .002). The attrition group also had significantly more years of education (M = 12.68) than the non-attrition group (M=10.81) (t = -2.268, df = 34, p = .03).

ClozHal Illness Characteristics

One illness characteristic (see Appendix K, Table 18), age at onset of psychosis, was significant, with the attrition group older at the onset of psychosis (M = 22.56) than the non-attrition group (M = 18.91) (t = -3.345, df = 33.007, p=.002). Levene's test was significant (.011). There was no significant difference between the attrition and non-attrition groups in any of the other illness characteristics.

ClozHal Treatment Characteristics

Analyses of the treatment characteristics (see Appendix K, Table 19) showed no significant difference between the attrition and non-attrition groups. In the ClozHal study 69.4% (n = 25) did not complete the study with 36% (n = 9) leaving the study before entering the double-blind phase. In the attrition group, participants completed, on average, 8.5 weeks of double-blind treatment (range 1 – 21 weeks). Two reasons for termination, including lack of efficacy and patient withdrawal of consent, occurred most frequently (24% each); the next two most frequent reasons for leaving were adverse events and patients moving away (16% each). Even though it did not reach a level of significance, the majority (81.8%) of the participants who completed the study were taking the atypical agent clozapine (Fisher's Exact = .109). Those who did not complete the study were divided between the typical and atypical agents (56.2% and 43.8% respectively).

ClozHal Summary

The ClozHal attrition group was:

- significantly older at study entry with more years of education
- older at age of onset of psychosis

*OlzHal*

OlzHal Demographic Profile

The demographic profile (see Appendix L, Table 20) showed significant differences between the attrition and non-attrition groups in three variables. Two measures involved education. The first variable measured school attendance in the past year. The second variable measured if the participant left school due to psychiatric illness in the past year. The third variable measured the participants living situation in the past year. In a comparison of the attrition and non-attrition groups, 37.9% (n = 11) were in school in the past year, and all eleven people were in the attrition group (Fisher's Exact p =.005). Likewise, all of the people who left school due to psychiatric illness were in the attrition group (n = 8, 29.6%) (Fisher's Exact p=.026). There was a significant different between the attrition and non-attrition groups and living situation in the past year ($X^2$ (2, n = 29) = 8.112, p = .017). The majority of the people in the attrition group were living with family (70%). Two other demographic characteristics, number of years of education and median household income, approached significance. The majority of the participants were in the attrition group (n = 20, 69%) and had a higher number of years of education (M = 12.9) than those who completed the study (M = 11.6) (p = .066). The attrition group had a lower household income (M = $31,613) than the non-attrition group (M = $45,066) (p = .065).

OlzHal Illness and Treatment Characteristics

There were no significant differences between the attrition and non-attrition groups and illness and treatment characteristics (see Appendix L, Table 21, 22). In the OlzHal study, 62.5% (n = 15) did not complete the study, with 17% (n = 5) leaving the study before entering the double-blind phase. In the attrition group, participants completed an average of 9.3 weeks of double-blind treatment (range 1 – 20 weeks). The most frequent reason for termination from the study was lack of efficacy (n = 10, 50%). The next most frequent reason was patient withdrawal of consent (n = 3, 15%). There was no difference between the attrition and non-attrition groups in type of medication, but 66.7% of the non-attrition group received the atypical agent, olanzapine (p = .423).

OlzHal Summary

The OlzHal attrition group was:

- More likely to be in school in the previous year and to have left school due to psychiatric illness
- More likely to be living with family

*OlzQueRis*

It is important to note this group was small (n = 17), with very small cell sizes. Therefore, these results should be treated tentatively. They are underpowered and the small sample size also limits robustness for violations of statistical assumptions of normality and homogeneity of group variances. Mann-Whitney U was used for the analysis of the continuous variables when they were skewed, the groups were equal in size and if Levene's test of equality of variance was significant. This study had more skewed variables than the other two studies. Data were skewed in age at the onset of the

study (2.048), highest number of hours worked in the past year (4.0), age at onset of psychosis (1.869), and memory functioning (3.182). Levene's test for equality of variance was significant for the baseline CGI (.030) only.

OlzQueRis Demographic Profile and Illness Characteristics

There were no demographic or illness variables (see Appendix M, Table 23 and 24 respectively) on which the two groups differed. There was a trend in the baseline CGI, with the attrition group's mean rank (9.58) higher than the non-attrition group's mean rank (5.94) $z = -1.799$, $p = .072$.

OlzQueRis Treatment Characteristics

There were no significant differences in treatment characteristics between the attrition and non-attrition groups (see Appendix M, Table 25). In the OlzQueRis study, 52.9% (n = 9) did not complete the study with 29.4% (n = 5) leaving the study before entering the double-blind phase. In the attrition group, participants completed an average of 10 weeks of double-blind treatment (range 6 – 12 weeks). The two most frequent reasons for termination from the study were patient withdrawal of consent and lost to follow-up (n = 3, 33.3% each). There were no significant differences between the three atypical medications and the attrition and non-attrition groups.

OlzQueRis Summary

There was no significant difference in the OlzQueRis group between the attrition and non-attrition groups.

## Question 2 Summary

In two of the three groups, educational variables (school attendance in the past year, left school due to psychiatric illness and more years of education) were significantly associated with the attrition group, although the significant variables differed between the studies.

*Question 3:* What is the effect size in analyses comparing those who withdraw and those who remain in terms of their demographic profiles, illness and treatment characteristics in: (a) each of the three double-blind randomized drug trials; and, (b) a merged data set combining all three double-blind randomized drug trials?

*Question 3a:*

Description of Methods

Effect sizes (Cohen's d) were calculated for each variable as described in the methods section. The criteria used for the effect size was small ($\geq$.20 to <.50), medium ($\geq$.50 to <.80), and large ($\geq$.80) (Huck, 2008). Table 26 presents the effect size for the variables in rank order. Effect sizes meeting criteria for small, medium or large are in bold to facilitate ease in reading the table. Effect sizes are not reported for Chi Square analysis with greater than a 2 x 2 contingency table. Significant differences between the attrition and non-attrition groups are noted (e.g., * $p \leq .05$ ** $p \leq .01$ *** $p \leq .001$). Several of the variables did not meet statistical significance but did show a trend, which was noted as well (e.g., $^{1}p \leq .066$ and $^{2}p \leq .089$).

Table 26.

*Effect Size for the Comparison of the Attrition and Non-attrition Groups*[A]

| Dependent Variable | Effect Size Cohen's d | | | |
|---|---|---|---|---|
| | Merged data | ClozHal | OlzHal | OlzQueRis |
| Large ≥ .80 | (N = 82) | (N = 36) | (N = 29) | (N = 17) |
| Motor functioning | **.33** | .18 | **.59** | ***1.66***[1] |
| School Attendance | .10 | **.38** | ***1.23***** | **.73** |
| Severity of illness baseline | .17 | .05 | .16 | ***1.13***[1] |
| Number of years completed education | **.34** | **.70*** | **.65** | ***1.12***[1] |
| Age at start of study | **.28** | ***1.08**** | **.63** | .02 |
| Age at onset of psychosis | .16 | ***1.06**** | **.49** | .04 |
| Left school (past year) | .10 | .09 | ***1.03**** | **.72** |
| Median household income | **.36** | .15 | ***1.02***[1] | **.45** |
| Functional Level | **.32** | .12 | ***.89***[2] | .05 |
| Employment level (past year) | **.20** | .02 | ***.89***[2] | **.40** |
| Intellectual functioning | .17 | **.27** | .11 | ***.86*** |
| Typical versus atypical medication (ClozHal & OlzHal only) | **.62*** | ***.82*** | **.48** | - |

[1] p ≤ .066
[2] p ≤ .089
* p ≤ .05 ** p ≤ .01 *** p ≤ .001
[A] Effect sizes equal to or exceeding the cut off for small (.20), medium (.50) and large (.80) are in bold.

Table 26 (continued).

*Effect Size for the Comparison of the Attrition and Non-attrition Groups*[A]

| Medium ≥ .50 - < .80 | Merged data (N = 82) | ClozHal (N = 36) | OlzHal (N = 29) | OlzQueRis (N = 17) |
|---|---|---|---|---|
| Previous hospitalizations | .17 | ***.51*** | **.41** | ***.72*** |
| Executive functioning – categories achieved | **.34** | .05 | ***.68*** | .11 |
| Alcohol (Age 1st use) | .06 | **.37** | **.30** | ***.68*** |
| Lifetime Marijuana | **.26** | ***.62*** | .10 | **.27** |
| Language functioning | .08 | **.32** | ***.58*** | .11 |
| Marijuana (Age 1st use) | .10 | **.41** | .08 | ***.58*** |
| Executive functioning – perseverative | .19 | .06 | ***.53*** | .12 |
| Employment (hours/week) | .08 | .003 | ***.51*** | **.29** |
| Memory functioning | **.31** | .02 | ***.50*** | .14 |

[A] Effect sizes equal to or exceeding the cut off for small (.20), medium (.50) and large (.80) are in bold.

Table 26 (continued).

*Effect Size for the Comparison of the Attrition and Non-attrition Groups*[A]

| Small ≥ .20 - < .50 | Merged data (N = 82) | ClozHal (N = 36) | OlzHal (N = 29) | OlzQueRis (N = 17) |
|---|---|---|---|---|
| Gender | .18 | .18 | .03 | ***.48*** |
| Screening severity of illness | .05 | .13 | ***.45*** | .05 |
| Race | ***.29*** | .12 | ***.39*** | ***.37*** |
| Lifetime alcohol | .19 | .13 | ***.29*** | ***.39*** |
| Visual Attention functioning | .11 | .06 | ***.39*** | ***.34*** |
| Duration of untreated psychosis | .15 | .06 | ***.37*** | ***.27*** |
| Lifetime use of other drugs | ***.27*** | .17 | ***.22*** | ***.20*** |

[A] Effect sizes equal to or exceeding the cut off for small (.20), medium (.50) and large (.80) are in bold.

*Question 3a: ClozHal*

ClozHal Effect Size - Large

In the demographic profile of the ClozHal study (see Appendix K, Table 17), there were two significant findings, age at study entry and years of education (see Table 26 effect size). The difference in age at study entry showed a large effect size (d = 1.08) with an older attrition group (M = 22.6 as compared to M = 18.9 in non-attrition group).

In the illness characteristics (see Appendix K, Table 18), the attrition group was older at the onset of psychosis (M = 22.56) than the non-attrition group (M = 18.91) with a large effect size (d = 1.06). The treatment characteristic, type of medication, showed a large effect size (d = .82) between the two groups, with the majority of the attrition group receiving a typical antipsychotic (56%) as compared to the non-attrition group (18%).

ClozHal Effect Size - Medium

The demographic profile of the attrition group found significantly more years of education (M = 12.7) with a moderately large effect size (d = .70) as compared to the non-attrition group (M = 10.8). Illness characteristics did not reach statistical significance but did have a medium effect size. Lifetime use of marijuana (p = .141) had a medium effect size (d = .62), with 41% of the attrition group diagnosed with marijuana abuse or dependence as compared to 73% of the non-attrition group. The number of previous hospitalizations did not differ significantly between the groups (p = .137) but had a medium effect size (d = .51), with 56% of the attrition group having one previous hospitalizations as compared to 82% of the non-attrition group. The attrition group had 2 or more previous hospitalization (44%) as compared to the non-attrition group (18%).

ClozHal Effect Size - Small

A non significant demographic variable, school attendance had a small effect size (d = .38) with the majority of the attrition group (65%) not in school in the past year as compared to 46% in the non-attrition group. There was a small effect size (d = .41) for the age at first marijuana use with the attrition group older (M = 15.4, d = 41) as compared to the non-attrition group (M = 14.5). The effect size (d = .37) for mean age at first use of alcohol found the attrition group was older (M = 14.75) as compared to (M = 14) the non-attrition group. The effect size of two neuropsychological tests, language functioning (d = .32) and estimated premorbid IQ (d = .27), were small. Language functioning in the attrition group had a higher percentile score (48.8) than in the non-attrition group (41.5). The estimated premorbid IQ was higher (100.47) in the attrition group as compared to non-attrition group (97).

Summary – ClozHal Effect Size Attrition vs. Non-attrition Groups

With a large effect size, the attrition group:

- was older at study entry (d = 1.08)
- was older at onset of psychosis (d = 1.06)
- was more likely to have received a typical antipsychotic medication (d = .82)

With a medium effect size, the attrition group was:

- was more likely to have more years of education (d = .70)
- was less likely to be diagnosed with marijuana abuse or dependence (d = .62)
- was more likely to have fewer previous psychiatric hospitalizations (d = .51)

With a small effect size, the attrition group:

- was less likely to be in school in the previous year (d = .38)
- was older at first use of marijuana (d = .41) and alcohol (d = .37)
- was more likely to have a higher scores in language function (d = .32) and a higher estimated premorbid IQ (d = .27)

*Question 3a: OlzHal*

OlzHal Effect Size - Large

In the demographic characteristics (see Appendix L, Table 20), there was a significant difference between the attrition and non-attrition groups in three variables (see Table 26 for effect size). Both educational variables had a large effect size, attendance in school in the past year (d = 1.23), and did the participant leave school due to psychiatric illness in the past year (d = 1.03). In the attrition group, 55% were in school in the previous year while 100% of the non-attrition group was not in school. In the attrition group, 56% did not leave school due to psychiatric symptoms as compared to 100% of the non-attrition group. The third variable, living situation in the past year, was not calculated for effect size because it was not a dichotomous variable. Two other demographic characteristics, median household income and years of education approached significance. There was a large effect size for income (d = 1.02), with a lower median income ($29,072) in the attrition group than in the non-attrition group ($43,751). Despite not achieving a significant difference between the groups other demographic variables, functional level and employment status each had a large effect size (d = .89). The majority of both groups were employed or a student functioning at the higher level in both groups (attrition 100%; non-attrition 77.8%).

OlzHal Effect Size - Medium

The demographic profile found years of education to have a medium effect size (d = .65), with more years of education (12.9) in the attrition group than in the non-attrition group (11.6). A medium effect size was found with age at the start of the study (d = .63) and number of hours employed per week (d = .51). The attrition group was younger (M = 22.3) than the non-attrition group (M = 25.4) and working less hours (M = 20.5) than the non-attrition group (M = 30). Medium effect sizes were found for the neuropsychological tests, including executive functioning categories achieved (d = .68), motor functioning (d = .59), language functioning (d = .58), executive functioning perseverative errors (d = .53), and memory functioning (d = .50). The attrition group had lower percentile scores in executive functioning but higher scores in language, memory and motor functioning.

OlzHal Effect Size - Small

It is important to note that the following results reflect small effect sizes and non significant differences. The majority of the attrition group was Caucasian (65% vs 44.4%) with a small effect size (d = .39). For the illness characteristics, age at onset of psychosis (d = .49), and screening severity of illness approached a medium effect size (d = .45). A small effect size was found for duration of untreated psychosis (d = .37), age at first alcohol (d = .30), lifetime use of alcohol (d = .29) and lifetime use of other drugs (d = .22). The attrition group was younger (M = 21.5 vs 23.89) at onset of illness, with a higher screening severity of illness (M = 4.6 vs 4.3) and fewer hospitalizations (d = .41), with 55% of the attrition group with one or no previous hospitalizations versus 33% of the non-attrition group. The attrition group was split between longer (47.2%) and shorter

(52.6%) DUP, while the majority of the non-attrition group had a longer (66.7%) DUP. For the substance use variables the attrition group was slightly older at first alcohol use (M= 14.88 vs 14) and 60% did not meet criteria for alcohol abuse or dependence as compared to 44.4% of the non-attrition group. Only 5% of the attrition group meets criteria for abuse or dependence of other drugs of abuse as compared to 11% in the non-attrition group. In the visual attention domain the vast majority of participants were in the abnormal group for both the attrition (91%) and non-attrition (100%) groups (d = .39). There was no significant difference between the attrition and non-attrition groups in type of medication, but 53.3% of the attrition group were receiving the typical agent, haloperidol (p = .423), while only 33.3% of the non-attrition group were receiving haloperidol, almost reaching a medium effect size (d = .48).

Summary – OlzHal Effect Size Attrition vs. Non-attrition Groups

With a large effect size, the attrition group:

- was less likely to be in school in the past year (d = 1.23)
- was more likely to have left school due to psychiatric symptoms (d = 1.03)
- had a lower income level (d = 1.02)
- was employed or a student (d = .89)

With a medium effect size, the attrition group:

- had more years of education (d = .65)
- was younger at the start of the study (d = .63)
- was more likely to not be working or a student (d = .51)
- had lower scores in executive functioning (categories) (d = .68) and perseverative

errors (d = .53)

- had higher scores in motor (d = .59), language (d = .58), and memory functioning (d = .50)

With a small to medium effect size, the attrition group:

- was more likely to be receiving typical antipsychotic medication (d = .48)
- was younger at the onset of psychosis (d = 49)

With a small effect size, the attrition group:

- was more severely ill at screening (d = .45)
- had fewer previous hospitalizations (d = .41)
- was more likely to be Caucasian (d = .39)
- had fewer abnormal scores in visual attention (d = .39)
- had a shorter DUP (d = .37)
- was older at age of first alcohol use (d = .30)
- had less participants diagnosed with alcohol abuse or dependence (d = .29)
- had more participants with no diagnosis of abuse or dependence of other drugs (d = .22)

*Question 3a: OlzQueRis*

OlzQueRis Effect Size - Large

It is important to remember this group was small (n=17) with very small cell sizes; therefore, these results should be treated tentatively. There were no demographic or illness variables (see Appendix M, Table 23 and 24 respectively) on which the two groups differed. There were several variables with a large effect size including motor

functioning (d = 1.66), baseline severity of illness (d = 1.13), number of years of completed education (d = 1.12) and intellectual functioning (d = .86). The motor functioning percentile score was higher in the attrition group (M = 70.67 vs 35.75). The baseline severity of illness was higher in the attrition group (M = 4.83 vs 3.88). The attrition group had fewer years of completed education (M = 10 vs 12.5). The attrition group had a lower estimated premorbid IQ (M = 101 vs 109.75).

OlzQueRis Effect Size - Medium

There was a medium effect size in two measures of education, school attendance (d = .73) and left school in past year due to psychiatric illness (d = .72). The majority of the participants in the attrition group were not in school (83.3% vs 50%) and did not leave due to illness (71.4% vs 37.5%). Previous psychiatric hospitalizations had a medium effect size (d = .72) with the vast majority of the participants in the attrition group having two or more prior hospitalizations (87.5%) as compared to the non-attrition group (37.5%). Age at first use of alcohol (d = .68) and marijuana (d = .58) showed a medium effect size. Age at first alcohol use was younger in the attrition group (13.3 years) than in the non-attrition group (14.88 years). Similarly, age at first marijuana use was younger (14 years) for the attrition group than the non-attrition group (15.12 years).

OlzQueRis Effect Size - Small

Close to a medium effect size was found for gender (d = .48); but the female sample size is too small for valid comparison purposes and race (d = .37), in which more Caucasian participants were in the attrition group (55.6%) than in the non-attrition group (37.5%). Median household income approached a medium effect size (d = .45), while employment status (d = .40) and number of hours working per week (d = .29) were

smaller. The median household income was lower in the attrition group ($35,874) as compared to the non-attrition group ($43,751). Participants in the attrition group were less likely to be working or students (42.9% vs 62.5%), but the attrition group was working more hours per week (M = 18 vs 11.4). A small effect size was found for lifetime alcohol use (d = .39), lifetime marijuana use (d = .27) and use of other drugs (d = .20). The attrition group had more participants with a diagnosis of marijuana (87.5%) abuse or dependence than the non-attrition group (75%). Alcohol abuse or dependence was also high in both groups, but lower in the attrition group (57.1%) than in the non-attrition group (75%). Similarly, the attrition group was less likely to be diagnosed with abuse or dependence of other drugs (16.7%) than in the non-attrition group (25%). Other variables with a small effect size include visual attention (d = .34) and DUP (d = .27). In the attrition group an equal number of participants (50% each) had normal or abnormal scores on visual attention, and the attrition group had more participants (50%) with an abnormal score when compared to the non-attrition group (33.3%). The majority of the attrition participants were in the shorter DUP group (75%) as compared to the non-attrition group (66.7%).

Summary – OlzQueRis Effect Size Attrition vs. Non-attrition Groups

With a large effect size, the attrition group:

- had a higher motor functioning percentile score (d = 1.66)
- was more severely ill at baseline (d = 1.13)
- had fewer years of completed education (d = 1.12)
- had a lower estimated premorbid IQ (d = .86)

With a medium effect size, the attrition group:

- was less likely to be in school (d = .73)
- did not leave school due to psychiatric illness (d = .72)
- was more likely to have had 2 or more previous hospitalizations (d = .72)
- was more likely to be younger at first use of alcohol (d = .68) and marijuana (d = .58)

With a small effect size, the attrition group:

- had more Caucasian participants (d = .37)
- had a lower median income (d = .45)
- was less likely to be working or students (d = .40) but worked more hours per week (d = .29)
- had more participants with a diagnosis of marijuana abuse or dependence (d = .27)
- was less likely to be diagnosed with alcohol (d = .39) and other drug (d = .20) abuse or dependence
- was more likely to have an abnormal score in visual attention (d = .34)
- was more likely to have a shorter DUP (d = .27)

*Question 3b:* Three Combined Studies

Combined Studies Effect Size - Large

For the combined study there was no significant difference between the attrition and non-attrition groups in demographic or illness characteristics and no large effect size (see Table 26 for effect sizes).

Combined Studies Effect Size - Medium

The one significant difference in treatment characteristics, typical versus atypical antipsychotic medication ($p = .034$) showed a medium effect size ($d = .62$) in the combined ClozHal and OlzHal studies only. The majority of the participants in the attrition group were receiving a typical antipsychotic medication (55%) rather than an atypical antipsychotic medication (45%). In the non-attrition group, the majority (75%) were receiving atypical antipsychotic medication.

Combined Studies Effect Size - Small

There were several small effect sizes although most were very small ($d = .05$ to .19). The attrition group was slightly older at the start of the study ($d = .28$) ($M = 22.9$ vs 22.36), had more Caucasians ($d = .29$) (57% vs 42.9%), and a slightly higher number of years of completed education ($d = .34$) ($M = 12.36$ vs 11.54). The functional level ($d = .32$) of the attrition group was higher (83%) than the non-attrition group (69%) with the attrition group more likely to be working or a student (80%) than the non-attrition group (71%) ($d = .20$). The median household income was lower ($d = .36$) ($M = \$39,507$) in the attrition group than in the non-attrition group ($44,260).

Small effect sizes were found with three of the neuropsychological domains: executive functioning categories achieved ($d = .34$), memory functioning ($d = .31$) and motor functioning ($d = .33$). Executive functioning categories achieved was lower ($M = 2.16$) in the attrition group as compared to the non-attrition group ($M = 2.7$). Memory functioning ($M = 22.9$) and motor functioning ($M = 34$) were higher in the attrition group as compared to memory functioning ($M = 15.3$) and motor functioning ($M = 25$) in the non-attrition group. Lifetime marijuana ($d = .26$) had a small effect size with fewer

participants in the attrition group with a diagnosis of marijuana abuse or dependence (51%) as compared to the non-attrition group (64.3%). Similarly, in the attrition group fewer participants had a diagnosis of abuse or dependence (6.4%) for lifetime use of other drugs (d = .27) as compared to the non-attrition group (14.3%).

Summary – Three Combined Studies Effect Size Attrition vs. Non-attrition Groups

There were no large effect sizes in the three combined studies.

With a medium effect size, the attrition group:

- was more likely to be receiving a typical antipsychotic medication (d = .62)

With a small effect size, the attrition group:

- was slightly older (d = .28) and more likely to be Caucasian (d = .29)
- had more years of education (d = .34)
- had a higher level of functioning (d = .32)
- was more likely to be working or a student (d = .20)
- had a lower median household income (d = .36)
- had lower executive functioning (categories achieved) (d = .34)
- had higher memory (d = .31) and motor functioning (d = .33)
- was less likely to have a diagnosis of marijuana (d = .26) and other drug (d = .27) abuse or dependence

## *Summary*

*Comparison of three studies*

- There were minor differences in demographic and illness characteristics between the three studies but no consistent pattern of differences.

- Overall, there were no serious differences between the three studies which allowed, therefore, for the use of the merged database.

*Attrition and Non-attrition in the three studies and merged database*

- No significant difference between the attrition and non-attrition groups in the merged data in demographic and illness characteristics.
- No consistent pattern in demographic and illness characteristics between the three studies and the attrition and non-attrition groups.
- Treatment characteristics consistently found lack of efficacy and patient withdrawal of consent to be the two most frequent reasons for attrition from the studies.
- Participants receiving a typical agent were less likely to complete the study.

*Effect size*

- Each individual study had a range from small to large effect sizes.
- The following variables were identified in three out of four of the studies and merged data (ClozHal, OlzHal, OlzQueRis, and merged) based on effect size. The attrition group:
    - was more likely to be Caucasian (range d = .29 - .39)
    - had more years of education (range d = .34 – 1.12)
    - was less likely to be in school in the year prior to the study (range d = .38 – 1.23)
    - was less likely to have a diagnosis of abuse or dependence for other drugs (range d = .20 - .27)
    - had a lower median income (range d = .36 – 1.02)

    - had higher scores on motor functioning (range d = .33 - 1.66)
    - was receiving typical antipsychotic medication (range d = .48 - .82)
- In the merged database effect sizes were mostly small.
- The only consistent effect size across the studies that included a typical agent was the higher use of typical agents in the attrition group (d = .62).

The direction of the effect size was not consistent between the studies and the merged data. The attrition group:

- was older at the start of the study in two (merged and ClozHal) of the three (OlzHal)
- was more likely to be working in two (merged and OlzHal) of the three (OlzQueRis)
- had fewer hospitalizations in two (ClozHal and OlzHal) of the three (OlzQueRis)
- was older at first use of alcohol in two (ClozHal and OlzHal) of the three (OlzQueRis)
- was less likely to have a lifetime diagnosis of marijuana abuse or dependence in the merged data and the ClozHal group, and much more likely in OlzQueRis

# CHAPTER 5

## Discussion

*Question 1:*

What are the demographic profiles, illness and treatment characteristics of the participants in the three double-blind, randomized drug trials?

This study provides a snapshot in time of a group of participants in a first episode of a schizophrenia spectrum disorder who participated in one of three double-blind, randomized drug trials. The study participants are more similar than different based on the lack of significant differences between the three studies. The differences identified may actually be a reflection of the range of characteristics found in larger first episode samples and in the natural course of the illness (Perkins et al., 2006b).

Overall, the data paints a picture of the devastating effects of psychosis on the lives of these young participants. The effect on educational and occupational role functioning is great, as exemplified by an inability to complete high school (27%, n = 22) as compared to the Massachusetts 2000 - 2001 statewide annual high school dropout rate of 3.5% (Massachusetts Department of Education, 2002). In this study, 64% (n = 14) of those who did not complete high school came from cities with the highest dropout rates in Massachusetts (up to 50% in some schools). Of those who completed high school 38% (n = 31) entered college, but only 19% (n = 6) completed college resulting in an 81% dropout rate, a much higher than the current college dropout rate of more than 50% (Barefoot, 2004; The Associated Press, 2005). The inability to graduate high school or college may be a consequence of the onset of psychosis. Specifically, 27% had an onset of psychosis between 16 to 18 years of age, and 37% had an onset during the college

years. Occupational functioning (see Table 8) was also adversely affected, with 22% (n = 16) functioning at a level of less than 25% during the year prior to the study, suggesting a long period of very poor functioning for almost one quarter of the sample.

Substance use is a critical health and mental health problem in this age group of young adults. The Centers for Disease Control provide data on substance use in secondary education students using the Youth Risk Behavior Survey (YRBS) (Centers for Disease Control and Prevention (CDC), 2007) and on adults using the Behavioral Risk Factor Surveillance System (BRFSS) (Centers for Disease Control and Prevention (CDC), 2001). The Substance Abuse and Mental Health Services Administration (SAMHSA) also collects data using a National Survey on Drug Use and Health (NSDUH) (Substance Abuse and Mental Health Services Administration, 2007). The National Institute on Alcohol Abuse and Alcoholism (NIAAA) provides data on adolescent alcohol use based on the YRBS, NSDUH and MTF (Monitoring the Future) for ages 12 - 20 from 1991 to 2007 (Chen, Yi, Williams, & Faden, 2009). Another source for information on substance use is the Healthy People 2010, which provides information on a 1998 (baseline) and 2010 target goals for decreased use (Office of Disease Prevention and Health Promotion, 2005). The Healthy People 2010 obtains its data from the SAMHSA national survey (NSDUH).

*Higher Marijuana and Hallucinogen and Cocaine Use in FE SSD*

The three studies were conducted from 1996 to 2004 (ClozHal (1996 – 2003), OlzHal (1997 – 2001) and OlzQueRis (2002 – 2004)), with the majority of the participants entering one of the studies between 1997 and 2000. Although there was overlap in the studies, data for substance use is drawn from several different sources as

noted above. Whenever possible, the comparison data noted in this section used data from years closest to the collection of this study data to ensure a similar cohort comparison. The data reported in this study used age at first use and lifetime use.

The average age of first use of alcohol (14.5) and marijuana (15.1) observed in these studies is older than that found in the 1998 NSDUH survey's average age at first use of 13.1 for alcohol and 13.7 for marijuana. (The NSDUH reports very little difference in age at first use for males and females.) While the age at first use is slightly older in this study, never using alcohol and marijuana is much higher in both the national and Massachusetts population based surveys. In the 1998 national survey of high school seniors, the percentage of people who never used alcohol (19%) is higher than in this study (13%). There is a striking difference between the data in this study and the national data in which more than twice as many adolescents (46%) reported never using marijuana than in this study (22%) (Office of Disease Prevention and Health Promotion, 2005). Also in 1999, half of all Massachusetts adolescents reported lifetime marijuana use as compared to three-quarters (78%) in the FE SSD studies. Likewise, in 1999, the rate of lifetime alcohol use as reported by Massachusetts adolescents (80%) was only slightly lower than reported by study subjects (87%) (Governor's Adolescent Health Council and Massachusetts Department of Public Health, 2003). Overall, lifetime alcohol use is consistent with the national and state surveys but the higher rate of marijuana use in young people in a first episode SSD is notable.

In this sample the rates of marijuana misuse (56%) were higher than alcohol misuse (47%). This high rate of marijuana misuse in the first episode sample is consistent with the literature (Barnes, Mutsatsa, Hutton, Watt, & Joyce, 2006b; Barnett et al., 2007;

Van Mastrigt, Addington, & Addington, 2004) and a new meta-analysis (Koskinen, Lohonen, Koponen, Isohanni, & Miettunen, 2009) reports the highest rates of marijuana use (45%) to be in young males. It is unclear why there is such a high use of marijuana in schizophrenia, requiring further study beyond the scope of this study.

The higher rate of marijuana use relative to alcohol use in this sample is consistent with new thinking regarding the relationship between marijuana use and the risk of developing schizophrenia. Currently, it has been hypothesized that marijuana is an environmental factor that increases risk in participants with a genetic vulnerability and possibly in participants without genetic risk (Hambrecht & Hafner, 2000; Henquet et al., 2005; Hickman, Vickerman, Macleod, Kirkbride, & Jones, 2007; Smit et al., 2004). Several studies have shown a dose response relationship between increased use of cannabis and increased risk for psychosis with odds ratios ranging from 2.3 to 3.5 (Andreasson, Allebeck, Engstrom, & Rydberg, 1987; Arseneault et al., 2002; Fergusson, Poulton, Smith, & Boden, 2006; Henquet et al., 2005; van Os et al., 2002). Arseneault (Arseneault et al., 2002) found 10% of those using cannabis before age 15 developed schizophreniform disorder by age 26 as compared to 3% for the group who initiated cannabis use by age 18. An association between cannabis use and an earlier age at onset of psychosis has been suggested (Arendt, Rosenberg, Foldager, Perto, & Munk-Jorgensen, 2005; Barnes et al., 2006b).

The use of other drugs follows the same pattern of being higher in this sample of participants in a first episode of SSD than those reported in the national and state surveys. In this FE SSD study, subjects report of PCP use was five times higher (12%) than in national surveys (2.7%). Subjects reported twice as much use of LSD (43%), and cocaine

(32%) than in the 2002 national survey (LSD 24% and cocaine 15%) (Substance Abuse and Mental Health Services Administration, 2005). Stimulant use was only slightly higher in the FE SSD sample (13% vs. 10.8%), while opiate use was only half (11%) that of the national sample (22.1%) (Substance Abuse and Mental Health Services Administration, 2005).

These findings regarding high rates of marijuana and some illicit drugs underscore the treatment challenges facing young adults in the first episode of schizophrenia. Ongoing misuse of marijuana and some illicit drugs amplifies the challenges of treating a new onset of psychosis. Often, use of marijuana and some illicit drugs is associated with poor treatment adherence (Coldham et al., 2002; Green et al., 2004; Wade et al., 2007), poor symptomatic remission (Hambrecht & Hafner, 2000; Wade et al., 2007) and a high relapse rate (Caspari, 1999; Linszen et al., 1994). People in a first episode have a poor understanding of the nature and course of a SSD, the effect of marijuana on symptoms and outcome, and the need for medication adherence and abstinence from substances of abuse. Psychoeducational approaches are complicated by poor insight, which is associated with both use of substance use and psychosis (Drake, 2008; Drake et al., 2007; McEvoy et al., 2006; Perkins et al., 2008). Treatment programs that include the building of insight through psychoeducation on the nature of the illness, and the effects of marijuana and other substances, improve motivation for treatment adherence and abstinence of substances (Archie et al., 2007).

*Neurocognition FE SSD Variability*

The results of the neurocognitive tests in this study vary widely from below average to above average, consistent with the literature as noted in a recent meta-analysis

of neurocognition in first episode (Mesholam-Gately, Giuliano, & Seidman, 2009). This meta-analytic comparison of healthy controls and people in a first episode of schizophrenia found the magnitude of deficits to vary widely within and between domains. Analysis of the cognitive tests in this study suggests a similar picture of wide variation within domains as those found in the literature on schizophrenia. Neurocognitive functioning, in people with schizophrenia, is often impaired and is closely tied to functional impairment (Heinrichs & Zakzanis, 1998; Keefe & Eesley, 2006; Mesholam-Gately et al., 2009). The young people in this study of the first episode showed clear cognitive deficits at the onset of psychosis along with functional impairment. Three of the domains had a majority of participants in the below average range: verbal memory (73.8%); visual attention (68.4%); and motor speed (55.4%). Similarly, the executive functioning domain for the whole group had a much higher rate of perseverative errors than controls and were well below the average norm for number of categories achieved (Strauss et al., 2006). As expected, premorbid estimates of IQ were found to be in the normal range (M = 102.8) in this study.

Conclusions

- Similar to findings in the literature, high rates of marijuana, hallucinogens and cocaine use were associated with cognitive deficits, impaired educational and occupational functioning.

*Question 2:*

To what extent do patients' demographic profiles, illness, and treatment characteristics differ in those who withdraw for any reason and those who remain in the three double-blind randomized drug trials?

There are few differences in demographic, illness and treatment characteristics between the attrition and non-attrition groups in this study, but it is critical to note that this small exploratory study is underpowered. In this study, no consistent significant differences were found between the attrition and non-attrition groups in the merged data except for the type of antipsychotic medication. Typical antipsychotic medication, specifically haloperidol, was most often associated with attrition from the studies. Practice guidelines today suggest starting with an atypical agent and avoiding extrapyramidal side effects, commonly associated with the use of haloperidol (American Psychiatric Association, 2006). The two studies with haloperidol took place at a time before many of the atypical agents were on the market and their use reflected standard of care at that time. It remains important to not forget the one key point of this study; attrition rates are very high in studies of first episode SSD, even in those studies that do not include a typical agent. A better understanding of the reasons for attrition is still needed.

Unfortunately, this small sample limited the ability to use the detailed data on dropouts. Detailed analysis of the reasons for attrition and analysis of differences between the attrition and non-attrition groups in demographic profiles and illness and treatment characteristics of larger studies is still needed. The importance of a more careful and complete analysis of the reasons for attrition is recommended in the literature,

as noted above. For the purpose of this study, completion was defined at 6 months because the number of participants who remained in each of the studies at one year was too low (ClozHal (9), OlzHal (4), OlzQueRis (5) for analysis in this study. The actual length of the three studies varied, ClozHal two to five years (1996 – 2003), OlzHal two years (1997 – 2001), and OlzQueRis one year (2002 – 2004). In the ClozHal and OlzHal studies, lack of efficacy was the most common reason for study withdrawal (24% and 50% respectively), followed by withdrawal of consent (24% and 15% respectively). Only a small percentage of the non-attrition group received haloperidol (ClozHal 18% and OlzHal 33%). In the OlzQueRis study, withdrawal of consent and loss to follow-up (33% each) were the most common causes of attrition. OlzQueRis was an outpatient study and loss to follow-up could be considered a form of patient withdrawal of consent. Thus, these findings suggest that lack of efficacy and withdrawal of consent is a common reason for attrition across studies involving both typical and atypical antipsychotics.

In the individual studies, analysis of between-group differences, which is rarely done in the literature, found a significant difference between the attrition and non-attrition groups for several variables but the significant variable varied from study to study. For example, the ClozHal study found the attrition group to be significantly older (23.9 years old vs 20.1 for the non-attrition group $p = .002$) at study entry. But, the OlzHal and the OlzQueRis study did not find a significant difference in age between the attrition (22.3 and 21.9 years old respectively), and non-attrition group (25.4 and 22 years old respectively). Other significant variables varied between the individual studies as well. In the ClozHal study, the attrition group had more years of education (12.7 versus 10.8 in the non-attrition group $p = .03$), but, the attrition group in the OlzQueRis study

had fewer years of education (10 versus 12.5 in the non-attrition group p = .051). There was no significant difference in number of years of education in the OlzHal study. The attrition group was older at the onset of psychosis (22.6 versus 18.9 for the non-attrition group), but non-significant for the two other studies. Clinically, the difference between the attrition and non-attrition groups are non-significant and require a larger study sample to better answer the questions raised in this study.

*Implication of Findings for Design of Clinical Trials*

The studies in this sample were traditional double-blind, randomized clinical trials. Despite not being able to use detailed data in this study, it is important to note that participants were dropped from these studies for a variety of reasons such as needing an antidepressant, and missing more than one week of study medication. In the past ten years an increasing number of articles have called for more practical clinical trials (Glasgow, Magid, Beck, Ritzwoller, & Estabrooks, 2005; March et al., 2005; Tansella, Thornicroft, Barbui, Cipriani, & Saraceno, 2006; Tunis, Stryer, & Clancy, 2003). The purpose of these trials is to go beyond the usual randomized clinical trial used to obtain registration approval by the FDA. Practical clinical trials, based on an effectiveness model, take place in a wide range of clinic settings with diverse populations. The research questions are designed to evaluate real world clinical and treatment issues, and to provide more relevant information for evidence-based practice guidelines. Practical effectiveness trials are more flexible and participant friendly, without, for example, the strict inclusion and exclusion criteria, limits on allowable concomitant medications, and a low tolerance for missed doses. All of these issues can contribute to the high attrition rates in usual

clinical trials. The goal is a more clinician and patient friendly clinical trial and, it is hoped, in a real world setting the attrition rates would decrease.

The CATIE trial, the largest effectiveness study in the treatment of schizophrenia to date, followed many of the practical clinical trials guidelines (Lieberman et al., 2005b). Despite this, it had a large (74%) all-cause discontinuation of randomized medication rate by 18 months. This effectiveness study allowed for switching of the antipsychotic medication. Weiden (2007) reports this high rate of medication-switching and non-adherence are poorly understood from the patient's perspective (data was not collected for patient reason for study withdrawal). Clearly, the issue of high attrition rates is poorly understood, in both standard clinical trials, as well as, the more lenient effectiveness trials.

The use of Last Observation Carried Forward (LOCF) continues to be a common method of handling missing data in many of the first episode studies despite the identified weaknesses of this method. One basic assumption of LOCF is that no further change in a participant's response would have taken place if they had not dropped from a study, regardless of when they drop (Mazumdar et al., 2007; Streiner, 2008; Wood et al., 2004). LOCF fails to make use of all prior data points that could be used to show the direction of change (getting better, worse or no change) (Streiner, 2002). Bias may be introduced when there are different drop-out rates between treatment groups (Barnes et al., 2006a; Gueorguieva & Krystal, 2004; Mazumdar et al., 1999) and when missing data is not random but related to the medication, such as side effects and lack of efficacy, or to the study procedures such as subject burden (Leon et al., 2006; Mazumdar et al., 2007; Sheiner, 2002). Currently, there is no best way to handle attrition without it having some

impact on study results. Comparison of data using LOCF to different methods of multiple imputation and regression models have found significant differences in the results calling into question the validity of the LOCF method (Gueorguieva & Krystal, 2004; Houck et al., 2004; Lavorie, Dawson, & Shera, 1995; Mazumdar et al., 2007).

The results of this study of attrition in three double-blind randomized treatment studies were similar to the results found by Leucht, Engel, Bauml, and Davis (2007) in a reanalysis of several large clinical trials of atypical antipsychotic medication as compared to a typical antipsychotic. Leucht et al. (2007) compared results for their four models for handling missing data under two different conditions: (a) data pooled across multiple studies; and (b) data analyzed separately for each study. When data were pooled across studies, the researchers did not find a difference in effect size between the various models. However, when they analyzed the data separately, the use of the first LOCF model (similar to the approach most frequently used in FE SSD research) resulted in higher effect sizes in favor of the atypical antipsychotic medications in 50% of the study data sets. The authors concluded further study comparing results using other statistical methods was needed. The point to be made here is not the finding regarding atypical antipsychotic medication, but the lack of findings in pooled samples and positive findings in the individual studies. This is similar to the lack of findings in the merged data for the three first episode studies and positive findings (effect sizes) for each of the individual studies. Further study is needed to better understand why this has occurred in the larger sample studies of Leucht et al. (2007) and the smaller samples found in this present study.

In the last five years, some data analysis plans include comparison of newer sophisticated statistical modeling methods to the LOCF method (Green et al., 2006; Lieberman et al., 2003b; McEvoy et al., 2007). Green et al., (2006), Lieberman et al., (2003b), and McEvoy et al. (2007) participated in two of the studies discussed in chapter 2. Only one of the studies (Lieberman et al., 2003b) reported on differences between the results of the LOCF analysis and more sophisticated statistical methods (random regression analysis).

The newer, more sophisticated statistical methods of structural equation modeling include latent growth curve analysis, random effects regression, mixed effects regression, and hierarchical linear modeling. Each is used for longitudinal treatment data but the use of a specific method is dependent on the type of question asked, type of data collected, and the number of time points. These methods are dependent on having a minimum of three available data points for each participant. For example, latent growth curve analysis allows for the inclusion of missing and irregularly collected data and can analyze the relationship between many different types of variables that may mediate, moderate or in other ways influence the process of change for each subject (Hser, Shen, Chou, Messer, & Anglin, 2001; Llabre, Spitzer, Siegel, Saab, & Schneiderman, 2004). Many of these types of regression models create a slope of the line and its intercept (baseline severity level) for each person. Taken together, the slope of each group and each individual will indicate differences in treatment response (Streiner, 2008). The newer modeling methods vary from fairly simple to very complex. These techniques address some of the problems encountered with LOCF as they use all available data on each person and can model effects over time when there is missing data. Understanding the dropout mechanism is

critical. However, the problem of an inability to identify if missing data is random (ignorable) or non-random (non-ignorable) continues. Randomness is assessed by the use of sensitivity tests, such as Little's test or the index of sensitivity to ignorability (ISNI), which should be employed to assess the impact of non-random missing data (dropouts) on outcome (Houck et al., 2004; Mazumdar et al., 2007). Non-random missing data can affect the reliability of the modeled data. Overall, the use of statistical modeling methods to analyze data and deal with non-random missing data is very complex and requires statistical sophistication and a sufficiently large sample size.

*Question 3:*

> What is the effect size in analyses comparing those who withdraw and those who remain in terms of their demographic profiles, illness and treatment characteristics in: (a) each of the three double-blind randomized drug trials; and, (b) a merged data set combining all three double-blind randomized drug trials?

Statistical significance conveys a degree of confidence or reliability in the difference between groups, but is very dependent on the sample size. A very large sample can easily achieve a stringent level of statistical significance that is much more difficult for a small sample. The purpose of effect size calculations is to provide additional information about the magnitude of the difference between two groups, usually two different treatment groups (Coe, 2002; Cohen, 1988; Faraone, 2008). In this study, effect size is utilized to better explore the magnitude of the difference between those who remain in a study and those who leave. Because this study had small sample sizes, the calculated effect sizes helps us understand the degree of difference between the groups.

In the individual studies there were several large effect sizes, but in the merged data the effect seem to have washed out. This may possibly be due to the heterogeneous nature of the course and severity of schizophrenia (Huber, 1997) which leads to differences in patient characteristics in each study or to the heterogeneous nature of the studies. Two of the studies compared haloperidol against an atypical medication and one study compared three atypical medications. One of these studies was conducted as an outpatient, while the other two were conducted on a dedicated inpatient research unit where participants were discharged to outpatient status when they were clinically stable. There were also differences between the studies on allowable concomitant medication.

A review of the literature found no published studies on the effect sizes for the differences between those who remain in a double-blind randomized treatment study and those who leave. To better understand the magnitude of the findings in this study, effect sizes published in the literature on schizophrenia were reviewed including three treatment studies (Haas et al., 2009; Hodge et al., 2008; Joffe et al., 2009), one review of twenty studies on the effects of atypical antipsychotic medication on cognition (Harvey & Keefe, 2001), and three meta-analyses including the neurocognition in the first episode (Mesholam-Gately et al., 2009), cognitive behavioral therapy (Wykes, Steel, Everitt, & Tarrier, 2008), and social skill training (Kurtz & Mueser, 2008).

Effect sizes (Cohen's d) found in treatment studies have varied widely depending upon the dependent variable and study design. One randomized treatment study evaluated the effectiveness of cognitive remediation in schizophrenia (Hodge et al., 2008). The authors found significant improvement with small (d =.18) to medium (d = .65) effect sizes in memory, attention and executive functioning that persisted for four months after

the end of training. The change in cognition resulted in clinically significant improvement in psychosocial functioning as measured by clinical ratings.

Joffe et al., (2009) reported an effect size of 1.0 for differences in symptom severity as measured by the Positive and Negative Symptom Scale in a randomized placebo controlled study of the addition of mirtazapine, an antidepressant, to typical antipsychotic medication. This report suggests the antidepressant may enhance the antipsychotic effect of typical antipsychotics.

Haas et al., (2009) in their study, compared two dosing regimens (1.5 to 6 mg/day as compared to 0.15 to 0.6mg/day) of risperidone in the treatment of adolescent schizophrenia. A small to medium effect size of .49 (Cohen's d) was found. There was a significant improvement in mean Positive and Negative Symptom Scale (PANSS) positive and negative subscales for 1.5 to 6mg/day treatment group.

Meta-analyses report effect size, using standard deviation units as a way to standardize various statistical tests, allowing for comparison of many different research studies, including studies with a small sample size (Lipsey & Wilson, 2001). Although not a meta-analysis, the next report is a methodological assessment of twenty studies on the effect of atypical antipsychotic medications on cognition found a mix of open label, randomized open label and randomized double-blind treatment studies (Harvey & Keefe, 2001). This review found effect sizes for these novel atypical antipsychotics ranging from very small (.13) to medium small (.43) (Harvey & Keefe, 2001). When compared with the effect sizes for the cognitive deficits in the first episode of schizophrenia (-1.59 to -.28) (Mesholam-Gately et al., 2009), the effect of atypical antipsychotic medications on cognition is very small. Harvey and Keefe (2001) assert that the effect sizes obtained may

have reached statistical significance but may not be clinically significant based on the magnitude of the underlying cognitive deficit. The effect size for the difference in cognitive deficits between the attrition and non-attrition groups in the merged data for the present study was small (.08. to 34) similar to that observed in Harvey and Keefe's (2001) estimate for the novel atypical antipsychotics. (See Table 26 for details on effect size for the individual studies).

The first meta-analysis, conducted by Mesholam-Gately et al., (2009), found a large difference in neurocognition (d = -.28 to -1.59) in a comparison of healthy controls and people in a first episode of schizophrenia. They also noted a significant difference between and within neuropsychological tests and domains, providing further evidence that neurocognitive deficits in first episode schizophrenia are heterogeneous with wide individual variation.

A second meta-analysis of cognitive behavioral therapy in schizophrenia explored the effect sizes (Cohen's d) in thirty-four treatment trials (Wykes et al., 2008). They found an effect size of .40 for positive symptoms. This meta-analysis identified methodological issues that can result in inflated effect sizes such as lack of randomization and a lack of masking of treatment assignment for the clinical raters. Both of these issues, randomization and masking of treatment assignment, were controlled for in the three combined studies of FE SSD. Each was a randomized, double-blind study and the clinical raters did not conduct the assessments for side effects to further protect the blind and prevent any potential inflation of the effect sizes from these methodological issues. In the last meta-analysis, Kurtz & Mueser (2008) evaluated 22 randomized controlled trials of social skill training. The mean effect sizes ranged from the largest (d = 1.20) for

content mastery to the smallest (d = .15) for the effect of social skill training on overall psychiatric symptoms.

It is difficult to compare the effect sizes found in this study of attrition and non-attrition to those obtained in the literature for two reasons. First, treatment response was not analyzed and second, the sample was divided by attrition, not by treatment assignment. The usefulness of this review of effect sizes is in their ability to provide a sense of the magnitude of change for different types of treatments (medication, cognitive behavioral therapy, cognitive remediation and social skills training) and the magnitude of the cognitive deficits found in schizophrenia. Cognitive deficits in schizophrenia are large and the treatment effect sizes are only small to medium. Additionally, statistically significant results can be associated with a small effect size (Haas et al., 2009; Hodge et al., 2008; Kurtz & Mueser, 2008; Wykes et al., 2008).

The effect sizes found in this study fall within the ranges observed in the literature. In this study of attrition, the individual studies each had some large effect sizes, but within any one variable there was great variation between studies. In addition, not all of the large effect sizes reached statistical significance. It remains unclear why, in the merged database, many of these large effect sizes decreased in size from the effect size found in each individual study. It may be that the large effect sizes and statistical significance in the individual studies truly reflects the wide variation in demographic and illness characteristics seen in first episode schizophrenia or the effect sizes could be inflated by the small sample size. Further study is required to better understand the relationship between demographic, illness and treatment characteristics and attrition and non-attrition in first episode SSD.

*Limitations*

This secondary analysis of data has four major limitations. First, as noted earlier, this study is underpowered, and significant tests of differences between the attrition and non-attrition group may be misleading. However, effect size analysis was conducted to offset this limitation and provide readers with effect sizes for attrition/non-attrition group differences that can be used to inform their interpretation of the results reported here. Moreover, as an exploratory study, these data on differences between those who remain in a study and those who leave may begin to identify those who are at high risk for attrition.

A second limitation is the small number of females in this study, which did not allow for analysis of gender differences in the variables of interest, limiting its generalizability to women. This is a serious limitation, identified in many different areas of clinical research, which results in an inability to analyze data for gender differences. In 1994, the National Institute of Health issued guidelines for the inclusion of women and minorities in clinical research studies (Federal Registry, 1994). Since that time, two reports were published (Geller, Adams, & Carnes, 2006; Vidaver, Lafleur, Tong, Bradshaw, & Marts, 2000) on compliance with this guideline. In 2000, 20% of the studies reviewed did not include women, and of those who did include women, only one quarter to one third of the studies included analysis of the results by gender (Vidaver et al., 2000). There was little improvement by 2006; 37% of the sample, in the studies evaluated, were women, and when only drug trials were evaluated, the number of women decreased to 24%. In addition, 87% of the studies evaluated did not include analysis by

gender or with the use of gender as a covariate (Geller et al., 2006). Qualitative studies can help identify barriers to enrolling women in FE SSD studies.

Howard, de Salis, Tomlin, Thornicroft and Donovan (2009) studied barriers to enrollment for a randomized clinical trial of supported employment in people with a serious mental illness and found several areas of concern expressed by the clinical care coordinators that impacted on referral to the study. Barriers to enrollment included a lack of understanding about the trial, especially the need for randomization and a control group. Treatment as usual (control) was viewed as less than adequate care, when compared to the treatment arm, and lead to a sense of inequality between the treatments offered. Individual clinicians interpreted inclusion criteria differently thus effecting who was referred. Lastly, care coordinators had a paternalistic attitude, wanting to protect the patient from stress and the potential for failure in the study which may result in a relapse of symptoms. Potential strategies to improve the participation of women in FE SSD studies could include in depth discussions with potential participants, their clinicians and care givers about barriers to participation. Discussions with women who participate in FE SSD studies may help to identify reasons for willingness to join a clinical research study. People with a serious mental illness, who are involved in the recovery and peer assistance movements, may further identify barriers and help to build pathways to research.

A third limitation is created by the inherent problems of combining three randomized double-blind treatment studies. There were variations in data collection where the same information was collected categorically in one study and continuously in another, resulting in the use of a lower level of measurement for the variables being assessed (e.g., substance use and functional measures). This may have limited our effect

sizes for differences involving such variables. Additionally, the length of the three studies and when they were conducted varied: ClozHal up to 5 years (1996 – 2003); OlzHal 2 years (1997 – 2001); and OlzQueRis for 1 year (2002 – 2004). Due to the high number of people in the attrition group, this study limited the focus to an analysis of attrition at 6 months.

A fourth limitation is the potential for inflation of alpha (galloping alpha). The exploratory nature of this study allowed for multiple analyses even though there is concern about a Type I error (when the null hypothesis of no difference between the groups is rejected, when it is in fact true) (Burns & Grove, 2001). A Bonferroni correction was used to adjust for multiple comparisons which corrects the p value for multiple comparisons by preventing the inflation of Type I errors, but at the same time increases the risk for Type II errors, potentially missing differences that really are significant.

*Implications for Future Research*

Further evaluation of the potential differences in demographic, illness and treatment characteristics in those who remain in studies and those who leave needs to be conducted with a larger sample size. Pharmaceutical companies who own the large first episode, randomized, double-blind treatment data could evaluate the data for differences between the attrition and non-attrition groups. A re-analysis of the pharmaceutical company data using the more sophisticated modeling methods could also identify mediators or moderators for risk of attrition (Holroyd et al., 2005). This is important because the utility of using statistical methods like LOCF has been questioned in the literature, especially when there are high attrition rates and a failure to evaluate the data

for randomness of missing data (Houck et al., 2004; Lavorie et al., 1995; Leon et al., 2006; Mazumdar et al., 2007; Streiner, 2008). If a re-analysis of past FE studies is not possible, then a meta-analysis of key demographic, illness and treatment variables, as related to attrition, would be useful. Results might identify which medications are most often associated with attrition.

Further study is needed to better understand why there are so few females in research studies on first episode SSD. Does an older age at onset for women and/or decreased substance use play a role? Identifying pathways to care and barriers to early identification and treatment in people, not just women, in a FE SSD clinical population may help to identify potential differences between men and women.

The present study had a high number of participants who withdrew consent (22%) similar to that found in studies of schizophrenia (see Table 5). Attrition due to withdrawal of consent in FE studies (see Table 3) varied from 2% to 42%. Understanding the rates of attrition due to patient withdrawal of consent, is further complicated by variations in the definition and classification of attrition. The reasons for patient withdrawal are unknown, but stigma-related hypotheses, such as fear of a diagnosis of a psychotic disorder, denial of the need for treatment, and a desire to return to home or school with the hope for a return to normal daily functioning, are common in the experience of the author. It would be helpful to conduct a qualitative study to better understand the participants' subjective experience of psychiatric care within a double-blind psychopharmacology research study.

The use of cannabis by participants in this study was high and the role of the neurobiological mechanisms by which cannabis affects the development of schizophrenia and long-term outcomes is poorly understood. Cannabis, via the cannabinoid-1 (CB-1)

receptors, affects the regulation of dopamine and serotonin (known to play a role in psychosis) and in particular, raises dopamine levels in the limbic system and neocortex (Fergusson et al., 2006). Additional evidence is found in the catechol-o-methyltransferase (COMT) gene which encodes dopamine. Individuals who were homozygous for the Val/Val (valine) polymorphism of COMT and used cannabis are at higher risk (odds ratio 10.9, 95% CI 2.2 – 54.1) for developing a schizophreniform psychosis. People without this polymorphism, who used cannabis, had a much lower risk for developing psychosis (Odds ratio 1.1, 95% CI 0.2 – 5.3) (Caspi et al., 2005). Additional genetic research is needed to better characterize the role of COMT in cannabis users and non-users and clinical outcome.

CB-1 has been found to affect electrophysiological functioning in the limbic system by interfering with neuronal oscillations and impairing sensory gating (Hajós, Hoffmann, & Kocsis, 2008). People in a first episode of schizophrenia who use cannabis have been found to have a greater increase in brain volume loss in the right posterior cingulate cortex, an area rich in CB-1 receptors (Bangalore et al., 2008), anterior cingulate (Szeszko et al., 2007) and over time to have greater brain volume reduction (Rais et al., 2008) than in those who do not use cannabis. Overall, researchers continue to try to better understand the role of cannabis in brain structure and function and its potential influence on the onset and course of schizophrenia.

Insel (2009) recently published a report on the priorities of the National Institute of Mental Health, including the need for early detection of mental illness and for individualized care. In order to achieve these goals further research is needed to understand the trajectory of the illness, the barriers that prevent optimal treatment

response, and disparities in mental health care. In addition, new, more individualized interventions are needed. Moreover, better methods to disseminate research findings in a more timely and effective manner are essential. These are all important goals, but before these goals can be attained researchers must gain a better understanding of why so many people with this illness drop out of studies and standard treatment.

## *Implications for Practice*

### *Attrition*

There are several important implications for practice that are highlighted by this study. In this research study, based on effect sizes, the attrition group was older, had more years of education, was less likely to be diagnosed with abuse or dependence of cannabis or other drugs, and was higher functioning with a history of working in the year prior to entry into the study. These characteristics may have played a role in the high attrition rate in this research study. Participants may become anxious to get back to their usual level of functioning, once they start to feel better. This group also had lower scores on executive functioning, which may have an impact on problem solving and future planning. The researcher team needs to provide psychoeducation to study participants and their families about the importance of intensive treatment and relapse prevention in the early phase of schizophrenia.

The high attrition rate associated with research studies is troubling, but there is also a high rate of dropping out of standard treatment, which is even more troubling. What constitutes standard treatment is variable ranging from individual and/or group treatment, psychosocial rehabilitation, or receiving only a minimal amount of treatment such as medication appointments only. The type of available treatment is often dependent

on several factors, including federal and state funding for mental health care, rural or urban area of the country, and perceived need for treatment. The availability of intensive treatment programs for people in a first episode of psychosis as described in this study are limited.

In a review of epidemiological surveys (Mojtabai et al., 2009), about 40% of people with a diagnosis of schizophrenia reported receiving no treatment in the preceding 6 to 12 months. In a longitudinal study, the Suffolk County Mental Health Project followed people with a first hospital admission for schizophrenia and found 20% were not receiving medication treatment and another 40% were not receiving any form of psychosocial treatment. This longitudinal study identified people who dropped out of treatment, or had minimal treatment, as less likely to achieve remission of psychotic symptoms, and more likely to have an increased number of hospitalizations, than those fully engaged in treatment (Mojtabai et al., 2005).

In another review of treatment non-adherence, Nose, Barbui and Tansella (2003) found 26% of clients had medication and treatment non-adherence. Those at highest risk for non-adherence included young males in the first episode with positive symptoms, a lack of insight, unemployed, and a history of substance abuse and poor social functioning. These findings are not consistent with the findings in this study of attrition from three double-blind drug studies, because dropping out of a study, while in the initial treatment phase, may be different from dropping out of non-research outpatient treatment. Understanding this difference requires further study.

*Antipsychotic Medication*

This study of attrition from three double-blind research studies found typical antipsychotic medication to be associated with a high attrition rate, but atypical antipsychotic medications also had high attrition rates as noted in the CATIE study (Lieberman et al., 2005a). The two most common reasons for attrition, in the present study, were lack of efficacy and withdrawal of consent. Clearly, these reasons highlight patient dissatisfaction with current medications, and are similar to the reasons for the high rate of medication turnover in the CATIE study (Weiden, 2007). Research methodologies (randomized controlled trials) include careful observation and measurement of symptoms, cognitive functioning, psychosocial and vocational/educational functioning (to name only a few of the areas studied in first episode of schizophrenia) along with the provision of clinical care. Developing a partnership, where an ongoing dialogue with active listening and responding to participants' concerns, fears and descriptions of the effects of medication, along with the participants' experience of research, are crucial. Of course, the level of psychosis and cognitive disorganization will influence the ability of the participant to engage with the researcher/clinicians, who must adjust their approach, as appropriate, to the situation.

Cognitive deficits may be also associated with non-adherence (Perkins, 1999, 2002) and are associated with a poor outcome and a low levels of psychosocial and vocational functioning (Green, 2006; Robinson et al., 2004). But, cognition is not affected by antipsychotic medication and a misunderstanding of the expected effects of medication may play a role in patient dissatisfaction with medication, with resultant non-adherence.

*Advances in Treatment for First Episode SSD*

The factors identified in this study on attrition in FE SSD clinical trials can help inform nursing practice about potential risk factors that may contribute to treatment non-adherence in this vulnerable population. Early identification of psychosis and treatment adherence has been demonstrated to significantly decrease the morbidity associated with schizophrenia. Subsequently, many countries have developed large networks of specialized first episode treatment centers. England has over 50 clinic sites, Australia, a national early intervention program, and Canada has many sites ranging from Nova Scotia to British Columbia. Other European and Scandinavian countries have been in the forefront of early intervention and also have many specialized treatment programs.

All of these countries have moved much further along than the United States in the development of combined early identification and intervention with intensive specialized treatment for first episode SSD. The United States has lagged behind, with too few clinics providing intensive specialized care early on in treatment, providing less than what is now considered the standard of care worldwide (Falloon et al., 1998b; McGorry, 2005). Often, in the US, these specialized treatment centers only exist in academic settings, often associated with research in first episode of psychosis, as opposed to the nationally funded treatment centers found in many parts of the world. Additionally, the American Psychiatric Association practice guidelines (2006) for the treatment of schizophrenia includes a very brief, cursory mention of the first episode. In contrast, the Royal Australian and New Zealand College of Psychiatrists (2005) published very detailed guidelines for people in a first episode of psychosis calling this a critical period in the treatment of schizophrenia. Ongoing evaluation is needed to better understand what types

of intensive treatment programs are most effective in the US. This is especially important due to the culturally diversity found in the US, with its very large urban population centers and large underserved rural areas. More research is needed to better understand culturally based views of mental illness, and culturally acceptable treatment strategies.

Nursing, psychology, social work, psychiatry and other mental health practitioners are part of a multidisciplinary team integral to the treatment of young people in a first episode of psychosis. First and foremost is the early identification of psychosis and rapid intervention to treat symptoms and prevent disability in a culturally acceptable manner. Early identification may occur in a variety of non mental health settings, such as schools, pediatrician and primary care offices, requiring outreach and education to providers about the identification of early psychosis. A survey (Etheridge, Yarrow, & Peet, 2004) of service users and their caregivers on their pathways to care reported frequent difficulty finding appropriate help, frustration at the service delivery system and unhelpful professionals. Etheridge, Yarrow and Peet (2004) also found a lack of recognition of psychotic symptoms by primary care, and delays in treatment due to substance misuse in these young people with psychosis. Most often, a primary care physician and school personnel were first approached for help with the psychotic symptoms. Lack of recognition of symptoms results in a longer duration of untreated psychosis, in the present study the average duration of untreated psychosis was 30 weeks (range 0 – 208 weeks).

Prevention and early intervention include identification of young adults with early clinical symptoms and/or those who are at a high genetic risk (a first degree relative with a psychotic disorder). These symptoms, indicators of clinical high risk for psychosis, are

usually identified retrospectively, after the onset of psychosis and are known as prodromal symptoms (Yung & McGorry, 2007). Prodromal symptoms often include educational difficulties, ineffective social behavior and/or withdrawal, and affective instability such as depression, anxiety and emotional turmoil. Early identification and intervention requires the development of prevention and treatment strategies to address early symptoms, and the ongoing assessment of the effectiveness of these strategies (Cannon et al., 2008; Cornblatt & Auther, 2005). Early identification of psychosis results in a shorter duration of untreated psychosis which is associated with improved outcomes (Norman et al., 2007; Schimmelmann et al., 2008)

Service users have described their experience in a specialized first episode treatment program as a more humane approach to their illness, with involvement in decision making, and improvement in symptoms and quality of life, as well as higher treatment adherence in specialized treatment programs (O'Toole et al., 2004). Additional positive outcomes in specialized or integrated clinics have included fewer inpatient days (Agius, Shah, Ramkisson, Murphy, & Zaman, 2007; Cullberg et al., 2002; Cullberg et al., 2006), a decrease in the frequency of psychotic episodes (Agius et al., 2007; Falloon et al., 1998a), a decrease in positive and negatives symptoms, less substance misuse, better adherence and satisfaction with treatment (Agius et al., 2007; Petersen et al., 2005).

In addition to early identification, Hamilton Wilson, Hobbs, and Archie (2005) describe an effective approach used by one early intervention clinic to assist young people in the recovery from a first episode of psychosis. In this model, clinicians must first examine their own beliefs about psychosis, beliefs often associated with a loss of hope for future functioning. Clinicians need to become more knowledgeable about the

effectiveness of early intervention clinics. A collaborative alliance between the staff, client and family focuses on the prevention of demoralization and provision of hope with a focus on recovery. Clinicians must be comfortable with a model that emphasizes shared power, is recovery oriented, and involves a participatory treatment style. Intensive support to the client and family is often required, ranging from daily contact to once or twice a week as needed. Ongoing psychoeducation, psychotherapeutic support, medication, family treatment, recovery oriented psychosocial rehabilitation and self-care relapse prevention are critical.

Taking a proactive approach to relapse prevention is another important issue in the treatment of psychosis. Nurse researchers van Meijel, van der Gaag, Kahn and Grypdonck (2003) have reported on nursing implementation issues to prevent relapse. A randomized controlled trial of usual care or a relapse prevention plan included the nurse, social network members and the patient. The prevention plan included four phases. The first phase consists of developing a working relationship and providing information about relapse prevention, as well as identifying network related factors that could hinder or assist in the implementation of a relapse prevention plan. The second phase is the identification of early warning signs, based on past symptoms and behaviors. The third monitoring phase develops a plan to evaluate early warning signs by the nurse, social network and patient, and requires agreement and cooperation by all for effective implementation. The final phase is the development of an action plan to be implemented when early signs and symptoms emerge and includes stress reduction, medication adjustment, enhancement of coping skills, and attention to safety issues with inpatient treatment an option, if necessary.

Evidence-based treatment modalities, such as cognitive remediation (McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007) and cognitive behavioral therapy (Waldheter et al., 2008; Wykes et al., 2008), with a focus on symptomatic and functional recovery, have been found to be effective, and when given early enough in the course of a psychotic disorder, may lessen the deterioration common in SSD (Grossman *et al.*, 2003). Vocational rehabilitation involving individual placement with supportive services is effective in improving rates of employment in people with FE SSD (Killackey, Jackson, & McGorry, 2008). Overall, psychosocial treatment is helpful but more stringent evaluation of their effectiveness is needed (Penn et al., 2005).

As one member of the treatment team, psychiatric nurses play an important role in addressing the health care priorities of people in a first episode. Self-management of symptoms in a client centered recovery model is a priority according to the National Institute of Nursing Research, The Institute of Medicine (IOM), and The President's New Freedom Commission on Mental Health (Committee on Quality of Health Care in America, 2001; New Freedom Commission on Mental Health, 2003; NINR, 2006). The stated priorities for managing symptoms include understanding the causes of symptoms; symptom recognition by patient, family and care givers; and interventions to improve response to symptoms over the phases of an illness. Self-management includes early self-detection of symptoms and early reporting; strategies for decision making in healthy life style choices; and defining behavior that supports adherence to treatment (NINR, 2006). Both the Institute of Medicine and The President's New Freedom Commission on Mental Health emphasize a change in the mental health care systems to client centered and recovery oriented. In the recovery model, the individual defines treatment goals and

outcomes. The treatment team uses evidence based practice as the cornerstone of treatment.

These standards of care rely on two different models, one based on the best evidence to date for treatment and another based on consumer identified principles of recovery oriented treatment (Bellack, 2006). Implementation of evidence based practice within a recovery oriented treatment model is still in its infancy. In the past, treatment of schizophrenia was based on a model of achieving stability, not of forward movement toward recovery. More recently, advances have been made in developing a description or roadmap toward evidence based individualized treatment (Weiden et al., 2009). Much work needs to be done to identify ways to better integrate the evidence based and recovery models with the experiences of the specialized treatment centers into usual care settings.

A psychiatric nurse, as a member of an early intervention treatment team, works collaboratively to provide comprehensive care and promote optimal health based on an understanding of the neurobiology of schizophrenia, its core cognitive deficits, the subjective experience of a client, psychosocial rehabilitation and psychopharmacology. Working with the individual collaboratively to identify treatment goals is essential in order to provide a level of care that will promote recovery. Treatment needs to be individualized, foster decision making and autonomy, include medication adherence, psychoeducation and encouragement of healthy alternative behaviors (Spear & Kulbok, 2004). Both short and long term goals need to be identified, including issues of illness management and functional recovery. Psychoeducation about recovery from psychosis focuses on improving social and role functioning, decreasing the use of substances, and

includes information about time needed for healing from the effects of a psychotic episode. Psychosocial withdrawal and post-psychotic depression are not uncommon occurrences requiring treatment. The development of a relapse prevention plan includes recognition of the triggers of symptoms, such as stress or substance abuse, and a plan for a rapid respond to early warning signs of relapse (E. Waldheter, personal communication, June 12, 2009).

Young adults often have their education interrupted by psychosis. In this study, of those in school, 40% had to leave school due to psychiatric symptoms. Twenty seven percent never completed high school and of those who attended college only 7% graduated. Young adults frequently identify a return to school as an important goal, but we do not know the outcome for those who did return to school as there is no available data. Discussions of how to maximize the young adult's strengths, while anticipating what components of classroom work will be difficult or easy are essential. Options include taking one class, a limited class load or a return to full time school. Young adults need guidance in developing supports at school, often available through a school's disability center. Clinicians need to have active discussions with each college based disability center, as their degree of comfort with working with people with a psychotic disorder varies greatly (M. Friedman-Yakoobian, personal communication, June 12, 2009).

A collaborative model supports self-control and self-determination over time. The provision of early intervention needs to take place in a non-stigmatizing location such as store fronts that are youth oriented and easily accessible. Health classes need to promote a better understanding of the role of stress and drugs of abuse in depression, anxiety,

eating disorders, substance misuse and psychosis. Teaching effective coping skills are essential, as well as helping young people learn ways to assist their friends in obtaining help. Schools need to work in conjunction with community mental health providers to provide early identification and treatment of at risk youth.

## Conclusion

Other than this study, there is no data on the effect size of the demographic, illness and treatment characteristics of the people who drop out of psychopharmacology research studies. The effect sizes generated for the small individual studies do vary markedly between the studies and reflect the magnitude of difference between those who stayed in a study and those who left. This variability may reflect the wide range seen in severity of illness and levels of psychosocial functioning.

The aim of this study was to evaluate the difference between those who withdraw and those who remain in a study on demographic profiles and illness and treatment characteristics of participants in three double-blind randomized drug trials. The participants were all young adults, in a first episode of a schizophrenia spectrum disorder, initially treated either in an inpatient research unit or as an outpatient. The group was representative of a wide range of socioeconomic groups, had an average age of 22.8 years, was predominately male, and never married. The average age at onset of psychosis was 21 years old. The participants were moderately to markedly ill with a range of neurocognitive deficits ranging from above average to well below average. The majority had a history of marijuana and alcohol use and misuse with almost half having used LSD and a third used cocaine.

Attrition was a major problem with 66% attrition rate from the three combined studies. The two most common reasons people left these studies were lack of efficacy and withdrawal of consent, the next most frequent reasons were due to side effects and loss to follow-up. It is important to understand not just the reason for attrition, but also if there is a difference between the attrition and non-attrition groups. This study highlighted some potential differences between the attrition and non-attrition groups such as a medium effect size for higher rates of attrition with typical antipsychotics. Small effect sizes were found for the attrition group, which was more likely to be Caucasian, slightly older, with more years of education, but not in school in the previous year. The attrition group had a higher level of functioning and was more likely to be either working or a student with a lower household median income. This group also was less likely to have a history of substance abuse or dependence for drugs other than alcohol and marijuana. These results are based on a small sample size, analysis of larger studies is needed. In addition, more work is needed to better understand the reasons for attrition from both research studies and standard psychiatric care.

There is currently enough evidence in the literature to question the continued use of Last Observation Carrier Forward, especially when there are differences in attrition rates between treatment groups. Further study, of these differences as well as differences between attrition and non-attrition groups is needed. One potential method is the use of a meta-analysis with the use of effect sizes to quantify the magnitude of difference between those who stay in a study or in treatment and those who do not. Exploration of the differences between pooled samples and individual studies of people in a first episode of schizophrenia spectrum disorders is also needed.

Psychiatric nurses and other mental health practitioners are in a key position to advocate for early identification, intervention and treatment in the first episode of a schizophrenia spectrum disorder. The incorporation of recovery oriented client centered care models into usual care will require learning and understanding the philosophy of these models and newer treatments and their methods. Ongoing research is needed to better understand the lived experience of people in a first episode, especially why they drop out of treatment in such high numbers, as well as to assess the effectiveness of different treatment methods. Reasons for attrition may be better understood when we have a clearer understanding of the barriers to care and those factors affecting alliance development with mental health practitioners. Existing mental health systems will need to be modified, to better meet the needs of young adults, as they move along a path toward recovery. Major goals include promoting skill development to enhance autonomy, symptom management and relapse prevention, along with promoting good healthy habits, and the prevention of disability, can lead to positive outcomes. Finding better ways to manage factors that result in poor outcomes, such as substance use, is critical. It is clear that recovery from a first episode SSD is enhanced by early intervention and adherence to treatment.

Early identification and intensive treatment may help improve treatment outcomes, but we can not forget that with over fifty years of modern psychopharmacology, more than half of the people with schizophrenia drop out of treatment and are not receiving medication or other forms of treatment. Medication used in the treatment of schizophrenia does not treat all dimensions of this illness, most

notable the neurocognitive deficits. Clearly, developing comprehensive treatment is complicated, and medication is only one piece of the puzzle.

# Appendix A.

1. Permission
2. Boston College IRB Approval
3. Beth Israel Deaconess Medical Center IRB approval

**DARTMOUTH MEDICAL SCHOOL**

Alan I. Green, M.D.
*Raymond Sobel Professor of Psychiatry*
*Professor of Pharmacology and Toxicology*
*Chairman Department of Psychiatry*

Dartmouth-Hitchcock Medical Center
One Medical Center Drive
Lebanon, NH 03756-0001
Telephone: (603) 650-7549
Fax: (603) 650-8415

May 6, 2007

Joanne D. Wojcik, APRN, BC
21 Fifield St.
Watertown, MA 02472

Dear Joanne:

As the Principal Investigator of the following three research projects, I give permission for their use in the secondary analysis of data for the dissertation of Joanne Wojcik, a PHD student at the Connell School of Nursing at Boston College. I understand data from the three studies will be combined. The purpose of this dissertation is to determine if there is a difference between those who remain in a study and those who withdraw from the study prior to its completion in demographic, illness and treatment characteristics.

1. Clozapine or Haloperidol in First Episode Schizophrenia (CHFE)
2. The Acute and Long-term Efficacy of Olanzapine in First Episode Psychotic Disorders:

   A Randomized Double-Blind Comparison with Haloperidol (OLZ)

   (MMHC site only)
3. Efficacy and Tolerability of Olanzapine, Quitiapine and Risperidone in the

   Treatment of First Episode Psychosis: A Randomized Double-Blind 52-week

   Comparison (CAFÉ) (MMHC site only)

Sincerely,

Alan I. Green, M.D.

**BOSTON COLLEGE**
**Institutional Review Board**
Office for Research Protections
Waul House, 3rd Floor
Phone: (617) 552-4778, fax: (617) 552-0948

**Protocol IRB: 09.046.01**

TO: Joanne Wojcik

FROM: Institutional Review Board – Office for Research Protections

DATE: August 5, 2008

RE: Clinical Characteristics Of People In Randomized Clinical Trials Of First Episode Schizophrenia Spectrum Disorders: Attrition Versus Non-Attrition Groups

**Notice of Evaluation- [EXEMPT 45 CFR 46.101(b) (4)]**

The Office for Research Protections (ORP) has evaluated the project named above. According to the information provided, you intend to study attrition versus non-attrition groups of people in randomized clinical trials of first episode schizophrenia spectrum disorders. This is a minimal risk study.

This study has been granted an exemption from Boston College IRB review in accordance with 45 CFR 46.101 (b) (4), which provides exemption for research with pre-existing data sources in which the information will not be recorded in such a manner that subjects can be identified, directly or through identifiers linked to the subjects. This designation is based on the assumption that the materials that you submitted to the ORP contain a complete and accurate description of all the ways in which human subjects are involved in your research.

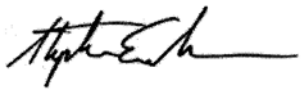
This exemption is given with the following conditions:

1. You will conduct the project according to the plans and protocol you submitted;
2. No further contact with the ORP is necessary unless you make changes to your project or adverse events or injuries to subjects occur;
3. If you propose to make any changes in the project, you must submit the changes to the ORP for IRB review; you will not initiate any changes until they have been reviewed and approved by the IRB;
4. If any adverse events or injuries to subjects occur, you will report these immediately to the ORP.

The University appreciates your efforts to conduct research in compliance with the federal regulations that have been established to ensure the protection of human subjects in research.

**Date of Exemption: August 5, 2008**

Sincerely,



Stephen Erickson
Interim Director
Office for Research Protections
TSL

# Application: Notification of Determination of Exemption

## Protocol #: 2008P-000248; BIDMC

To: Joanne Wojcik, M.S., A.P.R.N., B.C.
Psychiatry

Title of Protocol: **Clinical Characteristics of People in Randomized Clinical Trials of First Episode Schizophrenic Spectrum Disorders: Attrition Versus Non-Attrition Groups**

Issue Date: 7/3/08
Determination Date: 7/14/08

The Beth Israel Deaconess Medical Center Committee on Clinical Investigations certifies the exempt status of the referenced protocol, under exemption number 4 ("research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects") of the Code of Federal Regulations, 45 CFR 46.101(b).

You are not required to provide the CCI with records or reports and do not need to communicate with the CCI regarding your protocol unless you alter the design of your study. In addition, the CCI is not required to review and approve exempt research annually at continuing review. Please direct any questions to the Committee on Clinical Investigations (CCI) at (617)667-0476. The fax number for the CCI is (617)975-5050. Additional information can be found on the CCI website: http://research.bidmc.harvard.edu/OST/ClinicalTrials/default.asp.

Alan Lisbon, MD
Chair, Committee on Clinical Investigations

7/17/2008
Date of Correspondence

Appendix B. *Combined Studies Entry and Attrition*

| | ClozHal | OlzHal | OlzQueRis | Combined |
|---|---|---|---|---|
| Phase I | N | N | N | N |
| Consented | 44 | 32 | 19 | 95 |
| Withdrew Consent | 1 | 2 | | 3 |
| Lost to Follow-up | | | 2 | 2 |
| Fail Inclusion Criteria | 7 | 1 | | 8 |
| Evaluable | 36 | 29 | 17 | 82 |
| Withdrew too Psychotic | 2 | | | 2 |
| Withdrew Consent | 2 | 2 | 2 | 6 |
| Fail Inclusion Criteria | 5 | 3 | 3 | 11 |
| Phase II | | | | |
| Randomization | | | | |
| Study Medication (wk 1-24) | 27 | 24 | 12 | 63 |
| Withdrew Consent | 2 | 1 | 1 | 4 |
| Lack of Efficacy | 6 | 10 | 1 | 17 |
| Adverse Events | 4 | 1 | 1 | 6 |
| Moved | 4 | | 1 | 5 |
| Medication Non-adherence | | 1 | | 1 |
| Require Disallowed Medication | | 2 | | 2 |
| Complete 24 Weeks | 12 | 9 | 8 | 29 |

Appendix C.

*Demographic Characteristics From Each Study and Final Variables*

---

Independent or grouping variables:

Attrition

did not complete study (no) = 0

completed study (yes) = 1

Research study:

ClozHal = 1

OlzHal = 2

OlzQueRis = 3

Dependent Variables:

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| 1. Age | date of birth | date of birth | date of birth | age in years at baseline |
| 2. Gender | male=1, female=2 | male, female | male, female | male=0, female=1 |

Appendix C (continued).

*Demographic Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| 3. Race/Ethnicity | | | | |
| | 1 = White | Caucasian | White | 1= Caucasian |
| | 2 = Black, not Hispanic | African Descent | Black or | 2 = African American |
| | 3 = East/SE Asian or | East/SE Asian | African American | 3 = Asian |
| | Pacific Islander | Western Asian | American Indian or | 4 = Hispanic |
| | 4 = Western Asian (India and Pakistan) | Hispanic | Alaskan Native Asian | |
| | 5 = Hispanic | | Native Hawaiian or other Pacific Islander | |
| 4. Marital Status | 1 = single/never married | From record review | married | 1 = single/never married |
| | 2 = married/common law | | widowed | 2 = married/common law |

Appendix C (continued).

*Demographic Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| | 3 = separated | | divorced | 3 = separated |
| | 4 = divorced | | separated | 4 = divorced |
| | 5 = widowed | | never married | |
| 5. Marital Status (collapsed) | | | | |
| | | | | 0 = never married |
| | | | | 1 = ever married |

6. School attendance in past 12 months prior to baseline _____,

| If student, current education level | Level of school past 12 months | Level completed | Highest level of school in past year |
|---|---|---|---|
| 1 = high school | 1 = GED | GED/ high school | 0 = not in school |
| 2 = GED | 2 = secondary | some college, did | 1 = in GED/HS classes |
| 3 = technical school | 3 = adult education | not graduate | 2 = in college/graduate school |

Appendix C (continued).

*Demographic Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| | 4 = non-degree college program<br>5 = two-year college<br>6 = four-year college<br>7 = graduate School<br>8 = Doctoral Level<br>97 = Other _____ | 4 = community college<br>5 = vocational/ technical center<br>6 = trade school<br>7 = 4 year college<br>8 = college/university graduate level<br>9 = other | community college/ technical school degree<br>college graduate<br>college graduate and some master's level courses<br>Master's degree completed<br>Advanced degree courses, not graduated<br>Advanced degree completed | |

Appendix C (continued).

*Demographic Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| 7. Number of years of completed education (HS/GED = 12) | | | | |
| | From above item | From above item | From above item | # of years education___ |
| 8. Left school due to symptoms from research record and admission history | | | | |
| | Admission History | Admission History | Admission History | no = 0, yes = 1 |
| Living situation | | | | |
| 9. Highest level in the previous year and | | | | |
| 10. Highest level in the month prior to baseline | | | | |
| | 1 = Independent<br>2 = Sheltered apartment<br>3 = Halfway house<br>4 = Quarterway house<br>5 = Foster home | 1 = Independent<br>2 = Apartment - supervised<br>3 = Apartment - therapeutic | 1 = Independent<br>2 = Apartment - supervised<br>3 = Apartment - therapeutic | 1 = Independent<br>2 = Dormitory<br>3 = Family shelter<br>4 = Homeless, street |

Appendix C (continued).

*Demographic Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| | 6 = Live with family in dependent status | 4 = Apartment - association | 4 = Apartment - association | |
| | 7 = Street or shelter | 5 = Apartment - therapeutic family | 5 = Apartment - therapeutic family | |
| | 8 = Inpatient | 6 = Group home | 6 = Group home | |
| | 97 = Other:_____ | 7 = Family | 7 = Family | |
| | 98 = Refused to answer | 8 = Hospital or institution | 8 = Hospital or institution | |
| | | 9 = Homeless | 9 = Homeless | |
| | | 99 = Other_____ | 99 = Other_____ | |
| 11. The highest level of employment in the year prior to baseline and | | | | |
| 12. the month prior to baseline | | | | |
| | Is patient currently employed (no = 0, | Work status (majority of time during the 12 months | Work status (majority time since last visit or | Work status as defined above |

Appendix C (continued).

*Demographic Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| | yes = 1) and from detailed chart of employment history as per final variable | prior to entering study) and from admission history 1 = working for pay 2 = full-time sheltered program 3 = part-time sheltered program 4 = student (full or part-time) 5 = retired 6 = keeping house 7 = volunteer work | past month for baseline visit and history) 1 = working for pay 2 = full-time sheltered program 3 = part-time sheltered program 4 = student – full-time 5 = student – part-time 6 = retired 7 = housekeeping | 0 = Unemployed, due to study disease disability 1 = working for pay 2 = student |

Appendix C (continued).

*Demographic Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| | | 8 = unemployed, not due to study disease disability<br>9 = Unemployed, due to study disease disability | 8 = volunteer work<br>9 = Unemployed, not due to study disease disability<br>10 = Unemployed, due to study disease disability | |
| 13. highest number of hours of work per week in the year prior to baseline | | | | |
| | # of hours per week__ | # of hours per week__ | # of hours per week__ | # of hours per week__ |
| 14. Level of functioning (includes working for pay, student, and housekeeping) majority of time in the year prior to baseline | | | | |
| From admission history, NPQST, & Heinrich QOL | 1 = no useful functioning<br>2 = >0 to ≤25% of time<br>3 = >25% to ≤50% of time<br>4 = >50% to ≤75% of time | 1 = no useful functioning<br>2 = >0 to ≤25% of time<br>3 = >25% to ≤50%<br>4 = >50% to ≤75% | 1 = no useful functioning<br>2 = >0 to ≤25% of time<br>3 = >25% to ≤50%<br>4 = >50% to ≤75% | |

Appendix C (continued).

*Demographic Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| | | 5 = >75% to ≤100% of time | 5 = >75% to ≤100% | 5 = >75% to ≤100% |
| 15. Median household income | | | | $_____ |

Appendix D.

*Variables for Illness Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| 16. Psychiatric Axis I diagnosis | | | | |
| | SADS interview | SCID interview | SCID interview | |
| | Schizophrenia | Schizophrenia | Schizophrenia | Schizophrenia |
| | | Schizophreniform | Schizophreniform | Schizophreniform |
| | | Schizoaffective | Schizoaffective | Schizoaffective |
| | | Depressed type | Depressed type | Depressed type |
| 17. Age at onset of psychosis | | | | age in years_____ |
| 18. Severity of psychiatric symptoms at screening, | | | | |
| 19. Severity of psychiatric symptoms at baseline, | | | | |
| | Clinical Global Impression (CGI) | (CGI) Severity | (CGI) Severity | (CGI) Severity |
| | 1 = Normal, not at all ill | 1 = Normal, not at all ill | 1 = Normal, not at all ill | 1 = Normal, not at all ill |
| | 2 = Borderline mentally ill | 2 = Borderline mentally ill | 2 = Borderline mentally ill | 2 = Borderline mentally ill |

Appendix D (continued).

*Variables for Illness Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| | 3 = Mildly ill | 3 = Mildly ill | 3 = Mildly ill | 3 = Mildly ill |
| | 4 = Moderately ill | 4 = Moderately ill | 4 = Moderately ill | 4 = Moderately ill |
| | 5 = Markedly ill | 5 = Markedly ill | 5 = Markedly ill | 5 = Markedly ill |
| | 6 = Severely ill | 6 = Severely ill | 6 = Severely ill | 6 = Severely ill |
| | 7 = Among the most extremely ill patients | 7 = Among the most extremely ill patients | 7 = Among the most extremely ill patients | 7 = Among the most extremely ill patients |

20. Duration of untreated psychosis (DUP) – difference in the dates in weeks between the date (month/year) of onset of the first psychotic symptom and the date (month/year) of onset of first antipsychotic drug use: DUP weeks_____

21. Number of psychiatric hospitalizations prior to the study _____

Lifetime History of Alcohol and Drug Use – for the following substance use variables (plus the use of weekly visit questionnaires).

| | | | | |
|---|---|---|---|---|
| | SADS | SCID | SCID | |
| | Lifetime history | Lifetime history | Lifetime history | Lifetime history |

Appendix D (continued).

*Variables for Illness Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| | Absent | Absent | Absent | |
| | Abuse | Abuse | Abuse | |
| | Dependence | Dependence | Dependence | |

| Variable | Final Variable |
|---|---|
| 22. Lifetime history of alcohol misuse | |
| 23. Lifetime history of marijuana use | |
| 24. Lifetime history of cocaine | 0 = no use |
| 25. Lifetime history of opiates | 1 = use |
| 26. Lifetime history of PCP | 2 = abuse |
| 27. Lifetime history of LSD | 3 = dependence |
| 28. Lifetime history of Amphetamines | |
| 29. Lifetime use of other drugs (combines cocaine, opiates, PCP, LSD, and amphetamine) | |

Appendix D (continued).

*Variables for Illness Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| Alcohol - Alcohol Use Scale/Drug Use Scale (AUS/DUS) | | | | 1 = abstinent |
| 30 - 31. Alcohol use during month before baseline and during double-blind study | | | | 2 = use |
| . | | | | |
| Marijuana - Alcohol Use Scale/Drug Use Scale (AUS/DUS) | | | | 3 = abuse |
| 32 - 33. marijuana use during month before baseline and during double-blind study | | | | 4 = dependence |
| | | | | 5 = dependence w/ hosp |
| 34. Age at first alcohol use | | | | |
| | Age in years | Age in years | Age in years | Age in years |
| 35. Age at first marijuana use | | | | |
| | Age in years | Age in years | Age in years | Age in years |
| Cognitive Functioning | | | | |
| Estimated premorbid IQ - Wide Range Achievement Test (WRAT III) or National Adult Reading Test (NART) | | | | |
| | WRAT III | NART | WRAT III | WRAT III or NART |

Appendix D (continued).

*Variables for Illness Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| 36. Executive Functioning | Standard Score Percentile | Standard Score Percentile | Standard Score Percentile | Standard Score ___ Percentile_____ |
| Wisconsin Card Sort (WCST-64) | | | | |
| 37. | WCST-64 percentile rank for perseverative responses | WCST-64 percentile rank for perseverative responses | WCST-64 (computer) percentile rank for perseverative responses | WCST-64 percentile rank for perseverative responses___ |
| 38. | # categories completed | # categories completed | # categories completed | # categories completed ___ |
| Language Functioning | | | | |
| Controlled Word Association Test (COWAT - FAS) _____ | | | | |
| 39. | Total # words Percentile score | Total # words Percentile score | Total # words Percentile score | Total # words_____ Percentile score_____ |

Appendix D (continued).

*Variables for Illness Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| Memory Functioning | | | | |
| Wechsler Memory Scale – Revised (WMS-R) Logical Memory (LM) or Hopkins Verbal Learning Test (HVLT) | | | | |
| Immediate | WMS-R LM Standardized Scores | WMS-R LM Standardized Scores | HVLT Standardized Scores | WMS-R or HVLT Standardized Scores |
| 40. | Percentile | Percentile | Percentile | Percentile |
| Motor Functioning | | | | |
| Finger Tapping or Grooved Pegboard Dominant hand | | | | |
| 41. | Finger Tapping Standardized T scores and percentile rank | Finger Tapping Standardized T scores and percentile rank | Grooved Pegboard (GP) Standardized T scores and percentile rank | Finger Tapping or GP Standardized T scores and percentile rank |

Appendix D (continued).

*Variables for Illness Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| Attention (visual attention) | | | | |
| Cancellation Test (CT) will use the organizational score and time to complete task to yield a score of normal or abnormal. Visual CPT-IP (identical pairs version) standard score and percentile rank will be converted to a score of no impairment (<-1.5 standard deviation), mild to moderate impairment (≥1.5 - < 3.0 standard deviation), and severe impairment (≥3.0 standard deviation). | | | | |
| | Cancellation Test Organizational score Time to completion | Visual CPT-IP d-prime score | Visual CPT-IP d'prime score | CT or Visual CPT-IP |
| 42. | | | | normal or abnormal |

Appendix E.

*Variables for Treatment Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| 43. Participation is the timing of withdrawal – early = screening to baseline; double-blind = weeks 1- 24. | | | | |
| | | | | 1 = early withdrawal |
| | | | | 2 = double-blind withdrawal |
| 44. Number of weeks completed in the double-blind phase from study book. | | | | |
| | # of weeks | # of weeks | # of weeks | # of weeks _____ |
| 45. Reason for study termination obtained from study book | | | | |
| | 1. adverse event | 1. protocol complete | 1. adverse event | 1. adverse event |
| | 2. lack of efficacy (LOE) patient perception | 2. adverse event 3. satisfactory response | 2. (LOE) patient perception | 2. (LOE) patient perception |
| | 3. LOE – MD perception | 4. LOE – MD perception | 3. LOE – MD perception | 3. LOE - MD perception |
| | 4. LOE patient & MD agree | 5. LOE – patient & MD agree | 4. LOE – patient & MD agree | 4. LOE – patient & MD agree |

Appendix E (continued).

*Variables for Treatment Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| | 5. patient withdrew consent | 6. patient withdrew consent | 5. patient withdrew consent | 5. patient withdrew consent |
| | 6. lost to follow-up | 7. lost to follow-up | 6. lost to follow-up | 6. lost to follow-up |
| | 7. patient moved | 8. patient moved | 7. patient moved | 7. patient moved |
| | 8. inclusion/exclusion criteria not met | 9. inclusion/exclusion criteria not met | 8. inclusion/exclusion criteria not met | 8. inclusion/exclusion criteria not met |
| | 9. protocol violation | 10. protocol violation | 9. protocol violation | 9. too psychotic for procedures |
| | | | | 10. requires disallowed medication |
| | | | | 11. patient stopped study medication |
| | | | | 12. severity criteria not met |

Appendix E (continued).

*Variables for Treatment Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| 46. Study termination collapsed into 3 groups | | | | 1. Patient related issues (withdraw consent, move, lost to follow-up)<br>2. Medication related issues (lack of efficacy, adverse events)<br>3. Protocol related issues (entry severity criteria, disallowed medication) |
| 47. Washout classified as either having a antipsychotic medication washout or not | | | | |
| | Had washout | Had washout | No washout | 0. no washout<br>1. washout |

Appendix E (continued).

*Variables for Treatment Characteristics From Each Study and Final Variables*

| Variable | ClozHal | OlzHal | OlzQueRis | Final Variable |
|---|---|---|---|---|
| 48. Number of days in washout phase of study (OLZQUERIS did not have a washout phase) from study book | | | | |
| | # of days | # of days | No washout phase | # of days_____ |
| 49. Randomized Antipsychotic Medication | | | | 0 = not randomized |
| | Haloperidol | Haloperidol | Quetiapine | 1 = Clozapine |
| | Clozapine | Olanzapine | Olanzapine | 2 = Olanzapine |
| | | | Risperidone | 3 = Haloperidol |
| | | | | 4 = Quetiapine |
| | | | | 5 = Risperidone |
| 50. Randomized Antipsychotic medication as typical and atypical | | | | 0 = typical |
| | | | | 1 = atypical |

Appendix F. *Data Collection Tool*

---

CLOZHAL_____ OLZHAL_____ OLZQUERIS_____

Subject ID :_____

School attendance:

In the 12 months prior to baseline_____

Number of years of completed education_____ (GED/HS = 12)

Left school due to symptoms from research record and admission history_____

Living situation

highest level in the year prior to baseline_____

1 = Independent

2 = Family

3 = Apartment – off site supervised

4 = Apartment – live in supervision/therapeutic family

5 = Group home (halfway house, quarterway house

6 = Hospital or institution (inpatient)

7 = Homeless, shelter or on the street

8 = Other_____

Level of employment:

highest level in the year prior to baseline_____

Appendix F (continued). *Data Collection Tool*

1 = working for pay

2 = student - full-time

3 = student - part-time

4 = sheltered program full-time

5 = sheltered program part-time

6 = volunteer work

7 = retired

8 = housekeeping

9 = Unemployed, not due to study disease disability

10 = Unemployed, due to study disease disability

Number of hours worked/week

highest level in the year prior to baseline_____

Level of functioning (includes working for pay, student, housekeeping, and volunteer work) (CLOZHAL from admission history, NPQST & Heinrich QOL)

month prior to baseline_____

highest level in the year prior to baseline_____

1 = no useful functioning

2 = >0 to ≤25% of time

3 = >25% to ≤50% of time

4 = >50% to ≤75% of time

5 = >75% to ≤100% of time

Appendix F (continued). *Data Collection Tool*

---

Duration of untreated psychosis (DUP) – difference in the dates in weeks between the date (month/year) of onset of the first psychotic symptom and the date (month/year) of onset of first antipsychotic drug use DUP weeks _____

Lifetime history of alcohol use_____

Lifetime history of marijuana use_____

Lifetime history of cocaine use_____

Lifetime history of opiate use_____

Lifetime history of PCP use_____

Lifetime history of LSD use_____

Lifetime history of Amphetamine use_____

0 = no use 1 = use 2 = abuse 3 = dependence

Alcohol - Alcohol Use Scale/Drug Use Scale (AUS/DUS) during month before baseline_____

Marijuana - Alcohol Use Scale/Drug Use Scale (AUS/DUS) during month before baseline_____

Cocaine - Alcohol Use Scale/Drug Use Scale (AUS/DUS) during month before baseline_____

Opiates - Alcohol Use Scale/Drug Use Scale (AUS/DUS) during month before baseline_____

PCP - Alcohol Use Scale/Drug Use Scale (AUS/DUS) during month before baseline_____

Appendix F (continued). *Data Collection Tool*

---

LSD - Alcohol Use Scale/Drug Use Scale (AUS/DUS) during month before baseline_____

Amphetamines - Alcohol Use Scale/Drug Use Scale (AUS/DUS) during month before baseline_____

1 = abstinent

2 = use

3 = abuse

4 = dependence

5 = dependence w/ hosp

Age at first alcohol use_____

Age at first marijuana use_____

Number of days in washout phase_____

Did participant complete study? 0 = no, 1 = yes_____

What phase did participant leave study?

1 = screening

2 = drug taper

3 = washout

4 = double-blind treatment

Timing of withdrawal

1 = early (screening to baseline)

2 = double-blind weeks 1-24

Appendix F (continued). *Data Collection Tool*

Number of weeks completed double-blind phase_____

Reason for termination from study_____

0 = completed

1 = adverse event

2 = lack of efficacy (LOE) patient perception

3 = LOE MD perception

4 = LOE patient and MD agree

5 = patient withdrew consent

6 = lost to follow-up

7 = patient moved

8 = inclusion/exclusion criteria not met

9 = protocol violation

Appendix G. *Study Variables by Type of Proposed Analysis*

| Chi Square | t-test (Mann-Whitney U) |
|---|---|
| Demographic Variables (variable number as listed in Appendix C): | |
| Gender (2) | Age (1) |
| Race, Ethnicity (3) | |
| Marital Status (4, 5) | |
| Level of School Attendance (6) | Total number of years of education (7) |
| Left school due to symptoms (8) | |
| Living Situation (9, 10) | |
| Level of Employment (11, 12) | Employment # of hours (13) |
| Level of Functioning (14) | Median Household Income (15) |
| Illness Characteristics (variable number as listed in Appendix D): | |
| Chi Square | t-test (Mann Whitney U) |
| Major Diagnostic Group (16) | Age at onset of psychosis (17) |
| Substance Use (22 - 33) | Symptom Severity – CGI (18 -19) |
| Visual Attention Functioning (42) | Duration of Untreated Psychosis (20) |
| | Number of Previous Hospitalizations (21) |
| | Age at First Alcohol Use (34) |
| | Age at First Marijuana Use (35) |
| | Cognitive Functioning (36 - 41) |

Appendix G (continued). *Study Variables by Type of Proposed Analysis*

---

Treatment Characteristics (variable number as listed in Appendix E):

| Chi Square | t-test (Mann Whitney U) |
|---|---|
| Timing of Withdrawal (43) | Double-blind Completion in Weeks (44) |
| Reason for Study Withdrawal (45 - 46) | Antipsychotic Drug Washout (days) (48) |
| Washout (47) | |
| Antipsychotic Medication (49 - 50) | |

Appendix H: *Effect Size Calculator Used for Continuous Variables*

Retrieved from on May 15, 2009: http://web.uccs.edu/lbecker/Psy590/escalc3.htm

# Effect Size Calculators

Calculate Cohen's *d* and the effect-size correlation, $r_{Y\lambda}$, using --

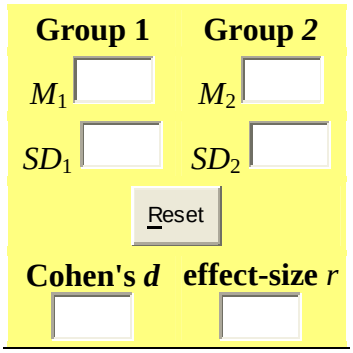
- **means and standard deviations**
- **independent groups *t* test values and *df***

For a discussion of these effect size measures see Effect Size Lecture Notes

---

## Calculate *d* and *r* using means and standard deviations

Calculate the value of Cohen's *d* and the effect-size correlation, $r_{Y\lambda}$, using the means and standard deviations of two groups (treatment and control).




Cohen's $d = M_1 - M_2 / \sigma_{pooled}$
where $\sigma_{pooled} = \sqrt{[(\sigma_1^2 + \sigma_2^2) / 2]}$

$r_{Y\lambda} = d / \sqrt{(d^2 + 4)}$

Note: d and $r_{Y\lambda}$ are positive if the mean difference is in the predicted direction.

# Appendix I. *Question 1*

Table 11.

*Demographic Characteristics - Comparison of the Three Double-blind, Randomized Studies*

Table 12.

*Illness Characteristics - Comparison of the Three Double-blind, Randomized Studies*

Table 13.

*Treatment Characteristics - Comparison of the Three Double-blind, Randomized Studies*

Appendix I.

Table 11.

*Demographic Characteristics - Comparison of the Three Double-blind, Randomized Studies*[1]

| | | ClozHal | OlzHal | OlzQueRis | |
|---|---|---|---|---|---|
| Dependent Variables | | | | | p[a] |
| Age | (N) | (36) | (29) | (17) | .648 |
| | Mean | 22.72 | 23.28 | 21.94 | |
| | (SD) | (4.25) | (4.72) | (4.59) | |
| | Median | 21.5 | 20.3 | 20.0 | |
| | (Range) | (18 - 34) | (17 - 34) | (18 - 36) | |
| Education (years) | (N) | (36) | (29) | (16) | .296 |
| | Mean | 12.11 | 12.48 | 11.26 | |
| | (SD) | (2.40) | (2.42) | (2.52) | |
| | Median | 12.0 | 12.0 | 12.0 | |
| | (Range) | (3 - 16) | (8 - 19) | (6 - 16) | |
| Employment (hours/week) | (N) | (29) | (29) | (12) | .217 |
| | Mean | 15.62 | 23.45 | 14.17 | |
| | (SD) | (17.7) | (18.71) | (21.9) | |
| | Median | 0 | 30.0 | 0 | |
| | (Range) | (0 - 40) | (0 - 50) | (0 - 50) | |

Table 11 (continued).

*Demographic Characteristics - Comparison of the Three Double-blind, Randomized Studies*[1]

| | | ClozHal | | OlzHal | | OlzQueRis | | |
|---|---|---|---|---|---|---|---|---|
| Dependent Variables | | | | | | | | p[a] |
| Median Income | (N) | (33) | | (17) | | (17) | | .031* |
| | Mean | $49,722 | | $36,362 | | $41,295 | | |
| | (SD) | ($18,975) | | ($14,491) | | ($20,933) | | |
| | Median | $45,984 | | $32,022 | | $41,186 | | |
| | (Range) | (11 - 97k) | | (11 - 66k) | | (11 - 98k) | | |
| | | (N) | % | (N) | % | (N) | % | p[b] |
| Gender | | (n = 36) | | (n = 29) | | (n = 17) | | .678 |
| Male | | (31) | 86.1% | (26) | 89.7% | (16) | 94.1% | |
| Female | | (5) | 13.9% | (3) | 10.3% | (1) | 5.9% | |
| Race | | (n = 36) | | (n = 29) | | (n = 17) | | .695 |
| Non-Caucasian | | (18) | 50% | (12) | 41.4% | (9) | 52.9% | |
| Caucasian | | (18) | 50% | (17) | 58.6% | (8) | 47.1% | |

Table 11 (continued).

*Demographic Characteristics - Comparison of the Three Double-blind, Randomized Studies*

| Dependent Variables | ClozHal | | OlzHal | | OlzQueRis | | p[b] |
|---|---|---|---|---|---|---|---|
| School Attendance | (n = 34) | | (n = 28) | | (n = 14) | | .930 |
| not in school | (20) | 58.8% | (18) | 62.1% | (9) | 64.3% | |
| in school | (14) | 41.2% | (11) | 37.9% | (5) | 35.7% | |
| Left school | (n = 30) | | (n = 27) | | (n = 15) | | .361 |
| no | (16) | 53.3% | (19) | 70.4% | (8) | 53.3% | |
| yes | (14) | 46.7% | (8) | 29.6% | (7) | 46.7% | |
| Living situation (past year) | (n = 34) | | (n = 29) | | (n = 14) | | .760 |
| independent/dorm | (10) | 29.4% | (9) | 31% | (4) | 28.6% | |
| Family | (22) | 64.7% | (17) | 58.6% | (10) | 71.4% | |
| Homeless | (2) | 5.9% | (3) | 10.3% | (0) | | |
| Employment Status (past year) | (n = 34) | | (n = 29) | | (n = 15) | | .01** |
| not working | (9) | 26.5% | (2) | 6.9% | (7) | 46.7% | |
| working/student | (25) | 73.5% | (27) | 93.1% | (8) | 53.3% | |

Table 11 (continued).

*Demographic Characteristics - Comparison of the Three Double-blind, Randomized Studies*

| Dependent Variables | ClozHal | | OlzHal | | OlzQueRis | | |
|---|---|---|---|---|---|---|---|
| | (N) | % | (N) | % | (N) | % | p[b] |
| Functional Level (past year) | (n = 31) | | (n = 29) | | (n = 13) | | .033* |
| no useful functioning to 25% | (9) | 29% | (2) | 6.9% | (5) | 38.5% | |
| 25 to 100% | (22) | 71% | (27) | 93.1% | (8) | 61.5% | |

[1] p values are reported without Bonferroni correction
[a] Welch Test
[b] Chi Square
* $p \leq .05$ ** $p \leq .01$ *** $p \leq .001$

Table 12.

*Illness Characteristics - Comparison of the Three Double-blind, Randomized Studies*[1]

| | | ClozHal | OlzHal | OlzQueRis | |
|---|---|---|---|---|---|
| Dependent Variables | | | | | p[a] |
| Age at onset | (N) | (36) | (28) | (17) | .747 |
| | Mean | 21.4 | 22.3 | 21.5 | |
| | (SD) | (4.14) | (4.67) | (4.78) | |
| | Median | 20 | 21 | 20 | |
| | (Range) | (16 - 33) | (16 - 33) | (17 - 36) | |
| Severity of illness - Screening | (N) | (34) | (24) | (14) | .005** |
| | Mean | 4.62 | 4.54 | 5.36 | |
| | (SD) | (0.82) | (0.66) | (0.74) | |
| | Median | 5 | 4 | 5 | |
| | (Range) | (2 – 6) | (4 – 6) | (4 – 7) | |
| Severity of illness – Baseline | (N) | (31) | (23) | (14) | .761 |
| | Mean | 4.52 | 4.39 | 4.29 | |
| | (SD) | (0.99) | (0.99) | (0.99) | |
| | Median | 5 | 4 | 5 | |
| | (Range) | (2 – 6) | (2 – 6) | (2 – 5) | |

Table 12 (continued).

*Illness Characteristics - Comparison of the Three Double-blind, Randomized Studies*[1]

| | | ClozHal | OlzHal | OlzQueRis | |
|---|---|---|---|---|---|
| Dependent Variables | | | | | p[a] |
| Alcohol | (N) | (12) | (12) | (11) | .994 |
| (Age 1st use) | Mean | 14.5 | 14.58 | 14.45 | |
| | (SD) | (2.07) | (1.15) | (2.25) | |
| | Median | 15 | 15.5 | 14 | |
| | (Range) | (10 - 17) | (7 - 19) | (12 - 18) | |
| Marijuana | (N) | (19) | (11) | (12) | .621 |
| (Age 1st use) | Mean | 15.11 | 15.6 | 14.75 | |
| | (SD) | (2.28) | (1.84) | (1.96) | |
| | Median | 15 | 16 | 14.5 | |
| | (Range) | (8 - 19) | (13 - 19) | (12 -18) | |
| Intellectual Functioning | (N) | (30) | (15) | (11) | .033* |
| | Mean | 101.5 | 106.6 | 107.36 | |
| | (SD) | (11.64) | (7.79) | (9.70) | |
| | Median | 101 | 106 | 109 | |
| | (Range) | (70 - 116) | (92 - 118) | (92 - 119) | |

Table 12 (continued).

*Illness Characteristics - Comparison of the Three Double-blind, Randomized Studies*[1]

| Dependent Variables | | ClozHal | OlzHal | OlzQueRis | p[a] |
|---|---|---|---|---|---|
| Executive Functioning - Perseverative | (N) | (31) | (23) | (11) | .838 |
| | Mean | 49.48 | 52.08 | 45.36 | |
| | (SD) | (34.89) | (33.94) | (28.63) | |
| | Median | 42 | 50 | 50 | |
| | (Range) | (0.5 - 99.9) | (1 – 99) | (1 – 82) | |
| Executive Functioning - Categories | (N) | (31) | (22) | (11) | .599 |
| | Mean | 2.23 | 2.41 | 2.82 | |
| | (SD) | (1.56) | (1.7) | (1.66) | |
| | Median | 2 | 2 | 3 | |
| | (Range) | (0 - 6) | (0 - 5) | (0 - 5) | |
| Language Functioning | (N) | (30) | (24) | (11) | .528 |
| | Mean | 46.37 | 37.58 | 43.27 | |
| | (SD) | (23.13) | (30.83) | (33.49) | |
| | Median | 44.5 | 34.5 | 38 | |
| | (Range) | (4 - 84) | (2 - 96) | (3 - 99) | |

Table 12 (continued).

*Illness Characteristics - Comparison of the Three Double-blind, Randomized Studies*[1]

| Dependent Variables | | ClozHal | OlzHal | OlzQueRis | p[a] |
|---|---|---|---|---|---|
| Memory Functioning | (N) | (30) | (23) | (12) | .000*** |
| | Mean | 27.5 | 19.57 | 0.59 | |
| | (SD) | (29.8) | (18.94) | (1.10) | |
| | Median | 14 | 16 | 0.15 | |
| | (Range) | (1 - 94) | (1 - 74) | (0.1-4) | |
| Motor Functioning | (N) | (31) | (23) | (11) | .161 |
| | Mean | 26.84 | 27.7 | 45.27 | |
| | (SD) | (22.07) | (31.35) | (27.94) | |
| | Median | 24 | 16 | 47 | |
| | (Range) | (2 - 76) | (0.06 - 97) | (4 - 85) | |

| | (N) | % | (N) | % | (N) | % | p[b] |
|---|---|---|---|---|---|---|---|
| Visual Attention Functioning | (n = 29) | | (n = 18) | | (n = 10) | | .007** |
| normal | (11) | 37.9% | (1) | 5.6% | (6) | 60% | |
| abnormal | (18) | 62.1% | (17) | 94.4% | (4) | 40% | |
| Duration of Untreated Psychosis | (n = 32) | | (n = 28) | | (n = 16) | | .291 |
| ≤13 weeks | (15) | 46.9% | (13) | 46.4% | (11) | 68.8% | |
| >13 weeks | (17 ) | 53.1% | (15) | 53.6% | (5) | 31.2% | |

Table 12 (continued).

*Illness Characteristics - Comparison of the Three Double-blind, Randomized Studies*

| Dependent Variables | ClozHal | | OlzHal | | OlzQueRis | | p[b] |
|---|---|---|---|---|---|---|---|
| Psychiatric Hospitalizations | (n = 36) | | (n = 29) | | (n = 15) | | .350 |
| ≤1 | (23) | 63.9% | (14) | 48.3% | (7) | 46.7% | . |
| ≥2 | (13) | 36.1% | (15) | 51.7% | (8) | 53.3% | |
| Lifetime Alcohol | (n = 32) | | (n = 29) | | (n = 15) | | .235 |
| no use and use | (19) | 59.4% | (16) | 55.2% | (5) | 33.3% | |
| abuse and dependence | (13) | 40.6% | (13) | 44.8% | (10) | 66.7% | |
| Lifetime Marijuana | (n = 33) | | (n = 29) | | (n = 15) | | .107 |
| no use and use | (16) | 48.5% | (15) | 51.7% | (3) | 20% | |
| abuse and dependence | (17) | 51.5% | (14) | 48.3% | (12) | 80% | |
| Lifetime other drugs | (n = 32) | | (n = 29) | | (n = 14) | | .225 |
| no use and us | (30) | 93.8% | (27) | 93.1% | (11) | 78.6% | |
| abuse and dependence | (2) | 6.2% | (2) | 6.9% | (3) | 21.4% | |

[1] p values are reported without Bonferroni correction
[a] Welch Test
[b] Chi Square
* $p \leq .05$ ** $p \leq .01$ *** $p \leq .001$

Table 13.

*Treatment Characteristics - Comparison of the Three Double-blind, Randomized Studies*[1]

| Dependent Variables | ClozHal | OlzHal | OlzQueRis | p[a] |
|---|---|---|---|---|
| Double-Blind (weeks) | (27)<br>14.8<br>(9.1)<br>15<br>(1 - 24) | (24)<br>14.8<br>(8.9)<br>17<br>(1 - 24) | (12)<br>19.3<br>(7.1)<br>24<br>(6 - 24) | .189 |

| | (N) | % | (N) | % | (N) | % | p[b] |
|---|---|---|---|---|---|---|---|
| Termination Phase | (n = 25) | | (n = 20) | | (n = 9) | | .279 |
| screening to baseline | (9) | 36% | (5) | 25% | (5) | 55.6% | |
| double-blind | (16) | 64% | (15) | 75% | (4) | 44.4% | |
| Study Completion | (n = 36) | | (n = 29) | | (n = 17) | | .451 |
| No | (25) | 69.4% | (20) | 69% | (9) | 52.9% | |
| Yes | (11) | 30.6% | (9) | 31% | (8) | 47.1% | |

Table 13 (continued).

*Treatment Characteristics - Comparison of the Three Double-blind, Randomized Studies*

| | ClozHal | | OlzHal | | OlzQueRis | | |
|---|---|---|---|---|---|---|---|
| Termination Reason[2] | (n = 25) | | (n = 20) | | (n = 9) | | |
| Lack of efficacy | (6) | 24% | (10) | 50% | (1) | 11.1% | n/a[2] |
| Patient withdrew consent | (6) | 24% | (3) | 15% | (3) | 33.3% | |
| Adverse event | (4) | 16% | (1) | 5% | (1) | 11.1% | |
| Patient moved | (4) | 16% | | | (1) | 11.1% | |
| Inclusion criteria not met | (2) | 8% | (2) | 10% | | | |
| Lost to follow-up | | | | | (3) | 33.3% | |
| Severity criteria not met | (2) | 8% | (1) | 5% | | | |
| Requires disallowed medication | | | (2) | 10% | | | |
| Patient stopped medication | | | (1) | 5% | | | |
| Too psychotic for procedures | (1) | 4% | | | | | |
| Termination (collapsed) | (n = 25) | | (n = 20) | | (n = 9) | | .058 |
| research design | (5) | 20% | (5) | 25% | (0) | | |
| patient related | (10) | 40% | (4) | 20% | (7) | 77.8% | |
| medication related | (10) | 40% | (11) | 55% | (2) | 22.2% | |

Table 13 (continued).

*Treatment Characteristics - Comparison of the Three Double-blind, Randomized Studies*

| Dependent Variables | ClozHal | | OlzHal | | OlzQueRis | | |
|---|---|---|---|---|---|---|---|
| | (N) | % | (N) | % | (N) | % | p |
| Washout (days) (ClozHal & OlzHal only) | (n = 30) | | (n = 27) | | | | .008** |
| ≤ 3 days | (21) | 70% | (9) | 33.3% | | | |
| ≥ 4 days | (9) | 30% | (18) | 66.7% | | | |
| Randomized Medication | (n = 27) | | (n = 24) | | (n = 12) | | - |
| Typical (n = 22) | (11) | 40.7% | (11) | 45.8% | (0) | | |
| Atypical (n = 41) | (16) | 59.3% | (13) | 54.2% | (12) | 100% | |

[1] p values are reported without Bonferroni correction
[a] Welch
[b] Chi Square/Fisher's Exact
[2] Provided for descriptive purposes only.
* p ≤ .05 ** p ≤ .01 *** p ≤ .001

# Appendix J. Question 2

Table 14.

*Demographic Characteristics – Comparison of Attrition versus Non-Attrition in Merged Group*

Table 15.

*Illness Characteristics – Comparison of Attrition versus Non-Attrition in Merged Group*

Table 16.

*Treatment Characteristics – Comparison of Attrition versus Non-Attrition in Merged Group*

Appendix J.

Table 14.

*Demographic Characteristics – Comparison of Attrition versus Non-Attrition in Merged Group*

| | | Attrition Group | Non-Attrition Group | |
|---|---|---|---|---|
| Dependent Variables | | | | |
| | | | | p[c] |
| Age | (N) | (54) | (28) | |
| | Mean | 22.96 | 22.36 | .563 |
| | (SD) | (4.45) | (4.55) | |
| | Median | 22.5 | 20 | |
| | (Range) | (17 – 36) | (18 – 34) | |
| Education (years) | (N) | (53) | (28) | .150 |
| | Mean | 12.36 | 11.54 | |
| | (SD) | (4.45) | (2.38) | |
| | Median | 12 | 12 | |
| | (Range) | (6 – 19) | (3 – 16) | |
| Employment (hours/week) | (N) | (45) | (25) | .748 |
| | Mean | 18.07 | 19.6 | |
| | (SD) | (18.41) | (20.1) | |
| | Median | 18 | 20 | |
| | (Range) | (0 – 50) | (0 – 50) | |
| Median Income | (N) | (42) | (25) | .136 |
| | Mean | $41,765 | $48,275 | |
| | (SD) | ($21,499) | ($13,787) | |
| | Median | $39,507 | $44,260 | |
| | (range) | ($11 – 98k) | ($27 – 84k) | |

| | (N) | % | (N) | % | p[b] |
|---|---|---|---|---|---|
| Gender | (n = 54) | | (n = 28) | | .711 |
| Male | (47) | 87% | (26) | 92.9% | |
| Female | (7) | 13% | (2) | 7.1% | |
| Race | (n = 54) | | (n = 28) | | .249 |
| Non-Caucasian | (23) | 42.6% | (16) | 57.1% | |
| Caucasian | (31) | 57.4% | (12) | 42.9% | |

Table 14 (continued).

*Demographic Characteristics – Comparison of Attrition versus Non-Attrition in Merged Group*

| Dependent Variables | Attrition Group | | Non-Attrition Group | | |
|---|---|---|---|---|---|
| | (N) | % | (N) | % | p[b] |
| School Attendance | (n = 49) | | (n = 28) | | .809 |
| not in school | (29) | 59.2% | (18) | 64.3% | |
| in school | (20) | 40.8% | (10) | 35.7% | |
| Left school | (n = 45) | | (n = 27) | | .805 |
| no | (26) | 57.8% | (17) | 63% | |
| yes | (19) | 42.2% | (10) | 37% | |
| Living situation (past year) | (n = 49) | | (n = 28) | | .304 |
| independent/dorm | (17) | 34.7% | (6) | 21.4% | |
| Family | (30) | 61.2% | (19) | 67.9% | |
| Homeless | (2) | 4.1% | (3) | 10.7% | |
| Employment Status (past year) | (n = 50) | | (n = 28) | | .413 |
| not working | (10) | 20% | (8) | 28.6% | |
| working/student | (40) | 80% | (20) | 71.4% | |
| Functional Level (past year) | (n = 54) | | (n = 28) | | .249 |
| no useful functioning to 25% | (8) | 17% | (8) | 30.8% | |
| 25 to 100% | (39) | 83% | (18) | 69.2% | |

[b] Chi Square/Fisher's Exact
[c] t-tests

Table 15.

*Illness Characteristics – Comparison of Attrition versus Non-Attrition in Merged Group*

| Dependent Variables | | Attrition Group | Non- Attrition Group | $p^c$ |
|---|---|---|---|---|
| Age at onset | (N) | (53) | (28) | |
| | Mean | 22 | 21.29 | .493 |
| | (SD) | (4.49) | (4.35) | |
| | Median | 21 | 19.5 | |
| | (Range) | (16 – 36) | (16 – 33) | |
| Severity of illness – Screening | (N) | (47) | (25) | .856 |
| | Mean | 4.72 | 4.76 | |
| | (SD) | (0.85) | (0.72) | |
| | Median | 5 | 5 | |
| | (Range) | (2 – 7) | (4 – 6) | |
| Severity of illness - Baseline | (N) | (43) | (25) | |
| | Mean | 4.49 | 4.32 | .500 |
| | (SD) | (0.94) | (1.07) | |
| | Median | 5 | 4 | |
| | (Range) | (2 – 6) | (2 – 6) | |
| Alcohol (Age 1st use) | (N) | (19) | (16) | .869 |
| | Mean | 14.58 | 14.44 | |
| | (SD) | (2.87) | (1.97) | |
| | Median | 16 | 14 | |
| | (Range) | (7 – 19) | (12 – 18) | |
| Marijuana (Age 1st use) | (N) | (25) | (17) | .762 |
| | Mean | 15.2 | 15 | |
| | (SD) | (2.22) | (1.87) | |
| | Median | 15 | 15 | |
| | (Range) | (8 – 19) | (12 – 18) | |
| Intellectual Functioning | (N) | (29) | (27) | .516 |
| | Mean | 101.9 | 103.8 | |
| | (SD) | (9.53) | (12.32) | |
| | Median | 103 | 108 | |
| | (Range) | (77 – 118) | (70 – 119) | |

Table 15 (continued).

*Illness Characteristics – Comparison of Attrition versus Non-Attrition in Merged Group*

| | | Attrition Group | Non-Attrition Group | |
|---|---|---|---|---|
| Dependent Variables | | | | p[c] |
| Executive Functioning - Perseverative | (N) | (38) | (27) | .449 |
| | Mean | 47.06 | 53.43 | |
| | (SD) | (32.16) | (34.79) | |
| | Median | 42 | 50 | |
| | (Range) | (0.5 – 99.9) | (1 – 99.9) | |
| Executive Functioning - Categories | (N) | (37) | (27) | .183 |
| | Mean | 2.16 | 2.7 | |
| | (SD) | (1.57) | (1.6) | |
| | Median | 2 | 2 | |
| | (Range) | (0 – 6) | (0 – 5) | |
| Language Functioning | (N) | (38) | (27) | .753 |
| | Mean | 43.53 | 41.3 | |
| | (SD) | (29.27) | (29.19) | |
| | Median | 39.5 | 37 | |
| | (Range) | (2 – 99) | (2 – 96) | |
| Memory Functioning | (N) | (38) | (27) | .234 |
| | Mean | 22.87 | 15.34 | |
| | (SD) | (26.28) | (22.8) | |
| | Median | 11 | 4 | |
| | (Range) | (0.10 – 81) | (0.10 – 94) | |
| Motor Functioning | (N) | (37) | (28) | .198 |
| | Mean | 34.03 | 25.3 | |
| | (SD) | (29.16) | (23.72) | |
| | Median | 27 | 17 | |
| | (Range) | (0.06 – 97) | (0.5 – 73) | |

Table 15 (continued).

*Illness Characteristics – Comparison of Attrition versus Non-Attrition in Merged Group*

| Dependent Variables | Attrition Group | | Non-Attrition Group | | |
|---|---|---|---|---|---|
| | (N) | % | (N) | % | p[b] |
| Visual Attention Functioning | (n = 34) | | (n = 23) | | .774 |
| normal | (10) | 29.4% | (8) | 34.8% | |
| abnormal | (24) | 70.6% | (15) | 65.2% | |
| Duration of Untreated Psychosis | (n = 50) | | (n = 26) | | .630 |
| ≤13 weeks | (27) | 54% | (12) | 46.2% | |
| >13 weeks | (23) | 46% | (14) | 53.8% | |
| Psychiatric Hospitalizations | (n = 52) | | (n = 28) | | .488 |
| ≤1 | (27) | 51.9% | (17) | 60.7% | |
| ≥2 | (25) | 48.1% | (11) | 39.3% | |
| Lifetime Alcohol | (n = 48) | | (n = 28) | | .479. |
| no use and use | (27) | 56.2% | (13) | 46.4% | |
| abuse and dependence | (21) | 43.8% | (15) | 53.6% | |
| Lifetime Marijuana | (n = 49) | | (n = 28) | | .341 |
| no use and use | (24) | 49% | (10) | 35.7% | |
| abuse and dependence | (25) | 51% | (18) | 64.3% | |
| Lifetime use of other drugs | (n = 47) | | (n = 28) | | .413 |
| no use and use | (44) | 93.6% | (24) | 85.7% | |
| abuse and dependence | (3) | 6.4% | (4) | 14.3% | |

[b] Chi Square/Fisher's Exact
[c] t-test

Table 16.

*Treatment Characteristics – Comparison of Attrition versus Non-Attrition in Merged Group*

| | Attrition Group | | Non-Attrition Group | | |
|---|---|---|---|---|---|
| Dependent Variables | (N) | % | (N) | % | p[b] |
| Termination Reason[2] | | | | | - |
| Lack of efficacy | (17) | 31.5% | | | |
| Patient withdrew consent | (12) | 22.2% | | | |
| Adverse event | (6) | 11.1% | | | |
| Patient moved | (5) | 9.3% | | | |
| Inclusion criteria not met | (4) | 7.4% | | | |
| Lost to follow-up | (3) | 5.6% | | | |
| Severity criteria not met | (3) | 5.6% | | | |
| Requires disallowed medication | (2) | 3.7% | | | |
| Patient stopped medication | (1) | 1.9% | | | |
| Too psychotic for procedures | (1) | 1.9% | | | |
| Washout (days) (ClozHal & OlzHal only) | (n = 44) | | (n = 28) | | .808 |
| ≤ 3 days | (28) | 63.6% | (17) | 60.7% | |
| ≥ 4 days | (16) | 36.4% | (11) | 39.3% | |
| Study Medication (ClozHal & OlzHal only) | (n = 31) | | (n = 20) | | .034* |
| Typical | (17) | 54.8% | (5) | 25% | |
| Atypical | (14) | 45.2% | (15) | 75% | |
| Individual Study Medications | (n = 35) | | (n = 28) | | .125 |
| Clozapine | (6) | 17.1% | (9) | 32.1% | |
| Olanzapine | (8) | 22.9% | (10) | 35.7% | |
| Seroquel | (1) | 2.9% | (2) | 7.1% | |
| Risperidone | (3) | 8.6% | (2) | 7.1% | |
| Haloperidol | (17) | 48.6% | (5) | 17.9% | |

[b] Chi Square/Fisher's Exact

[2] Provided for descriptive purposes only

* $p \leq .05$ ** $p \leq .01$ *** $p \leq .001$

# Appendix K. Question 3a

Table 17.

*ClozHal Study Demographic Characteristics – Comparison of Attrition versus Non-Attrition Groups*

Table 18.

*ClozHal Study Illness Characteristics – Comparison of Attrition versus Non-Attrition Groups*

Table 19.

*ClozHal Study Treatment Characteristics – Comparison of Attrition versus Non-Attrition Group*

Appendix K.

Table 17.

*ClozHal – Demographic Characteristics – Comparison of Attrition versus Non-Attrition Groups*

| Dependent Variables | | Attrition Group | Non-Attrition Group | p[c] |
|---|---|---|---|---|
| Age | (N) | (25) | (11) | .002[a]** |
| | Mean | 23.88 | 20.09 | |
| | (SD) | (4.45) | (2.21) | |
| | Median | 23 | 19 | |
| | (Range) | (18 - 34) | (18 – 26) | |
| Education (years) | (N) | (25) | (11) | .030* |
| | Mean | 12.68 | 10.81 | |
| | (SD) | (1.68) | (3.38) | |
| | Median | 12 | 12 | |
| | (Range) | (8 – 16) | (3 – 15) | |
| Employment (hours/week) | (N) | (20) | (9) | .990 |
| | Mean | 15.65 | 15.6 | |
| | (SD) | (17.4) | (19.4) | |
| | Median | 9 | 0 | |
| | (Range) | (0 – 40) | (0 – 40) | |
| Median Income | | (22) | (11) | .704 |
| | | $48,813 | $51,541 | |
| | | ($20.066) | ($17,354) | |
| | | $48,617 | $44,260 | |
| | | ($11 – 97k) | ($29 – 84k) | |

| | (N) | % | (N) | % | p[b] |
|---|---|---|---|---|---|
| Gender | (n = 25) | | (n = 11) | | 1.0 |
| Male | (21) | 84% | (10) | 90.9% | |
| Female | (4) | 16% | (1) | 9.1% | |
| Race | (n = 25) | | (n = 11) | | 1.0 |
| Non-Caucasian | (12) | 48% | (6) | 54.5% | |
| Caucasian | (13) | 52% | (5) | 45.5% | |

Table 17 (continued).

*ClozHal Demographic Characteristics - Comparison of Attrition versus Non-Attrition Groups*

| | Attrition Group | | Non-Attrition Group | | |
|---|---|---|---|---|---|
| Dependent Variables | (N) | % | (N) | % | p[b] |
| School Attendance | (n = 23) | | (n = 11) | | .458 |
| not in school | (15) | 65.2% | (5) | 45.5% | |
| in school | (8) | 34.8% | (6) | 54.5% | |
| Left school | (n = 20) | | (n = 10) | | 1.0 |
| no | (11) | 55% | (5) | 50% | |
| yes | (9) | 45% | (5) | 50% | |
| Living situation (past year) | (n = 23) | | (n = 11) | | .084 |
| independent/dorm | (9) | 39.1% | (1) | 9.1% | |
| Family | (12) | 52.2% | (10) | 90.9% | |
| Homeless | (2) | 8.7% | (0) | | |
| Employment Status (past year) | (n = 23) | | (n = 11) | | 1.0 |
| not working | (6) | 26.1% | (3) | 27.3% | |
| working/student | (17) | 73.9% | (8) | 72.7% | |
| Functional Level (past year) | (n = 22) | | (n = 9) | | 1.0 |
| no useful functioning to 25% | (6) | 27.3% | (3) | 27.3% | |
| 25 to 100% | (16) | 72.7% | (6) | 66.7% | |

[b] Chi Square/Fisher's Exact
[c] t-test
* $p \leq .05$ ** $p \leq .01$ *** $p \leq .001$

Table 18.

*ClozHal - Illness Characteristics - Comparison of Attrition versus Non-Attrition Groups*

| | | Attrition Group | Non-Attrition Group | |
|---|---|---|---|---|
| Dependent Variables | | | | p[c] |
| Age at onset | (N) | (25) | (11) | .002[a]** |
| | Mean | 22.56 | 18.91 | |
| | (SD) | (4.32) | (2.21) | |
| | Median | 22 | 19 | |
| | (Range) | (16 – 33) | (16 – 24) | |
| | | | | .727 |
| Severity of illness - Screening | (N) | (23) | (11) | |
| | Mean | 4.65 | 4.55 | |
| | (SD) | (0.88) | (0.69) | |
| | Median | 5 | 4 | |
| | (Range) | (2 – 6) | (4 – 6) | |
| | | | | .906 |
| Severity of illness - Baseline | (N) | (20) | (11) | |
| | Mean | 4.5 | 4.55 | |
| | (SD) | (0.94) | (1.13) | |
| | Median | 5 | 5 | |
| | (Range) | (2 – 6) | (2 - 6) | |
| Alcohol (Age 1st use) | (N) | (8) | (4) | .579 |
| | Mean | 14.75 | 14.0 | |
| | (SD) | (2.25) | (1.83) | |
| | Median | 15.5 | 14 | |
| | (Range) | (10 – 17) | (12 – 16) | |
| Marijuana (Age 1st use) | (N) | (13) | (6) | .448 |
| | Mean | 15.38 | 14.5 | |
| | (SD) | (2.53) | (1.64) | |
| | Median | 16 | 15 | |
| | (Range) | (8 – 19) | (12 – 16) | |

Table 18 (continued).

*ClozHal - Illness Characteristics - Comparison of Attrition versus Non-Attrition Groups*

| | | Attrition Group | Non-Attrition Group | |
|---|---|---|---|---|
| Dependent Variables | | | | p[c] |
| Intellectual Functioning | (N) | (19) | (11) | .465 |
| | Mean | 100.47 | 97.18 | |
| | (SD) | (10.22) | (14.06) | |
| | Median | 100 | 105 | |
| | (Range) | (77 – 116) | (70 – 109) | |
| Executive Functioning - Perseverative | (N) | (20) | (11) | .880 |
| | Mean | 48.76 | 50.79 | |
| | (SD) | (34.73) | (36.83) | |
| | Median | 48 | 42 | |
| | (Range) | (0.5 – 99.9) | (4 – 99.9) | |
| Executive Functioning - Categories | (N) | (20) | (11) | .904 |
| | Mean | 2.2 | 2.27 | |
| | (SD) | (1.64) | (1.49) | |
| | Median | 2 | 2 | |
| | (Range) | (0 – 6) | (1 – 5) | |
| Language Functioning | (N) | (20) | (10) | .425 |
| | Mean | 48.8 | 41.5 | |
| | (SD) | (24.0) | (21.63) | |
| | Median | 50.5 | 42 | |
| | (Range) | (12 – 84) | (4 – 80) | |
| Memory Functioning | (N) | (19) | (11) | .952 |
| | Mean | 27.79 | 27.09 | |
| | (SD) | (30.31) | (30.49) | |
| | Median | 16 | 12 | |
| | (Range) | (1 – 81) | (1 – 94) | |
| Motor Functioning | (N) | (20) | (11) | .616 |
| | Mean | 28.35 | 24.1 | |
| | (SD) | (20.86) | (24.93) | |
| | Median | 24 | 14 | |
| | (Range) | (2 – 76) | (2 – 73) | |

Table 18 (continued).

*ClozHal - Illness Characteristics – Comparison of Attrition versus Non-Attrition Groups*

| Dependent Variables | Attrition Group | | Non-Attrition Group | | |
|---|---|---|---|---|---|
| | (N) | % | (N) | % | p[b] |
| Visual Attention Functioning | (n = 19) | | (n = 10) | | 1.0 |
| normal | (7) | 36.8% | (4) | 40% | |
| abnormal | (12) | 63.2% | (6) | 60% | |
| Duration of untreated Psychosis | (n = 23) | | (n = 9) | | 1.0 |
| ≤13 weeks | (11) | 47.8% | (4) | 44.4% | |
| >13 weeks | (12) | 52.2% | (5) | 55.6% | |
| Psychiatric Hospitalizations | (n = 25) | | (n = 11) | | .137 |
| ≤1 | (14) | 56% | (9) | 81.8% | |
| ≥2 | (11) | 44% | (2) | 18.2% | |
| Lifetime Alcohol | (n = 21) | | (n = 11) | | 1.0 |
| no use and use | (12) | 57.1% | (7) | 63.6% | |
| abuse and dependence | (9) | 43.8% | (4) | 36.4% | |
| Lifetime Marijuana | (n = 22) | | (n = 11) | | .141 |
| no use and use | (13) | 59.1% | (3) | 27.3% | |
| abuse and dependence | (9) | 40.9% | (8) | 72.7% | |
| Lifetime Other Drugs | (n = 21) | | (n = 11) | | .631 |
| no use and use | (20) | 95.2% | (10) | 90.9% | |
| abuse and dependence | (1) | 4.8% | (1) | 9.1% | |

[b] Chi Square/Fisher's Exact
[c] t-test
* $p \leq .05$ ** $p \leq .01$ *** $p \leq .001$

Table 19.

*ClozHal - Treatment Characteristics - Comparison of Attrition versus Non-Attrition Groups*

| | Attrition Group | | Non-Attrition Group | | |
|---|---|---|---|---|---|
| Dependent Variables | (N) | (%) | (N) | (%) | p[b] |
| Termination Reason[2] | | | | | - |
| Lack of efficacy | (6) | 24% | | | |
| Patient withdrew Consent | (6) | 24% | | | |
| Adverse event | (4) | 16% | | | |
| Patient moved | (4) | 16% | | | |
| Severity criteria not met | (2) | 8% | | | |
| Inclusion criteria not met | (2) | 8% | | | |
| Too psychotic for procedures | (1) | 4% | | | |
| Termination (collapsed)[2] | | | | | - |
| Patient related | (10) | 40% | | | |
| Medication related | (10) | 40% | | | |
| Research design | (5) | 20% | | | |
| Washout (days) | (n = 19) | | (n = 11) | | .225 |
| $\leq$ 3 days | (15) | 78.9% | (6) | 54.5% | |
| $\geq$ 4 days | (4) | 21.1% | (5) | 45.5% | |
| Study Medication | (n = 16) | | (n = 11) | | .109 |
| Typical (Haldol) | (9) | 56.2% | (2) | 18.2% | |
| Atypical (Clozapine) | (7) | 43.8% | (9) | 81.8% | |

[2] provided for descriptive purposes only
[b] Chi Square/Fisher's Exact

# Appendix L. Question 3a

Table 20.

*OlzHal - Demographic Characteristics – Comparison of Attrition versus Non-Attrition Groups*

Table 21.

*OlzHal - Illness Characteristics – Comparison of Attrition versus Non-Attrition Groups*

Table 22.

*OlzHal - Treatment Characteristics – Comparison of Attrition versus Non-Attrition Groups*

Appendix L.

Table 20.

*OlzHal - Demographic Characteristics – Comparison of Attrition versus Non-Attrition Groups*

| | | Attrition Group | Non-Attrition Group | |
|---|---|---|---|---|
| Dependent Variables | | | | p[c] |
| Age | (N) | (20) | (9) | .170 |
| | Mean | 22.3 | 25.44 | |
| | (SD) | (3.88) | (5.88) | |
| | Median | 23 | 26 | |
| | (Range) | (17 – 30) | (19 – 34) | |
| Education (years) | (N) | (20) | (9) | .066 |
| | Mean | 12.9 | 11.55 | |
| | (SD) | (2.75) | (1.01) | |
| | Median | 12 | 12 | |
| | (Range) | (8 – 19) | (10 – 13) | |
| Employment (hours/week) | (N) | (20) | (9) | .212 |
| | Mean | 20.5 | 30 | |
| | (SD) | (18.42) | (18.71) | |
| | Median | 25 | 40 | |
| | (Range) | (0 – 40) | (0 – 50) | |
| Median Income | | (11) | (6) | .065 |
| | | $31,613 | $45,066 | |
| | | ($13,596) | ($12,718) | |
| | | $29,072 | $43,751 | |
| | | ($11 – 52k) | ($27 – 66k) | |

| | (N) | % | (N) | % | p[b] |
|---|---|---|---|---|---|
| Gender | (n = 20) | | (n = 9) | | 1.0 |
| Male | (18) | 90% | (8) | 88.9% | |
| Female | (2) | 10% | (1) | 11.1% | |
| Race | (n = 20) | | (n = 9) | | .422 |
| Non-Caucasian | (7) | 35% | (5) | 55.6% | |
| Caucasian | (13) | 65% | (4) | 44.4% | |

Table 20 (continued).

*OlzHal - Demographic Characteristics – Comparison of Attrition versus Non-Attrition Groups*

| | Attrition Group | | Non-Attrition Group | | |
|---|---|---|---|---|---|
| Dependent Variables | (N) | % | (N) | % | p[b] |
| School Attendance | (n = 20) | | (n = 9) | | .005 |
| not in school | (9) | 45% | (9) | 100% | |
| in school | (11) | 55% | (0) | | |
| Left School | (n = 18) | | (n = 9) | | .026* |
| no | (10) | 55.6% | (9) | 100% | |
| yes | (8) | 44.4% | (0) | | |
| Living situation (past year) | (n = 20) | | (n = 9) | | .017* |
| independent/dorm | (6) | 30% | (3) | 33.3% | |
| Family | (14) | 70% | (3) | 33.3% | |
| Homeless | (0) | | (3) | 33.3% | |
| Employment Status (past year) | (n = 20) | | (n = 9) | | .089 |
| not working | (0) | | (2) | 22.2% | |
| working/student | (20) | 100% | (7) | 77.8% | |
| Functional Level (past year) | (n = 20) | | (n = 9) | | .089 |
| no useful functioning to 25% | (0) | | (2) | 22.2% | |
| 25 to 100% | (20) | 100% | (7) | 77.8% | |

[b] Chi Square/Fisher's Exact
[c] t-tests
* $p \leq .05$ ** $p \leq .01$ *** $p \leq .001$

Table 21.

*OlzHal - Illness Characteristics – Comparison of Attrition versus Non-Attrition Groups*

| | | Attrition Group | Non-Attrition Group | |
|---|---|---|---|---|
| Dependent Variables | | | | p[c] |
| Age at onset | (N) | (19) | (9) | .218 |
| | Mean | 21.5 | 23.89 | |
| | (SD) | (4.17) | (5.51) | |
| | Median | 20 | 22 | |
| | (Range) | (16 – 30) | (18 – 33) | |
| Severity of illness - Screening | (N) | (18) | (6) | .382 |
| | Mean | 4.6 | 4.3 | |
| | (SD) | (0.70) | (0.52) | |
| | Median | 4.5 | 4 | |
| | (Range) | (4 - 6) | (4 – 5) | |
| Severity of illness - Baseline | (N) | (17) | (6) | .762 |
| | Mean | 4.35 | 4.5 | |
| | (SD) | (1.06) | (0.84) | |
| | Median | 4 | 4 | |
| | (Range) | (2 – 6) | (4 – 6) | |
| Alcohol (Age 1st use) | (N) | (8) | (4) | .671 |
| | Mean | 14.88 | 14 | |
| | (SD) | (3.72) | (1.83) | |
| | Median | 16 | 14 | |
| | (Range) | (7 – 19) | (12 – 16) | |
| Marijuana (Age 1st use) | (N) | (8) | (3) | .903 |
| | Mean | 15.5 | 15.67 | |
| | (SD) | (1.85) | (2.31) | |
| | Median | 15 | 17 | |
| | (Range) | (14 – 19) | (13 – 17) | |

Table 21 (continued).

*OlzHal - Illness Characteristics – Comparison of Attrition versus Non-Attrition Groups*

| | | Attrition Group | Non-Attrition Group | |
|---|---|---|---|---|
| Dependent Variables | | | | p[c] |
| Intellectual Functioning | (N) | (7) | (8) | .841 |
| | Mean | 106.14 | 107.0 | |
| | (SD) | (6.2) | (9.38) | |
| | Median | 104 | 109.5 | |
| | (Range) | (100 – 118) | (92 – 116) | |
| Executive Functioning - Perseverative | (N) | (15) | (8) | .222 |
| | Mean | 45.67 | 64.11 | |
| | (SD) | (30.16) | (39.33) | |
| | Median | 34 | 80 | |
| | (Range) | (1 – 98) | (4 – 99.9) | |
| Executive Functioning - Categories | (N) | (14) | (8) | .127 |
| | Mean | 2.0 | 3.12 | |
| | (SD) | (1.47) | (1.81) | |
| | Median | 2 | 3 | |
| | (Range) | (0 – 4) | (1 – 5) | |
| Language Functioning | (N) | (14) | (9) | .743 |
| | Mean | 34.3 | 17.33 | |
| | (SD) | (36.43) | (18.67) | |
| | Median | 29 | 37 | |
| | (Range) | (2 – 96) | (2 – 94) | |
| Memory Functioning | (N) | (15) | (8) | .304 |
| | Mean | 22.6 | 13.88 | |
| | (SD) | (21.63) | (11.63) | |
| | Median | 16 | 13.5 | |
| | (Range) | (1 – 74) | (2 – 31) | |
| Motor Functioning | (N) | (14) | (9) | .157 |
| | Mean | 34.3 | 17.33 | |
| | (SD) | (36.43) | (18.67) | |
| | Median | 27 | 10 | |
| | (Range) | (0.06 – 97) | (0.5 – 58) | |

Table 21 (continued).

*OlzHal - Illness Characteristics - Comparison of Attrition versus Non-Attrition Groups*

| | Attrition Group | | Non-Attrition Group | | |
|---|---|---|---|---|---|
| Dependent Variables | (N) | % | (N) | % | p[b] |
| Visual Attention Functioning | (n = 11) | | (n = 7) | | 1.0 |
| normal | (1) | 9.1% | (0) | | |
| abnormal | (10) | 90.9% | (7) | 100% | |
| Duration of Untreated Psychosis | (n = 19) | | (n = 9) | | .435 |
| ≤13 weeks | (10) | 52.6% | (3) | 33.3% | |
| >13 weeks | (9) | 47.2% | (6) | 66.7% | |
| Psychiatric Hospitalizations | (n = 20) | | (n = 9) | | .427 |
| ≤1 | (11) | 55% | (3) | 33.3% | |
| ≥2 | (9) | 45% | (6) | 66.7% | |
| Lifetime Alcohol | (n = 20) | | (n = 9) | | .688 |
| no use and use | (12) | 60% | (4) | 44.4% | |
| abuse and dependence | (8) | 40% | (5) | 55.6% | |
| Lifetime Marijuana | (n = 20) | | (n = 9) | | 1.0 |
| no use and use | (10) | 50% | (5) | 55.6% | |
| abuse and dependence | (10) | 50% | (4) | 44.4% | |
| Lifetime Other Drugs | (n = 20) | | (n = 9) | | .532 |
| no use and use | (19) | 95% | (8) | 88.9% | |
| abuse and dependence | (1) | 5% | (1) | 11.1% | |

[b] Chi Square/Fisher's Exact
[c] t-tests
[d] Mann Whitney

Table 22.

*OlzHal - Treatment Characteristics – Comparison of Attrition versus Non-Attrition groups*

| | Attrition Group | | Non-Attrition Group | | |
|---|---|---|---|---|---|
| Dependent Variables | (N) | % | (N) | % | p[b] |
| Termination Reason[2] | | | | | - |
| Lack of efficacy | (10) | 50% | | | |
| Patient withdrew Consent | (3) | 15% | | | |
| Adverse event | (1) | 5% | | | |
| Inclusion criteria not met | (2) | 10% | | | |
| Requires disallowed medication | (2) | 10% | | | |
| Patient stopped medication | (1) | 5% | | | |
| Severity criteria not met | (1) | 5% | | | |
| Termination[2] | | | | | - |
| Patient related | (4) | 20% | | | |
| Medication related | (11) | 55% | | | |
| Research design | (5) | 25% | | | |
| Washout (days) | (n = 18) | | (n = 9) | | |
| ≤ 3 days | (6) | 33.3% | (3) | 33.3% | 1.0 |
| ≥ 4 days | (12) | 66.7% | (6) | 66.7% | |
| Study Medication | (n = 14) | | (n = 9) | | .400 |
| Typical (Haldol) | (8) | 53.3% | (3) | 33.3% | |
| Atypical (Olanzapine) | (7) | 46.7% | (6) | 66.7% | |

[2] provided for descriptive purposes only;
[b] Chi Square/Fisher's Exact

# Appendix M. Question 3a

Table 23.

*OlzQueRis - Demographic Characteristics – Comparison of Attrition versus Non-Attrition Groups*

Table 24.

*OlzQueRis - Illness Characteristics - Comparison of the Attrition versus Non-Attrition Groups*

Table 25.

*OlzQueRis - Treatment Characteristics - Comparison of the Attrition versus Non-Attrition Groups*

Appendix M

Table 23.

*OlzQueRis -Demographic Characteristics – Comparison of Attrition versus Non-Attrition Groups*

| | | Attrition Group | Non-Attrition Group | |
|---|---|---|---|---|
| Dependent Variables | | | | $p^c$ |
| Age | (N) | (9) | (8) | .962 |
| | Mean | 21.89 | 22 | |
| | (SD) | (5.56) | (3.59) | |
| | Median | 20 | 21.5 | |
| | (Range) | (18 – 36) | (18 – 27) | |
| Education (years) | (N) | (8) | (8) | .051* |
| | Mean | 10 | 12.5 | |
| | (SD) | (2.56) | (1.85) | |
| | Median | 12 | 12 | |
| | (Range) | (6 – 13) | (10 – 16) | |
| Employment (hours/week) | (N) | (5) | (7) | .618 |
| | Mean | 18 | 11.43 | |
| | (SD) | (24.9) | (19.5) | |
| | Median | 0 | 0 | |
| | (Range) | (0 – 50) | (0 – 40) | |
| Median Income | (N) | (9) | (8) | .380 |
| | Mean | $36,944 | $46,190 | |
| | (SD) | ($27,663) | ($8,680) | |
| | Median | $35,874 | $43,751 | |
| | (Range) | ($11 – 98k) | ($35 – 59k) | |

| | (N) | % | (N) | % | $p^c$ |
|---|---|---|---|---|---|
| Gender | (n = 9) | | (n = 8) | | 1.0 |
| Male | (8) | 88.9% | (8) | 100% | |
| Female | (1) | 11.1% | (0) | | |
| Race | (n = 9) | | (n = 8) | | .637 |
| Non-Caucasian | (4) | 44.4% | (5) | 62.5% | |
| Caucasian | (5) | 55.6% | (3) | 37.5% | |

Table 23 (continued).

*OlzQueRis - Demographic Characteristics – Comparison of the Attrition versus Non-Attrition Groups*

| | Attrition Group | | Non-Attrition Group | | |
|---|---|---|---|---|---|
| Dependent Variables | (N) | % | (N) | % | p[c] |
| School Attendance | (n = 6) | | (n = 8) | | .301 |
| not in school | (5) | 83.3% | (4) | 50% | |
| in school | (1) | 16.7% | (4) | 50% | |
| Left School | (n = 7) | | (n = 8) | | .315 |
| no | (5) | 71.4% | (3) | 37.5% | |
| yes | (2) | 28.6% | (5) | 62.5% | |
| Living Situation (past year) | (n = 6) | | (n = 8) | | 1.0 |
| independent/dorm | (2) | 33.3% | (2) | 25% | |
| Family | (4) | 66.7% | (6) | 75% | |
| Homeless | (0) | | (0) | | |
| Employment Status (past year) | (n = 7) | | (n = 8) | | .619 |
| not working | (4) | 57.1% | (3) | 37.5% | |
| working/student | (3) | 42.9% | (5) | 62.5% | |
| Functional Level (past year) | (n = 5) | | (n = 8) | | 1.0 |
| no useful functioning to 25% | (2) | 40% | (3) | 37.5% | |
| 25 to 100% | (3) | 60% | (5) | 62.5% | |

[b] Chi Square/Fisher's Exact

Table 24.

*OlzQueRis - Illness Characteristics - Comparison of the Attrition versus Non-Attrition Groups*

| | | Attrition Group | Non-Attrition Group | |
|---|---|---|---|---|
| Dependent Variables | | | | p[d] |
| Age at onset | (N) | (9) | (8) | .941 |
| | Mean | 21.44 | 21.63 | |
| | (SD) | (5.81) | (3.7) | |
| | Median | 19 | 20.5 | |
| | (Range) | (17 – 36) | (18 – 27) | |
| Severity of illness - Screening | (N) | (6) | (8) | .922 |
| | Mean | 5.33 | 5.38 | |
| | (SD) | (1.03) | (0.52) | |
| | Median | 5 | 5 | |
| | (Range) | (4 – 7) | (5 – 6) | |
| Severity of illness - Baseline | (N) | (6) | (8) | .053* |
| | Mean | 4.83 | 3.88 | |
| | (SD) | (0.41) | (1.13) | |
| | Median | 5 | 4 | |
| | (Range) | (4 – 5) | (2 – 5) | |
| Alcohol (Age 1st use) | (N) | (3) | (8) | .338 |
| | Mean | 13.33 | 14.88 | |
| | (SD) | (2.31) | (2.23) | |
| | Median | 12 | 14 | |
| | (Range) | (12 – 16) | (12 – 18) | |
| Marijuana (Age 1st use) | (N) | (4) | (8) | .373 |
| | Mean | 14 | 15.12 | |
| | (SD) | (1.83) | (2.03) | |
| | Median | 14 | 14.5 | |
| | (Range) | (12 – 16) | (13 – 18) | |

Table 24 (continued).

*OlzQueRis - Illness Characteristics – Comparison of the Attrition versus Non-Attrition Groups*

| | | Attrition Group | Non-Attrition Group | |
|---|---|---|---|---|
| Dependent Variables | | | | p[d] |
| Intellectual Functioning | (N) | (3) | (8) | .197 |
| | Mean | 101 | 109.75 | |
| | (SD) | (11.53) | (8.51) | |
| | Median | 97 | 111.5 | |
| | (Range) | (92 – 114) | (92 – 119) | |
| Executive Functioning - Perseverative | (N) | (3) | (8) | .860 |
| | Mean | 42.67 | 46.38 | |
| | (SD) | (35.23) | (28.5) | |
| | Median | 32 | 54 | |
| | (Range) | (14 – 82) | (1 – 79) | |
| Executive Functioning - Categories | (N) | (3) | (8) | .864 |
| | Mean | 2.67 | 2.88 | |
| | (SD) | (2.08) | (1.64) | |
| | Median | 2 | 3 | |
| | (Range) | (1 - 5) | (0 – 5) | |
| Language Functioning | (N) | (3) | (8) | .864 |
| | Mean | 46.33 | 42.13 | |
| | (SD) | (46.49) | (31.29) | |
| | Median | 29 | 42.5 | |
| | (Range) | (11 – 99) | (3 – 96) | |
| Memory Functioning | (N) | (4) | (8) | .849 |
| | Mean | 0.50 | 0.64 | |
| | (SD) | (0.29) | (1.36) | |
| | Median | 0.55 | 0.1 | |
| | (Range) | (0.1 - 0.8) | (0.1 – 4) | |
| Motor Functioning | (N) | (3) | (8) | .059 |
| | Mean | 70.67 | 35.75 | |
| | (SD) | (14.5) | (25.98) | |
| | Median | 71 | 25.5 | |
| | (Range) | (56 – 85) | (4 – 73) | |

Table 24 (continued).

*OlzQueRis - Illness Characteristics - Comparison of the Attrition versus Non-Attrition Groups*

| Dependent Variables | Attrition Group | | Non-Attrition Group | | |
|---|---|---|---|---|---|
| | (N) | % | (N) | % | p[b] |
| Visual Attention Functioning | (n = 4) | | (n = 6) | | 1.000 |
| normal | (2) | 50% | (4) | 66.7% | |
| abnormal | (2) | 50% | (2) | 33.3% | |
| Duration of untreated Psychosis | (n = 8) | | (n = 8) | | 1.0 |
| ≤13 weeks | (6) | 75% | (5) | 62.5% | |
| >13 weeks | (2) | 25% | (3) | 37.5% | |
| Psychiatric Hospitalizations | (n = 7) | | (n = 8) | | .189 |
| 0, 1 | (2) | 28.6% | (5) | 62.5% | |
| 2+ | (5) | 71.4% | (3) | 37.5% | |
| Lifetime Alcohol | (n = 7) | | (n = 8) | | .608 |
| no use and use | (3) | 42.9% | (2) | 25% | |
| abuse and dependence | (4) | 57.1% | (6) | 75% | |
| Lifetime Marijuana | (n = 7) | | (n = 8) | | 1.0 |
| no use and use | (1) | 14.3% | (2) | 25% | |
| abuse and dependence | (6) | 87.5% | (6) | 75% | |
| Lifetime Other Drugs | (n = 6) | | (n = 8) | | 1.0 |
| no use and use | (5) | 83.3% | (6) | 75% | |
| abuse and dependence | (1) | 16.7% | (2) | 25% | |

[b] Chi Square/Fisher's Exact
[d] Mann Whitney U
* $p \leq .05$ ** $p \leq .01$ *** $p \leq .001$

Table 25.

*OlzQueRis - Treatment Characteristics - Comparison of the Attrition versus Non-Attrition Groups*

| | Attrition Group | | Non-Attrition Group | | |
|---|---|---|---|---|---|
| Dependent Variables | (N) | % | (N) | % | p[b] |
| Termination Reason[2] | | | | | |
| Lack of efficacy | (1) | 11.1% | | | |
| Patient withdrew Consent | (3) | 33.3% | | | |
| Adverse event | (1) | 11.1% | | | |
| Patient moved | (1) | 11.1% | | | |
| Lost to follow-up | (3) | 33.3% | | | |
| Termination[2] | | | | | |
| Patient related | (7) | 77.8% | | | |
| Medication related | (2) | 22.2% | | | |
| Washout (days) none | | | | | |
| Study Medication[2] | | | | | |
| olanzapine | (0) | | (4) | 50% | |
| quetiapine | (1) | 25% | (2) | 25% | |
| risperidone | (3) | 75% | (2) | 25% | |

[b] Chi Square/Fisher's Exact
[2] Provided for descriptive purposes only

*References*

Addington, J., & Addington, D. (1998). Effect of substance misuse in early psychosis. *British Journal of Psychiatry, 172*, 134-136.

Addington, J., & Addington, D. (2000). Neurocognitive and social functioning in schizophrenia: a 2.5 year follow-up study. *Schizophrenia Research, 44*, 47-56.

Addington, J., Cadenhead, K.S., Cannon, T.D., Cornblatt, B., McGlashan, T.H., Perkins, D.O., et al. (2007). North American Prodrome Longitudinal Study: a collaborative multisite approach to prodromal schizophrenia research. *Schizophrenia Bulletin, 33*, 665-672.

Addington, J., & Gleeson, J. (2005). Implementing cognitive-behavioral therapy for first-episode psychosis. *British Journal of Psychiatry, 187*(Suppl. 48), s72-76.

Addington, J., van Mastrigt, S., & Addington, D. (2003). Patterns of premorbid functioning in first-episode psychosis: initial presentation. *Schizophrenia Research, 62*, 23-30.

Agius, M., Shah, S., Ramkisson, R., Murphy, S., & Zaman, R. (2007). Three year outcomes of an early intervention for psychosis service as compared with treatment as usual for first episodes in a standard community mental health team - final results. *Psychiatria Danubina, 19*, 130-138.

Altamura, A.C., Bassetti, R., Sassella, F., Salvadori, D., & Mundo, E. (2001). Duration of untreated psychosis as a predictor in first-episode schizophrenia: a retrospective study. *Schizophrenia Research, 52*, 29-36.

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders, DSM-III-R* (3rd, Revised ed.). Washington, DC: American Psychiatric Association.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders - DSM-IV* (4th ed.). Washington, D.C.: American Psychiatric Association.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders DSM-IV-TR* (4th Edition, Text Revision ed.). Washington, DC: American Psychiatric Association.

American Psychiatric Association. (2006). *Quick reference to the American Psychiatric Association Practice Guidelines for the treatment of psychiatric disorders*. Arlington, Virginia: American Psychiatric Association.

Andreasen, N.C. (1982). Negative symptoms in schizophrenia: definition and reliability. *Archives of General Psychiatry, 39*, 784-788.

Andreasen, N.C., Flaum, M., Swayze, V.W., II, Tyrrell, G., & Arndt, S. (1990). Positive and negative symptoms in schizophrenia. *Archives of General Psychiatry, 47*, 615-621.

Andreasson, S., Allebeck, P., Engstrom, A., & Rydberg, U. (1987). Cannabis and Schizophrenia: A longitudinal study of Swedish concepts. *The Lancet, 2*, 1483-1486.

Andreasson, S., Allebeck, P., & Rydberg, U. (1989). Schizophrenia in users and nonusers of cannabis: A longitudinal study in Stockholm County. *Acta Psychiatrica Scandinavica, 79*, 505-510.

Archie, S., Rush, B.R., Akhtar-Danesh, N., Norman, R., Malla, A., Roy, P., et al. (2007). Substance use and abuse in first-episode psychosis: prevalence before and after early intervention. *Schizophrenia Bulletin, 33*, 1354-1363.

Arendt, M., Rosenberg, R., Foldager, L., Perto, G., & Munk-Jorgensen, P. (2005). Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: follow-up study of 535 incident cases. *British Journal of Psychiatry, 187*, 510-515.

Arnold, L.M., Rosen, A., Pritchett, Y.L., D'Souza, D.N., Goldstein, D.J., Iyengar, S., et al. (2005). A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain, 119*, 5-15.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., & Moffitt, T.E. (2002). Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *British Medical Journal, 325*, 1212-1213.

Babulas, V., Factor-Litvak, P., Goetz, R., Schaefer, C.A., & Brown, A.S. (2006). Prenatal exposure to maternal genital and reproductive infections and adult schizophrenia. *American Journal of Psychiatry, 163*, 927-929.

Bachmann, S., Bottmer, C., & Schroder, J. (2005). Neurological soft signs in first-episode schizophrenia: a follow-up study. *American Journal of Psychiatry, 162*, 2337-2343.

Bangalore, S.S., Prasad, K.M.R., Montrose, D.M., Goradia, D.D., Diwadkar, V.A., & Keshavan, M.S. (2008). Cannabis use and brain structural alterations in first episode schizophrenia -- A region of interest, voxel based morphometric study. *Schizophrenia Research, 99*, 1-6.

Barefoot, B.O. (2004). Higher education's revolving door: confronting the problem of student drop out in US colleges and universities. *Open Learning, 19*, 9-18.

Barnes, S.A., Lindborg, S.R., & Seaman, J.W.J. (2006a). Multiple imputation techniques in small sample clinical trials. *Statistics in Medicine, 25*, 233-245.

Barnes, T.R.E., Mutsatsa, S.H., Hutton, S.B., Watt, H.C., & Joyce, E.M. (2006b). Comorbid substance use and age at onset of schizophrenia. *British Journal of Psychiatry, 188*, 237-242.

Barnett, J.H., Werners, U., Secher, S.M., Hill, K.E., Brazil, R., Masson, K.I.M., et al. (2007). Substance use in a population-based clinic sample of people with first-episode psychosis. *The British Journal of Psychiatry, 190*, 515-520.

Becker, L.A. (2000). Effect Size Calculator. Retrieved January 15, 2009, from http://web.uccs.edu/lbecker/Psy590/escalc3.htm

Bellack, A.S. (2006). Scientific and Consumer Models of Recovery in Schizophrenia: Concordance, Contrasts, and Implications. *Schizophr Bull, 32*, 432-442.

Benedict, R., Schretlen, D., Groninger, L., & Brandt, J. (1998). Hopkins Verbal Learning Test " Revised: normative data and analysis of inter-form and test-retest reliability. *Clinical Neuropsychologist, 12*, 43.

Berk, M., Ng, F., Dodd, S., Callaly, T., Campbell, S., Bernardo, M., et al. (2008). The validity of the CGI severity and improvement scale as measures of clinical effectiveness suitable for routine clinical use. *Journal of Evaluation in Clinical Practice*.

Berube, M.S. (Ed.). (1985). *The American Heritage Dictionary* (2nd ed.). Boston:

Houghton Mifflin Company.
Bilder, R.M., Goldman, R.S., Robinson, D., Reiter, G., Bell, L., Bates, J.A., et al. (2000). Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *American Journal of Psychiatry, 157*, 549-559.
Bilder, R.M., Reiter, G., Bates, J., Lencz, T., Szeszko, P., Goldman, R.S., et al. (2006). Cognitive development in schizophrenia: follow-back from the first episode. *Journal of Clinical and Experimental Neuropsychology, 28*, 270-282.
Black, K., Peters, L., Rui, Q., Milliken, H., Whitehorn, D., & Kopala, L.C. (2001). Duration of untreated psychosis predicts treatment outcome in an early psychosis program. *Schizophrenia Research, 47*, 215-222.
Bombin, I., Arango, C., & Buchanan, R.W. (2005). Significance and meaning of neurological signs in schizophrenia: two decades later. *Schizophrenia Bulletin, 31*, 962-977.
Bove, E.A. (2008). Cognitive performance and basic symptoms in first-degree relatives of schizophrenic patients. *Comprehensive Psychiatry, 49*, 321-329.
Braff, D.L., Freedman, R., Schork, N.J., & Gottesman, I.I. (2007). Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disease. *Schizophrenia Bulletin, 33*, 21-32.
Brandt, J., & Benedict, R. (2001). *Hopkins Verbal Learning Test - Revised Professional Manual*. Lutz, Florida: Psychological Assessment Resources, Inc.
Brili, S., Tousoulis, D., Antoniades, C., Vasiliadou, C., Karali, M., Papageorgiou, N., et al. (2008). Effects of ramipril on endothelial function and the expression of proinflammatory cytokines and adhesion molecules in young normotensive subjects with successfully repaired coarctation of aorta: a randomized cross-over study. *Journal of the American College of Cardiology, 51*, 742-749.
Bromet, E.J., & Fennig, S. (1999). Epidemiology and natural history of schizophrenia. *Biological Psychiatry, 46*, 871-881.
Buhler, B., Hambrecht, M., Loffler, W., Van der Heiden, W., & Hafner, H. (2002). Precipitation and determination of the onset and course of schizophrenia by substance abuse -- a retrospective and prospective study of 232 population-based first illness episodes. *Schizophrenia Research, 54*, 243-251.
Burns, N., & Grove, S.K. (2001). *The Practice of Nursing Research Conduct, Critique and Utilization* (4th ed.). Philadelphia: W. B. Saunders Company.
Cannon, T.D., Cadenhead, K., Cornblatt, B., Woods, S.W., Addington, J., Walker, E., et al. (2008). Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Archives General Psychiatry, 65*, 28-37.
Cantwell, R., Brewin, J., Glazebrook, C., Dalkin, T., Fox, R., Medley, I., et al. (1999). Prevalence of substance misuse in first-episode psychosis. *British Journal of Psychiatry, 174*, 150-153.
Carpenter, W.T., Heinrichs, D.W., & Wagman, A.M.I. (1988). Deficit and nondeficit forms of schizophrenia: the concept. *American Journal of Psychiatry, 145*, 578-583.
Caspari, D. (1999). Cannabis and schizophrenia: results of a follow-up study. *European Archives of Psychiatry & Clinical Neuroscience, 249*, 45-49.
Caspi, A., Moffitt, T.E., Cannon, M., McClay, J., Murray, R., Harrington, H., et al. (2005). Moderation of the effect of adolescent-onset cannabis use on adult

psychosis by a functional polymorphism in the Catechol-O-Methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biological Psychiatry, 57*, 1117-1127.

Centers for Disease Control and Prevention (CDC). (2001). Behavioral Risk Factor Surveillance System Survey Data. Retrieved March 6, 2009, from http://www.cdc.gov/brfss/

Centers for Disease Control and Prevention (CDC). (2007). Youth Risk Behavior Survey. Retrieved March 6, 2009, from http://www.cdc.gov/HealthyYouth/partners/funded/yrbs.htm

Chen, C., Yi, H., Williams, G., & Faden, V. (2009). Trends in underage drinking in the United States, 1991 - 2007. *Surveillance Report # 86* Retrieved March 6, 2009, from http://pubs.niaaa.nih.gov/publications/surveillance86/Underage07.htm

Clarke, M.C., Harley, M., & Cannon, M. (2006). The role of obstetric events in schizophrenia. *Schizophrenia Bulletin, 32*, 3-8.

Coe, R. (2002). *It's the effect size, stupid. What effect size is and why it is important.* Paper presented at the British Educational Research Association Annual Conference, Exeter.

Cohen, J. (1988). *Statistical Power Analysis for the Behavior Sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Assoc.

Coldham, E.L., Addington, J., & Addington, D. (2002). Medication adherence of individuals with a first episode of psychosis. *Acta Psychiatra Scandinavia, 106*, 286-290.

Committee on Quality of Health Care in America. (2001). *Crossing the quality chasm: a new health system of the 21st century*. Washington D.C.: National Academies Press.

Corey, D., Hurley, M., & Foundas, A. (2001). Right and left handedness defined. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 14*, 144-152.

Cornblatt, B., & Auther, A. (2005). Treating early psychosis: who, what, and when? *Dialogues in Clinical Neuroscience, 7*, 39-49.

Cornblatt, B.A., Risch, N.J., Faris, G., Friedman, D., & Erlenmeyer-Kimling, L. (1988). The Continuous Performance Test, Identical Pairs version (CPT-IP): new findings about sustained attention in normal families. *Psychiatric Research, 26*, 223-238.

Crawford, J.R., Stewart, L.E., Besson, J.A.O., Parker, D.M., & De Lacey, G. (1989). Prediction of WAIS IQ with the National Adult Reading Test: cross-validation and extension. *British Journal of Clinical Psychology, 28*, 267-273.

Crawford, J.R., Stewart, L.E., Cochrane, R.H.B., Parker, D.M., & Besson, J.A.O. (1989). Construct validity of the National Adult Reading Test: a factor analytic study. *Personality and Individual Differences, 10*, 585.

Crespo-Facorro, B., Perez-Iglesias, R., Ramirez-Bonilla, M., Martinez-Garcia, O., Llorca, J., & Vazquez-Barquero, J. (2006). A practical clinical trial comparing haloperidol, risperidone, and olanzapine for the acute treatment of first-episode nonaffective psychosis. *Journal of Clinical Psychiatry, 67*, 1511-1521.

Csernansky, J.G., & Bardgett, M.E. (1998). Limbic-cortical neuronal damage and the pathophysiology of schizophrenia. *Schizophrenia Bulletin, 24*, 231-248.

Cullberg, J., Levander, S., Holmqvist, R., Mattsson, M., & Wieselgren, I. (2002). One year outcome in first episode psychosis patients in the Swedish "Parachute

Project". *Acta Psychiatra Scandinavia, 106*, 276-285.
Cullberg, J., Mattsson, M., Holmqvist, R., Tomsmark, L., Elingfors, C., & Wieselgren, I. (2006). Treatment costs and clinical outcome for first episode schizophrenia: a 3-year follow-up of the Swedish "Parachute Project" and two comparison groups. *Acta Psychiatra Scandinavia, 114*, 274-281.
Dickerson, F., Boronow, J., Stallings, C., Origoni, A., & Yolken, R. (2007). Toxoplasma gondii in individuals with schizophrenia: association with clinical and demographic factors and with mortality. *Schizophrenia Bulletin, 33*, 737-740.
Dickinson, D., Iannone, V., Wilk, C., & Gold, J.M. (2004). General and specific cognitive deficits in schizophrenia. *Biological Psychiatry, 55*, 826-833.
Drake, R.E., Osher, F.C., Noordsy, D.L., Hurlburt, S.C., Teague, G.B., & Beaudette, M.S. (1990). Diagnosis of alcohol use disorders in schizophrenia. *Schizophrenia Bulletin, 16*, 57-67.
Drake, R.J. (2008). Insight into illness: impact on diagnosis and outcome of nonaffective psychosis. *Current Psychiatry Reports, 10*, 210-216.
Drake, R.J., Dunn, G., Tarrier, N., Bentall, R., Haddock, G., & Lewis, S. (2007). Insight as a predictor of the outcome of first-episode nonaffective psychosis in a prospective cohort study in England. *Journal of Clinical Psychiatry, 68*, 81-86.
Eaton, W.W., & Chen, C. (2006). Epidemiology. In J. A. Lieberman, T. S. Stroup & D. O. Perkins (Eds.), *Textbook of Schizophrenia* (pp. 17-38). Washington, D. C.: American Psychiatric Publishing, Inc.
Edwards, J., McGorry, P.D., Waddell, F.M., & Harrigan, S.M. (1999). Enduring negative symptoms in first-episode psychosis: comparison of six methods using follow-up data. *Schizophrenia Research, 40*, 147-158.
Emsley, R.A. (1999). Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. *Schizophrenia Bulletin, 25*, 721-729.
Etheridge, K., Yarrow, L., & Peet, M. (2004). Pathways to care in first episode psychosis. *Journal of Psychiatric & Mental Health Nursing, 11*, 125-128.
Falloon, I.R., Coverdale, J.H., Laidlaw, T.M., Merry, S., Kydd, R.R., & Morosini, P. (1998a). Early Intervention for schizophrenic disorders. *British Journal of Psychiatry, 173*(suppl 33), 33-38.
Falloon, I.R.H., Coverdale, J.H., Laidlaw, T.M., Merry, S., Kydd, R.R., & Morosini, P. (1998b). Early intervention for schizophrenic disorders: Implementing strategies in routine clinical services. *British Journal of Psychiatry, 172*(suppl. 33), 33-38.
Faraone, S.V. (2008). Understanding effect size: how it is measured and what it means. Retrieved 3/31/09, from http://www.medscape.com/viewarticle/569729
Faraone, S.V., Glatt, S.J., & Taylor, L. (2004). The genetic basis of schizophrenia. In W. S. Stone, S. V. Faraone & M. T. Tsuang (Eds.), *Early Clinical Intervention and Prevention in Schizophrenia* (pp. 3-21). Totowa, NJ: Humana Press.
Faraone, S.V., Seidman, L.J., Kremen, W.S., Kennedy, D., Makris, N., Caviness, V.S., et al. (2003). Structural brain abnormalities among relatives of patients with schizophrenia: implications for linkage studies. *Schizophrenia Research, 60*, 125-140.
Faraone, S.V., Seidman, L.J., Kremen, W.S., Toomey, R., Pepple, J.R., & Tsuang, M.T. (2000). Neuropsychologic functioning among the nonpsychotic relatives of schizophrenic patients: the effect of genetic loading. *Biological Psychiatry, 48*,

120-126.
FDA. Good clinical practice in FDA-regulated clinical trials.
Federal Registry. (1994). NIH guidelines on the inclusion of women and minorities as subjects in clinical research (Vol. 59, pp. 43085).
Fergusson, D.M., Poulton, R., Smith, P.F., & Boden, J.M. (2006). Cannabis and psychosis. *British Medical Journal, 332*, 172-175.
First, M.B., Spitzer, R.L., Gibbon, M., & Williams, J.B.W. (1997). Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-1).
Fitzgerald, D., Lucas, S., Redoblado, M.A., Winter, V., Brennan, J., Anderson, J., et al. (2004). Cognitive functioning in young people with first episode psychosis: relationship to diagnosis and clinical characteristics. *Australian and New Zealand Journal of Psychiatry, 38*, 501-510.
Freudenreich, O., Cather, C., Evins, E., Henderson, D.C., & Goff, D.C. (2004). Attitudes of schizophrenia outpatients toward psychiatric medications: relationship to clinical variables and insight. *Journal of Clinical Psychiatry, 65*, 1372-1376.
Ganguli, R., & Brar, J. (1992). Generalizability of first-episode studies in schizophrenia. *Schizophrenia Bulletin, 18*, 463-469.
Gelber, E.I., Kohler, C.G., Bilker, W.B., Gur, R.C., Brensinger, C., Siegel, S.J., et al. (2004). Symptom and demographic profiles in first-episode schizophrenia. *Schizophrenia Research, 67*, 185-194.
Geller, S., Adams, M.G., & Carnes, M. (2006). Adherence to federal guidelines for reporting of sex and race/ethnicity in clinical trials. *Journal of Women's Health, 15*, 1123-1131.
Gilmore, J.H., & Murray, R.M. (2006). Prenatal and Perinatal Factors. In J. A. Lieberman, T. S. Stroup & D. O. Perkins (Eds.), *Textbook of Schizophrenia* (pp. 55-67). Washington, DC: American Psychiatric Publishing, Inc.
Glasgow, R., Magid, D., Beck, A., Ritzwoller, D., & Estabrooks, P. (2005). Practical clinical trials for translating research to practice. Design and measurement recommendations. *Medical Care, 43*, 551-557.
Gold, J.M. (2004). Cognitive deficits as treatment targets in schizophrenia. *Schizophrenia Research, 72*, 21-28.
Goldman, M.B., & Mitchell, C.P. (2004). What is the functional significance of hippocampal pathology in schizophrenia? *Schizophrenia Bulletin, 30*, 367-392.
Goldstein, G., & Watson, J. (1989). Test-retest reliability of the Halstead-Reitan Battery and the WAIS in a neuropsychiatric population. *The Clinical Neuropsychologist, 3*, 265-272.
Goldstein, J., & Link, B. (1988). Gender and the expression of schizophrenia. *Journal of Psychiatric Research, 22*, 141-155.
Goldstein, J.M. (2006). Sex, hormones and affective arousal circuitry dysfunction in schizophrenia. *Hormones and Behavior, 50*, 612-622.
Goldstein, J.M., Seidman, L.J., Goodman, J.M., Koren, D., Lee, H., Weintraub, S., et al. (1998). Are there sex differences in neuropsychological functions among patients with schizophrenia? *American Journal of Psychiatry, 155*, 1358-1364.
Goldstein, J.M., Seidman, L.J., Santangelo, S., Knapp, P., & Tsuang, M.T. (1994). Are schizophrenic men at higher risk for developmental deficits than schizophrenic women? Implications for adult neuropsychological functions. *Journal of*

*Psychiatric Research, 28*, 483-489.
Goldstein, J.M., Tsuang, M.T., & Faraone, S.V. (1989). Gender and schizophrenia: implications for understanding the heterogeneity of the illness. *Psychiatry Research, 28*, 243-253.
Governor's Adolescent Health Council and Massachusetts Department of Public Health. (2003). A shared vision for Massachusetts youth and young adults 2003: summary data on youth development in relation to key strategic goals: Massachusetts Department of Health and Human Services.
Gray, R., Wykes, T., & Gournay, K. (2002). From compliance to concordance: a review of the literature on interventions to enhance compliance with antipsychotic medication. *Journal of Psychiatric and Mental Health Nursing, 9*, 277-284.
Green, A.I., Lieberman, J.A., Hamer, R.M., Glick, I.D., Gur, R.E., Kahn, R.S., et al. (2006). Olanzapine and haloperidol in first episode psychosis: two-year data. *Schizophrenia Research, 86*, 234-243.
Green, A.I., Tohen, M.F., Hamer, R.M., Strakowski, S.M., Lieberman, J.A., Glick, I., et al. (2004). First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. *Schizophrenia Research, 66*, 125-135.
Green, M.F. (2006). Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *Journal of Clinical Psychiatry, 67*(suppl 9), 3-8.
Green, M.F., Kern, R.S., Braff, D.L., & Mintz, J. (2000). Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophrenia Bulletin, 26*, 119-136.
Grossman, A.W., Churchill, J.D., McKinney, B.C., Kodish, I.M., Otte, S.L., & Greenough, W.T. (2003). Experience effects on brain development: possible contributions to psychopathology. *Journal of Child Psychology and Psychiatry, 44*, 33-63.
Group., I.E.P.A.W. (2005). International clinical practice guidelines for early psychosis. *British Journal of Psychiatry, 187*(Supplement 48), s120-124.
Gueorguieva, R., & Krystal, J.H. (2004). Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. *Archives of General Psychiatry, 61*, 310-317.
Guy, W. (1976). Clinical Global Impression. In *ECDEU Assessment Manual for Psychopharmacology* (pp. 217-222). Rockville, MD: U. S. Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug and Mental Health Administration, National Institute of Mental Health Psychopharmacology Research Branch, Division of Extramural Research Programs.
Haas, M., Eerdekens, M., Kushner, S., Singer, J., Augustyns, I., Quiroz, J., et al. (2009). Efficacy, safety and tolerability of two dosing regimens in adolescent schizophrenia: double-blind study. *The British Journal of Psychiatry, 194*, 158-164.
Hajós, M., Hoffmann, W.E., & Kocsis, B. (2008). Activation of cannabinoid-1 receptors disrupts sensory gating and neuronal oscillation: relevance to schizophrenia. *Biological Psychiatry, 63*, 1075-1083.
Hambrecht, M., & Hafner, H. (2000). Cannabis, vulnerability, and the onset of schizophrenia: An epidemiological perspective. *Australian and New Zealand*

*Journal of Psychiatry, 34*, 468-475.
Hamilton Wilson, J., Hobbs, H., & Archie, S. (2005). The right stuff for early intervention in psychosis. *Journal of Psychosocial Nursing, 43*, 22-28.
Harvey, P.D., & Keefe, R.S.E. (2001). Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *American Journal of Psychiatry, 158*, 176-184.
Heaton, R., Chelune, G., Talley, J., Key, G., & Curtiss, G. (1993). *Wisconsin Card Sorting Test manual: revised and expanded*. Odessa, FL: Psychological Assessment Resources.
Heaton, R.K. (1981). *A manual for the Wisconsin Card Sorting Test*. Odessa, Florida: Psychological Assessment Resources.
Heaton, R.K., Gladsjo, J.A., Palmer, B.W., Kuck, J., Marcotte, T.D., & Jeste, D.V. (2001). Stability and course of neuropsychological deficits in schizophrenia. *Archives of General Psychiatry, 58*, 24-32.
Heaton, R.K., Grant, I., & Matthews, C. (1992). *Comprehensive norms for an expanded Halstead-Reitan Battery*. Lutz, Florida: Psychological Assessment Resources, Inc.
Heinrichs, D.W., & Buchanan, R.W. (1988). Significance and meaning of neurological signs in schizophrenia. *American Journal of Psychiatry, 145*, 11-18.
Heinrichs, R.W., & Zakzanis, K.K. (1998). Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology, 12*, 426-445.
Henquet, C., Murray, R., Linszen, D., & van Os, J. (2005). The environment and schizophrenia: the role of cannabis use. *Schizophrenia Bulletin, 31*, 608-612.
Hickman, M., Vickerman, P., Macleod, J., Kirkbride, J., & Jones, P.B. (2007). Cannabis and schizophrenia: model projections of the impact of the rise in cannabis use on historical and future trends in schizophrenia in England and Wales. *Addiction, 102*, 597-606.
Ho, B.-C., Nopoulos, P., Flaum, M., Arndt, S., & Andreasen, N.C. (1998). Two-year outcome in first-episode schizophrenia: predictive value of symptoms for quality of life. *American Journal of Psychiatry, 155*, 1196-1201.
Ho, B., Andreasen, N.C., Flaum, M., Nopoulos, P., & Miller, D. (2000). Untreated initial psychosis: it's relation to quality of life and symptom remission in first-episode schizophrenia. *American Journal of Psychiatry, 157*, 808-815.
Hodge, M.A.R., Siciliano, D., Withey, P., Moss, B., Moore, G., Judd, G., et al. (2008). A randomized controlled trial of cognitive remediation in schizophrenia. *Schizophrenia Bulletin*, 102.
Hoff, A.L., Sakuma, M., Razi, K., Heydebrand, G., Csernansky, J.G., & Delisi, L.E. (2000). Lack of association between duration of untreated illness and severity of cognitive and structural brain deficits at the first episode of schizophrenia. *American Journal of Psychiatry, 157*, 1824-1828.
Hoff, A.L., Sakuma, M., Wieneke, M., Horon, R., Kushner, M., & DeLisi, L.E. (1999). Longitudinal neuropsychological follow-up study of patients with first-episode schizophrenia. *American Journal of Psychiatry, 156*, 1336-1341.
Hoff, A.L., Wieneke, M., Faustman, W.O., Horon, R., Sakuma, M., Blankfeld, H., et al. (1998). Sex differences in neuropsychological functioning of first-episode and chronically ill schizophrenic patients. *American Journal of Psychiatry, 155*, 1437-1439.

Holroyd, K.A., Powers, S.W., & Andrasik, F. (2005). Methodological issues in clinical trials of drug and behavior therapies. *Headache: The Journal of Head and Face Pain, 45*, 487-492.

Horan, W.P., & Blanchard, J.J. (2003). Neurocognitive, social, and emotional dysfunction in deficit syndrome schizophrenia. *Schizophrenia Research, 65*, 125-137.

Horan, W.P., Braff, D.L., Nuechterlein, K.H., Sugar, C.A., Cadenhead, K.S., Calkins, M.E., et al. (2008). Verbal working memory impairments in individuals with schizophrenia and their first-degree relatives: findings from the consortium on the genetics of schizophrenia. *Schizophrenia Research, 103*, 218-228.

Houck, P.R., Mazumdar, S., Koru-Sengul, T., Tang, G., Mulsant, B.H., Pollock, B.G., et al. (2004). Estimating treatment effects from longitudinal clinical trial data with missing values: comparative analyses using different methods. *Psychiatry Research, 129*, 209-215.

Howard, L., de Salis, I., Tomlin, Z., Thornicroft, G., & Donovan, J. (2009). Why is recruitment to trails difficult? An investigation into recruitment difficulties in an RCT of supported employment in patients with severe mental illness. *Contemporary Clinical Trials, 30*, 40-46.

Hser, Y.-I., Shen, H., Chou, C.-P., Messer, S.C., & Anglin, M.D. (2001). Analytic Approaches for Assessing Long-Term Treatment Effects: Examples of Empirical Applications and Findings. *Evaluation Review, 25*, 233-262.

Huber, G. (1997). The heterogeneous course of schizophrenia. *Schizophrenia Research, 28*, 177-185.

Huber, G., Gross, G., & Schutter, R. (1975). A long-term follow-up study of schizophrenia: psychiatric course of illness and prognosis. *Acta Psychiatra Scandinavia, 52*, 49-57.

Huck, S.W. (2008). *Reading statistics and research.* Boston: Pearson Education, Inc.

Hudson, T., Owen, R., Thrush, C., Han, X., Pyne, J., Thapa, P., et al. (2004). A pilot study of barriers to medication adherence in schizophrenia. *Journal of Clinical Psychiatry, 65*, 211-216.

Hunt, G., Bergen, J., & Bashir, M. (2002). Medication compliance and comorbid substance abuse in schizophrenia: impact on community survival 4 years after a relapse. *Schizophrenia Research, 54*, 253-264.

Insel, T.R. (2009). Translating scientific opportunity into public health impact: a strategic plan for research on mental illness. *Archives of General Psychiatry, 66*, 128-133.

Jablensky, A. (1997). The 100 year epidemiology of schizophrenia. *Schizophrenia Research, 28*, 111-125.

Joffe, G., Terevnikov, V., Joffe, M., Stenberg, J.-H., Burkin, M., & Tiihonen, J. (2009). Add-on mirtazapine enhances antipsychotic effect of first generation antipsychotics in schizophrenia: A double-blind, randomized, placebo-controlled trial. *Schizophrenia Research, 108*, 245-251.

Johnstone, B., Callahan, C.D., Kapila, C.J., & Bouman, D.E. (1996). The comparability of the WRAT-R reading test and NAART as estimates of premorbid intelligence in neurologically impaired patients. *Archives of Clinical Neuropsychology, 11*, 513.

Kane, J.M. (2005). Reading reports of clinical trial results. *Journal of Clinical*

*Psychiatry, 66*, 653.
Keefe, R.S., Seidman, L.J., Christensen, B.K., Hamer, R.M., Sharma, T., Sitskoorn, M.M., et al. (2006a). Long-term neurocognitive effects of olanzapine or low-dose haloperidol in first-episode psychosis. *Biological Psychiatry, 59*, 97-148.
Keefe, R.S.E., Bilder, R.M., Harvey, P.D., Davis, S.M., Palmer, B.W., Gold, J.M., et al. (2006b). Baseline neurocognitive deficits in the CATIE schizophrenia trial. *Neuropsychopharmacology, 31*, 2033-2046.
Keefe, R.S.E., & Eesley, C.E. (2006). Neurocognitive impairments. In J. A. Lieberman, T. S. Stroup & D. O. Perkins (Eds.), *Textbook of Schizophrenia.* (pp. 245-260). Washington, DC: American Psychiatric Publishing, Inc.
Keefe, R.S.E., Sweeney, J.A., Gu, H., Hamer, R.M., Perkins, D.O., McEvoy, J.P., et al. (2007). Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. *American Journal of Psychiatry, 164*, 1061-1071.
Kelland, D., Lewis, R., & Gurevitch, D. (1992). Evaluation of the repeatable cognitive-perceptual-motor battery: reliability, validity and sensitivity to diazepam. *Journal of Clinical and Experimental Neuropsychology, 14*, 65.
Kemmler, G., Hummer, M., Widschwendter, C., & Fleischhacker, W. (2005). Dropout rates in placebo-controlled and active-control clinical trials of antipsychotic drugs. *Archives of General Psychiatry, 62*, 1305-1312.
Keshavan, M.S. (1999). Development, disease and degeneration in schizophrenia: a unitary pathophysiological model. *Journal of Psychiatric Research, 33*, 513-521.
Keshavan, M.S., Gilbert, A.R., & Diwadkar, V.A. (2006). Neurodevelopmental theories. In J. A. Lieberman, T. S. Stroup & D. O. Perkins (Eds.), *Textbook of Schizophrenia* (pp. 69-83). Washington, D. C.: American Psychiatric Press, Inc.
Keshavan, M.S., & Schooler, N.R. (1992). First-episode studies in schizophrenia: criteria and characterization. *Schizophrenia Bulletin, 18*, 491-513.
Khan, A., Schwartz, K., Redding, N., Kolts, R., & Brown, W. (2007). Psychiatric diagnosis and clinical trial completion rates: analysis of the FDA SBA reports. *Neuropsychopharmacology, 32*, 2422-2430.
Killackey, E., Jackson, H.J., & McGorry, P.D. (2008). Vocational intervention in first-episode psychosis: individual placement and support v. treatment as usual. *The British Journal of Psychiatry, 193*, 114-120.
Koskinen, J., Lohonen, J., Koponen, H., Isohanni, M., & Miettunen, J. (2009). Rate of cannabis use disorders in clinical samples of patients with schizophrenia: a meta-analysis. *Schizophrenia Bulletin*, sbp031.
Kremen, W.S., & Hoff, A.L. (2004). Neurocognitive deficits in the biological relatives of individuals with schizophrenia. In W. S. Stone, S. V. Faraone & M. T. Tsuang (Eds.), *Early Clinical Intervention and Prevention on Schizophrenia* (pp. 133-158). Totowa, NJ: Humana Press, Inc.
Kurtz, M.M., & Mueser, K.T. (2008). A meta-analysis of controlled research on social skills training for schizophrenia. *Journal of Consulting and Clinical Psychology, 76*, 491-504.
Lacro, J., Dunn, L., Dolder, C., Leckband, S., & Jeste, D. (2002). Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *Journal of Clinical Psychiatry, 63*,

892-909.
Larsen, T.K., McGlashen, T.H., & Moe, L.C. (1996). First episode schizophrenia: I. Early course parameters. *Schizophrenia Bulletin, 22*, 241-256.
Larsen, T.K., Melle, I., Auestad, B., Friis, S., Haahr, U., Johannessen, J.O., et al. (2006). Substance abuse in first-episode non-affective psychosis. *Schizophrenia Research, 88*, 55-62.
Lavorie, P.W., Dawson, R., & Shera, D. (1995). A multiple imputation strategy for clinical trials with truncation of patient data. *Statistics in Medicine, 14*, 1913-1925.
Leon, A.C., Mallinckrodt, C.H., Chuang-Stein, C., Archibald, D.G., Archer, G.E., & Chartier, K. (2006). Attrition in randomized controlled clinical trials: methodological issues in psychopharmacology. *Biological Psychiatry, 59*, 1001-1005.
Leucht, S., Engel, R.R., Bauml, J., & Davis, J.M. (2007). Is the superior efficacy of new generation antipsychotics an artifact of LOCF? *Schizophrenia Bulletin, 33*, 183-191.
Leucht, S., Kane, J.M., Etschel, E., Kissling, W., Hamann, J., & Engel, R.R. (2006). Linking the PANSS, BPRS, and CGI: clinical implications. *Neuropsychopharmacology, 31*, 2318-2325.
Leucht, S., Kane, J.M., Kissling, W., Hamann, J., Etschel, E.V.A., & Engel, R. (2005). Clinical implications of Brief Psychiatric Rating Scale scores. *The British Journal of Psychiatry, 187*, 366-371.
Leung, W.K., Wu, J.C.Y., Chan, F.K.L., Fung, S.S.L., Wong, V.W.S., Hui, A.J., et al. (2007). Initial treatment with lansoprazole in young dyspeptic patients with negative urea breath test result: a randomized controlled trial with 12-month follow-up. *The American Journal of Gastroenterology, 102*, 1483-1488.
Lewis, S.W., Tarrier, N., & Drake, R.J. (2005). Integrating non-drug treatment in early schizophrenia. *British Journal of Psychiatry, 187*(Suppl. 48), s65-71.
Lezak, M.D. (1995). *Neuropsychological Assessment* (3rd ed.). New York: Oxford University Press.
Lieberman, J., Jody, D., Geisler, S., Alvir, J., Loebel, A., Szymanski, S., et al. (1993). Time course and biologic correlates of treatment response in first-episode schizophrenia. *Archives of General Psychiatry, 50*, 369-376.
Lieberman, J.A., Perkins, D., Belger, A., Chakos, M., Jarskog, F., Boteva, K., et al. (2001). The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. *Biological Psychiatry, 50*, 884-897.
Lieberman, J.A., Phillips, M., Gu, H., Stroup, S., Zhang, P., Kong, L., et al. (2003a). Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. *Neuropsychopharmacology, 28*, 995-1003.
Lieberman, J.A., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., et al. (2005a). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine, 353*, 1209-1223.
Lieberman, J.A., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., et al. (2005b). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine, 353*, 1209-1223.

Lieberman, J.A., Tollefson, G., Tohen, M., Green, A.I., Gur, R.E., Kahn, R., et al. (2003b). Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. *American Journal of Psychiatry, 160*, 1396-1404.

Lindenmayer, J.P., & Khan, A. (2006). Psychopathology. In J. A. Lieberman, T. S. Stroup & D. O. Perkins (Eds.), *Textbook of Schizophrenia* (pp. 187-221). Washington, DC: American Psychiatric Publishing, Inc.

Linszen, D.H., Dingemans, P.M., & Lenior, M.E. (1994). Cannabis abuse and the course of recent-onset schizophrenic disorders. *Archives of General Psychiatry, 51*, 273-279.

Lipsey, M.W., & Wilson, D.B. (2001). *Practical meta-analysis*. Thousand Oaks, CA: Sage.

Llabre, M.M., Spitzer, S., Siegel, S., Saab, P.G., & Schneiderman, N. (2004). Applying Latent Growth Curve Modeling to the Investigation of Individual Differences in Cardiovascular Recovery From Stress. *Psychosomatic Medicine, 66*, 29-41.

Loebel, A.D., Lieberman, J.A., Alvir, J.M.J., Mayerhoff, D.L., Geisler, S.H., & Szymanski, S.R. (1992). Duration of psychosis and outcome in first-episode schizophrenia. *American Journal of Psychiatry, 149*, 1183-1188.

Malla, A., & Payne, J. (2005). First-episode psychosis: psychopathology, quality of life, and functional outcome. *Schizophrenia Bulletin, 31*, 650-671.

Malla, A.K., Takhar, J., Norman, R.M., Manchanda, R., Cortese, L., Haricharan, R., et al. (2002). Negative symptoms in first episode non-affective psychosis. *Acta Psychiatrica Scandinavica, 105*, 431-439.

March, J.S., Silva, S.G., Compton, S., Shapiro, M., Califf, R., & Krishnan, R. (2005). The case for practical clinical trials in psychiatry. *American Journal of Psychiatry, 162*, 836-846.

Mark, K., Corey, L., Meng, T., Magaret, A., Huang, M., Selke, S., et al. (2007). Topical Resiquimod 0.01% gel decreases herpes simplex virus type 2 genital shedding: a randomized, controlled trial. *The Journal of Infectious Disease, 195*, 1324-1331.

Marshall, M., Lewis, S., Lockwood, A., Drake, R., Jones, P., & Croudace, T. (2005). Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Archives of General Psychiatry, 62*, 975-983.

Massachusetts Department of Education. (2002). Dropout rates 2000 - 2001. Retrieved March 6, 2009, 2009, from http://www.doe.mass.edu/infoservices/reports/dropout/0001

Mazumdar, S., Liu, K.S., Houck, P.R., & Reynolds, C.F. (1999). Intent-to-treat analysis for longitudinal clinical trials: coping with the challenge of missing values. *Journal of Psychiatric Research, 33*, 87-95.

Mazumdar, S., Tang, G., Houck, P.R., Dew, M.A., Begley, A.E., Scott, J., et al. (2007). Statistical analysis of longitudinal psychiatric data with dropouts. *Journal of Psychiatric Research, 41*, 1032-1041.

McClure, R.K., & Lieberman, J.A. (2003). Neurodevelopmental and neurodegenerative hypothesis of schizophrenia: a review and critique. *Current Opinions in Psychiatry, 16*(suppl 2), S15-S28.

McEvoy, J.P., Johnson, J., Perkins, D.O., Lieberman, J.A., Hamer, R.M., Keefe, R.S., et

al. (2006). Insight in first-episode psychosis. *Psychological Medicine, 36*, 1385-1393.

McEvoy, J.P., Lieberman, J.A., Perkins, D.O., Hamer, R.M., Gu, H., Lazarus, A., et al. (2007). Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *American Journal of Psychiatry, 164*, 1050-1060.

McGlashen, T.H. (1988). A selective review of recent North American long-term follow-up studies of schizophrenia. *Schizophrenia Bulletin, 14*, 515-542.

McGorry, P.D. (2005). Early intervention in psychotic disorders: beyond debate to solving problems. *British Journal of Psychiatry, 187*(Supplement 28), 108-110.

McGrath, J.J. (2005). Myths and plain truths about schizophrenia epidemiology - the NAPE lecture 2004. *Acta Psychiatrica Scandinavica, 111*, 4-11.

McGrath, J.J. (2006). Variations in the incidence of schizophrenia: data versus dogma. *Schizophrenia Bulletin, 32*, 195-197.

McGrath, J.J., & Welham, J.L. (1999). Season of birth and schizophrenia: a systematic review and meta-analysis of data from the Southern Hemisphere. *Schizophrenia Research, 35*, 237-242.

McGurk, S.R., Twamley, E.W., Sitzer, D.I., McHugo, G.J., & Mueser, K.T. (2007). A meta-analysis of cognitive remediation in schizophrenia. *American Journal of Psychiatry, 164*, 1791-1802.

Mesholam-Gately, R., Giuliano, A.J., & Seidman, L.J. (2009). Neurocognition in first-episode schizophrenia: a meta-analysis review. *Neuropsychology, 23*, 315-336.

Mesulam, M. (1985). *Principles of Behavioral Neurology* (Vol. 26). Philadelphia: F. A. Davis.

Meyer, S.E., Bearden, C.E., Lux, S.R., Gordon, J.L., Johnson, J.K., O'Brien, M.P., et al. (2005). The psychosis prodrome in adolescent patients viewed through the lens of DSM-IV. *Journal of Child and Adolescent Psychopharmacology, 15*, 434-451.

Mojtabai, R., Fochtmann, L., Chang, S.-W., Kotov, R., Craig, T.J., & Bromet, E. (2009). Unmet Need for Mental Health Care in Schizophrenia: An Overview of Literature and New Data From a First-Admission Study. *Schizophrenia Bulletin, 35*, 679-695.

Mojtabai, R., Herman, D., Susser, E.S., Sohler, N., Craig, T.J., Lavelle, J., et al. (2005). Service Use and Outcomes of First-Admission Patients With Psychotic Disorders in the Suffolk County Mental Health Project. *American Journal of Psychiatry, 162*, 1291-1298.

Morgan, C., Abdul-Al, R., Lappin, J.M., Jones, P., Fearon, P., Leese, M., et al. (2006). Clinical and social determinants of duration of untreated psychosis in the AeSOP first-episode psychosis study. *British Journal of Psychiatry, 189*, 446-452.

Mortensen, P.B., Norgaard-Pedersen, B., Waltoft, B.L., Sorensen, T.L., Hougaard, D., & Yolken, R.H. (2007). Early infections of toxoplasma gondii and the later development of schizophrenia. *Schizophrenia Bulletin, 33*, 741-744.

Mortimer, A.M. (2007). Symptom rating scales and outcome in schizophrenia. *The British Journal of Psychiatry, 191*, s7-14.

Mullen, A., Murray, L., & Happell, B. (2002). Multiple family group interventions in first episode psychosis: enhancing knowledge and understanding. *International Journal of Mental Health Nursing, 11*, 225-232.

Nelson, H., & Willison, J. (1991). *National Adult Reading Test (NART) Test Manual* (2nd ed.). Berkshire, England: Nfer-Nelson Publishing Company LTD.

New Freedom Commission on Mental Health. (2003). *Achieving the promise: transforming mental health care in America. Final report* (No. DHHS Pub. No. SMA-03-3832). Rockville, MD: Department of Health and Human Services.

Niemi, L.T., Suvisaari, J.M., Tuulio-Henriksson, A., & Lonnqvist, J.K. (2003). Childhood developmental abnormalities in schizophrenia: evidence from high-risk studies. *Schizophrenia Research, 60*, 239-258.

Nieuwenstein, M.R. (2001). Relationship between symptom dimensions and neurocognitive functioning in schizophrenia. *Journal of Psychiatric Research, 35*, 119-125.

NINR. (2006). Draft of strategic plan of the NINR 2006-2010. Retrieved 4/11/06, from ttp://ninr.nih.gov/ninr/draft.html

Norman, R.M.G., Lewis, S.W., & Marshall, M. (2005). Duration of untreated psychosis and its relationship to clinical outcome. *British Journal of Psychiatry, 187*(Suppl. 48), s19-23.

Norman, R.M.G., Mallal, A.K., Manchanda, R., Windell, D., Harricharan, R., Takhar, J., et al. (2007). Does treatment delay predict occupational functioning in first-episode psychosis? *Schizophrenia Research, 91*, 259-262.

Nose, M., Barbui, C., Gray, R., & Tansella, M. (2003). Clinical Interventions for treatment non-adherence in psychosis: meta-analysis. *British Journal of Psychiatry, 183*, 197-206.

O'Donnell, P., & Grace, A. (1998). Dysfunctions in multiple interrelated systems as the neurobiological bases of schizophrenic symptom clusters. *Schizophrenia Bulletin, 24*, 267-283.

O'Toole, M.S., Ohlsen, R.I., Taylor, T.M., Purvis, R., Walters, J., & Pilowsky, L.S. (2004). Treating first episode psychosis - a service users' perspective: a focus group evaluation. *Journal of Psychiatric and Mental Health Nursing, 11*, 319-326.

Office of Disease Prevention and Health Promotion. (2005). Healthy People 2010. In U.S. Department of Health and Human Services (Ed.): Rockville, MD.

Penn, D.L., Waldheter, E.J., Perkins, D.O., Mueser, K.T., & Lieberman, J.A. (2005). Psychosocial treatment for first-episode psychosis: a research update. *American Journal of Psychiatry, 162*, 2220-2232.

Perkins, D.O. (1999). Adherence to antipsychotic medications. *Journal of Clinical Psychiatry, 60*(Suppl 21), 25-30.

Perkins, D.O. (2002). Predictors of noncompliance in patients with schizophrenia. *Journal of Clinical Psychiatry, 63*, 1121-1128.

Perkins, D.O., Gu, H., Boteva, K., & Lieberman, J.A. (2005). Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *American Journal of Psychiatry, 162*, 1785-1804.

Perkins, D.O., Gu, H., Weiden, P.J., McEvoy, J.P., Hamer, R.M., & Lieberman, J.A. (2008). Predictors of treatment discontinuation and medication nonadherence in patients recovering from a first episode of schizophrenia, schizophreniform disorder, or schizoaffective disorder: a randomized, double-blind, flexible-dose,

multicenter study. *Journal of Clinical Psychiatry, 69*, 106-113.
Perkins, D.O., Lieberman, J.A., & Lewis, S. (2006a). First Episode. In J. A. Lieberman, T. S. Stroup & D. O. Perkins (Eds.), *Textbook of Schizophrenia* (pp. 353-364). Washington, D. C.: American Psychiatric Publishing, Inc.
Perkins, D.O., Miller-Anderson, L., & Lieberman, J.A. (2006b). Natural history and predictors of clinical course. In J. A. Lieberman, T. S. Stroup & D. O. Perkins (Eds.), *Textbook of Schizophrenia* (pp. 289-301). Washington, DC: American Psychiatric Publishing, Inc.
Petersen, L., Jeppesen, P., Thorup, A., Abel, M.B., Ohlenschlaeger, J., Christensen, T.O., et al. (2005). A randomized multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. *British Medical Journal, 331*, 602-605.
Preston, N.J., Orr, K.G., Date, R., Nolan, L., & Castle, D.J. (2002). Gender differences in premorbid adjustment of patients with first episode psychosis. *Schizophrenia Research, 55*, 285-290.
Rais, M., Cahn, W., Van Haren, N., Schnack, H., Caspers, E., Hulshoff Pol, H., et al. (2008). Excessive brain volume loss over time in cannabis-using first-episode schizophrenia patients. *American Journal of Psychiatry, 165*, 490-496.
Rakfeldt, J., & McGlashan, T.H. (2004). The nature of the prodrome in schizophrenia. In W. S. Stone, S. V. Faraone & M. T. Tsuang (Eds.), *Early Clinical Intervention and Prevention in Schizophrenia* (pp. 75-91). Totowa, NJ: Humana Press.
Retsch-Bogart, G., Burns, J., Otto, K., Liou, T., McCoy, K., Oermann, C., et al. (2008). A phase 2 study of aztreonam lysine for inhalation to treat patients with cystic fibrosis and pseudomonas aeruginosa infection. *Pediatric Pulmonology, 43*, 47-58.
Robinson, D., Woerner, M., Alvir, J.M., Bilder, R., Hinrichsen, G., & Lieberman, J.A. (2002). Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. *Schizophrenia Research, 57*, 209-219.
Robinson, D., Woerner, M.G., Alvir, J.M.J., Bilder, R., Goldman, R., Geisler, S., et al. (1999a). Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Archives of General Psychiatry, 56*, 241-247.
Robinson, D., Woerner, M.G., McMeniman, M., Mendelowitz, A., & Bilder, R. (2004). Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. *American Journal of Psychiatry, 161*, 473-479.
Robinson, D.G., Woerner, M.G., Alvir, J.M., Geisler, S., Koreen, A., Sheitman, B., et al. (1999b). Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. *American Journal of Psychiatry, 156*, 544-549.
Robinson, D.G., Woerner, M.G., Napolitano, B., Patel, R.C., Sevy, S.M., Gunduz-Bruce, H., et al. (2006). Randomized comparison of olanzapine versus risperidone for the treatment of first-episode schizophrenia: 4-month outcomes. *American Journal of Psychiatry, 163*, 2096-2102.
Rosen, J.L., Miller, T.J., D'Andrea, J.T., McGlashan, T.H., & Woods, S.W. (2006). Comorbid diagnoses in patients meeting criteria for the schizophrenia prodrome. *Schizophrenia Research, 85*, 124-131.
Ross, T.P., Calhoun, E., Cox, T., Wenner, C., Kono, W., & Pleasant, M. (2007). The

reliability and validity of qualitative scores for the Controlled Oral Word Association Test. *Archives of Clinical Neuropsychology, 22*, 475-488.

Rosso, I.M., Bearden, C.E., Hollister, J.M., Gasperoni, T.L., Sanchez, L.E., Hadley, T., et al. (2000). Childhood neuromotor dysfunction in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophrenia Bulletin, 26*, 367-378.

Roy, M.-A., Maziade, M., Labbe, A., & Merette, C. (2001). Male gender is associated with deficit schizophrenia: a meta-analysis. *Schizophrenia Research, 47*, 141-147.

Royal Australian and New Zealand College of Psychiatrists. (2005). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders. *Australian and New Zealand Journal of Psychiatry, 39*, 1-30.

Ruff, R.M., Light, R.H., Parker, S.B., & Levin, H.S. (1996). Benton Controlled Oral Word Association Test: reliability and updated norms. *Archives of Clinical Neuropsychology, 11*, 329-338.

Rund, B.R., Melle, I., Friis, S., Johannessen, J.O., Larsen, T.K., Midboe, L.J., et al. (2007). The course of neurocognitive functioning in first-episode psychosis and its relation to premorbid adjustment, duration of untreated psychosis, and relapse. *Schizophrenia Research, 91*, 132-140.

Russell, E., W. (1982). Factor analysis of the revised Wechsler Memory Scale tests in a neuropsychological battery. *Perceptual and Motor Skills, 54*, 971-974.

Saha, S., Chant, D.C., Welham, J.L., & McGrath, J.J. (2006). The incidence and prevalence of schizophrenia varies with latitude. *Acta Psychiatrica Scandinavica, 114*, 36-39.

Sanbrook, M., Harris, A., Parada, R., & Young, P. (2003). The effectiveness of an early intervention team in the treatment of first-episode psychosis. *Journal of Advancement of Mental Health, 2*, 1-8.

Sanger, T.M., Lieberman, J.A., Tohen, M., Grundy, S., Beasley, C., & Tollefson, G.D. (1999). Olanzapine versus haloperidol treatment in first-episode psychosis. *American Journal of Psychiatry, 156*, 79-87.

Schear, J., & Sato, S. (1989). Effects of visual acuity and visual motor speed and dexterity on cognitive test performance. *Archives of Clinical Neuropsychology, 4*, 25-32.

Schimmelmann, B.G., Huber, C.G., Lambert, M., Cotton, S., McGorry, P.D., & Conus, P. (2008). Impact of duration of untreated psychosis on pre-treatment, baseline, and outcome characteristics in an epidemiological first-episode psychosis cohort. *Journal of Psychiatric Research, 42*, 982-990.

Schooler, N., Rabinowitz, J., Davidson, M., Emsley, R., Harvey, P.D., Kopala, L., et al. (2005). Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *American Journal of Psychiatry, 162*, 947-953.

Schreiber, S., Keshavarzian, A., Isaacs, K.L., Schollenberger, J., Guzman, J.P., Orlandi, C., et al. (2007). A randomized, placebo-controlled, phase II study of tetomilast in active ulcerative colitis. *Gastroenterology, 132*, 76-86.

Scully, P.J., Coakley, G., Kinsella, A., & Waddington, J.L. (1997). Psychopathology, executive (frontal) and general cognitive impairment in relation to duration of initially untreated versus subsequent treated psychosis in chronic schizophrenia.

*Psychological Medicine, 27*, 1303-1310.
Seidman, L.J., Faraone, S.V., Goldstein, J.M., Kremen, W.S., Horton, N.J., Makris, N., et al. (2002). Left hippocampal volume as a vulnerability indicator for schizophrenia: a magnetic resonance imaging morphometric study of nonpsychotic first-degree relatives. *Archives of General Psychiatry, 59*, 839-849.
Seidman, L.J., Thermenos, H.W., Koch, J.K., Ward, M., Breiter, H., Goldstein, J.M., et al. (2007). Auditory verbal working memory load and thalamic activation in nonpsychotic relatives of persons with schizophrenia: an fMRI replication. *Neuropsychology, 21*, 599-610.
Seidman, L.J., Thermenos, H.W., Poldrack, R.A., Peace, N.K., Koch, J.K., Faraone, S.V., et al. (2006). Altered brain activation in dorsolateral prefrontal cortex in adolescents and young adults at genetic risk for schizophrenia: a fMRI study of working memory. *Schizophrenia Research, 85*, 58-72.
Seidman, L.J., & Wencel, H.E. (2003). Genetically mediated brain abnormalities in schizophrenia. *Current Psychiatric Reports, 5*, 135-144.
Sergi, M.J., Rassovsky, Y., Widmark, C., Reist, C., Erhart, S., Braff, D.L., et al. (2007). Social cognition in schizophrenia: relationships with neurocognition and negative symptoms. *Schizophrenia Research, 90*, 316-324.
Shapiro, A.M., Benedict, R.H.B., Schretlen, D., & Brandt, J. (1999). Construct and concurrent validity of the Hopkins Verbal Learning Test - Revised. *Clinical Neuropsychologist, 13*, 348-358.
Sharma, T., & Antonova, L. (2003). Cognitive function in schizophrenia. Deficits, functional consequences and future treatment. *Psychiatric Clinics of North America, 26*, 25-40.
Sheiner, L.B. (2002). Is intent-to-treat analysis always (ever) enough? *British Journal of Clinical Pharmacology, 54*, 203-211.
Shtasel, D., Gur, R.E., Gallacher, F., Heimberg, C., & Gur, R.C. (1992). Gender differences in the clinical expression of schizophrenia. *Schizophrenia Research, 7*, 225-231.
Smit, F., Bolier, L., & Cuijpers, P. (2004). Cannabis use and the risk of later schizophrenia: a review. *Addiction, 99*, 425-430.
Spear, H.J., & Kulbok, P. (2004). Autonomy and adolescence: a concept analysis. *Public Health Nursing, 21*, 144-152.
Spencer, E., Birchwood, M., & McGovern, D. (2001). Management of first-episode psychosis. *Advances in Psychiatric Treatment, 7*, 133-142.
Spitzer, M. (1993). The psychopathology, neuropsychology, and neurobiology of associative and working memory in schizophrenia. *European Archives of Psychiatry & Clinical Neuroscience, 243*, 57-70.
Spitzer, R.L., Endicott, J., & Robins, E. (1975). *Research Diagnostic Criteria (RDC)*. New York: Biometrics Research, New York State Psychiatric Institute.
Spreen, O., & Strauss, E. (1998a). Controlled Oral Word Association. In *A Compendium of Neuropsychological Tests - Administration, Norms, and Commentary* (2nd ed., pp. 447-464). New York: Oxford University Press.
Spreen, O., & Strauss, E. (1998b). Motor Tests. In *A Compendium of Neuropsychological Tests - Administration, Norms, and Commentary* (pp. 577-598). New York: Oxford University Press.

Spreen, O., & Strauss, E. (1998c). National Adult Reading Test (NART). In *A Compendium of Neuropsychological Tests - Administration, Norms, and Commentary* (2nd ed., pp. 75-82). New York: Oxford University Press.

Spreen, O., & Strauss, E. (1998d). Profile of test results and meaning of scores. In *A Compendium of Neuropsychological Tests - Administration, Norms, and Commentary* (2nd ed., pp. 16-28). New York: Oxford University Press.

Spreen, O., & Strauss, E. (1998e). Wide Range Achievement Test 3 (WRAT 3). In *A Compendium of Neuropsychological Tests - Administration, Norms, and Commentary* (2nd ed., pp. 164-166). New York: Oxford University Press.

SPSS. (2008). Graduate Pack, 16.0.

Stahl, S.M., & Buckley, P.F. (2007). Negative symptoms of schizophrenia: a problem that will not go away. *Acta Psychiatrica Scandinavica, 115*, 4-11.

Stanford, M., & Barratt, E. (1996). Verbal skills, finger tapping and cognitive tempo define a second-order factor of temporal information processing. *Brain and Cognition, 31*, 35-45.

Stirling, J., White, C., Lewis, S., Hopkins, R., Tantam, D., Huddy, A., et al. (2003). Neurocognitive function and outcome in first-episode schizophrenia: a 10-year follow-up of an epidemiological cohort. *Schizophrenia Research, 65*, 75-86.

Strauss, E., Sherman, E., & Spreen, O. (2006). Wisconsin Card Sorting Test. In *A Compendium of Neuropsychological Tests*
(3rd ed., pp. 526-545). New York: Oxford University Pres.

Streiner, D.L. (2002). The case of the missing data: methods of dealing with dropouts and other research vagaries. *Canadian Journal of Psychiatry, 47*, 68-74.

Streiner, D.L. (2008). Missing data and the trouble with LOCF. *Evidence-Based Mental Health, 11*, 3-5.

Subotnik, K., Nuechterlein, K., Ventura, J., Green, M.F., & Hwang, S. (1998). Prediction of the deficit syndrome from initial deficit symptoms in the early course of schizophrenia. *Psychiatry Research, 80*, 53-59.

Substance Abuse and Mental Health Services Administration. (2005). Results from the 2002 National Survey on Drug Use and Health: National Findings. Retrieved March 6, 2009, from http://www.DrugAbuseStatistics.SAMHSA.gov

Substance Abuse and Mental Health Services Administration. (2007). Results from the 2006 National Survey on Drug Use and Health: National Findings. *NSDUH Series H-32* Retrieved March 6, 2009, from http://oas.samhsa.gov

Sullivan, E.V., Mathalon, D.H., Zipursky, R.B., Kersteen-Tucker, Z., Knight, R.T., & Pfefferbaum, A. (1993). Factors of the Wisconsin Card Sorting Test as measures of frontal-lobe function in schizophrenia and in chronic alcoholism. *Psychiatry Research, 46*, 175-199.

Szeszko, P.R., Robinson, D.G., Sevy, S., Kumra, S., Rupp, C.I., Betensky, J.D., et al. (2007). Anterior cingulate grey-matter deficits and cannabis use in first-episode schizophrenia. *British Journal of Psychiatry, 190*, 230-236.

Szymanski, S., Lieberman, J.A., Alvir, J.M., Mayerhoff, D., Loebel, A., Geisler, S., et al. (1995). Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients. *American Journal of Psychiatry, 152*, 698-703.

Tansella, M., Thornicroft, G., Barbui, C., Cipriani, A., & Saraceno, B. (2006). Seven

criteria for improving effectiveness trials in psychiatry. *Psychological Medicine, 36*, 711-720.

The Associated Press (Writer) (2005). U.S. college drop-out rate sparks concern. USA: MSNBC.

Thermenos, H.W., Seidman, L.J., Poldrack, R.A., Peace, N.K., Koch, J.K., Faraone, S.V., et al. (2007). Elaborative verbal encoding and altered anterior parahippocampal activation in adolescents and young adults at genetic risk for schizophrenia using fMRI. *Biological Psychiatry, 61*, 564-574.

Tollefson, G.D., Beasley, C.M., Tran, P.V., Street, J.S., Krueger, J.A., Tamura, R.N., et al. (1997). Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *American Journal of Psychiatry, 154*, 457-465.

Triggs, W., Calvanio, R., Levin, M., Heaton, R.K., & Heilman, K. (2000). Predicting hand preference with performance on motor tasks. *Cortex, 36*, 679-689.

Tsuang, H.-C., Lin, S.-H., Liu, S.K., Hsieh, M.-H., Hwang, T.J., Liu, C.-M., et al. (2006). More severe sustained attention deficits in nonpsychotic siblings of multiplex schizophrenia families than in those of simplex ones. *Schizophrenia Research, 87*, 172-180.

Tsuang, M.T., Stone, W.S., & Faraone, S.V. (1999). Schizophrenia: a review of genetic studies. *Harvard Review of Psychiatry, 7*, 185-207.

Tully, E.M., & McGlashan, T.H. (2006). The Prodrome. In J. A. Lieberman, T. S. Stroup & D. O. Perkins (Eds.), *Textbook of Schizophrenia* (pp. 341-352). Washington, DC: American Psychiatric Publishing, Inc.

Tunis, S.R., Stryer, D.B., & Clancy, C.M. (2003). Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *Journal of the American Medical Association, 290*, 1624-1632.

Turetsky, B.I., Calkins, M.E., Light, G.A., Olincy, A., Radant, A.D., & Swerdlow, N.R. (2007). Neurophysiological endophenotypes of schizophrenia: The viability of selected candidate measures. *Schizophrenia Bulletin, 33*, 69-94.

Turetsky, B.I., Greenwood, T.A., Olincy, A., Radant, A.D., Braff, D.L., Cadenhead, K.S., et al. (2008). Abnormal auditory N100 amplitude: a heritable endophenotype in first-degree relatives of schizophrenia probands. *Biological Psychiatry, 64*, 1051-1059.

United States Census Bureau. (2000). Factfinder April 1, 2000 census. 2009, from http://factfinder.census.gov/home/saff/main.html?_lang=en

Van Mastrigt, S., Addington, J., & Addington, D. (2004). Substance misuse at presentation to an early psychosis program. *Social Psychiatry & Psychiatric Epidemiology, 39*, 69-72.

van Meijel, B., van der Gaag, M., Kahn, R.S., & Grypdonck, M.H.F. (2003). Relapse prevention in patients with schizophrenia: the application of an intervention protocol in nursing practice. *Archives of Psychiatric Nursing, 17*, 165-172.

van Os, J., Bak, M., Hanssen, M., Bijl, R.V., de Graaf, R., & Verdoux, H. (2002). Cannabis use and psychosis: a longitudinal population-based study. *American Journal of Epidemiology, 156*, 319-327.

Velligan, D.I., Lam, Y.-W.F., Glahn, D.C., Barrett, J., Maples, N.J., Ereshefsky, L., et al. (2006). Defining and assessing adherence to oral antipsychotics: a review of the

literature. *Schizophrenia Bulletin, 32*, 724-742.
Velligan, D.I., Mahurin, R.K., Diamond, P.L., Hazelton, B.C., Eckert, S.L., & Miller, A.L. (1997). The functional significance of symptomatology and cognitive function in schizophrenia. *Schizophrenia Research, 25*, 21-31.
Vidaver, R.M., Lafleur, B., Tong, C., Bradshaw, R., & Marts, S. (2000). Women subjects in NIH-funded clinical research literature: lack of progress in both representation adn analysis by sex. *Journal of Women's Health and Gender-Based Medicine, 9*, 495-504.
Wade, D., Harrigan, S., McGorry, P.D., Burgess, P., & Whelan, G. (2007). Impact of severity of substance use disorder on symptomatic and functional outcome in young individuals with first-episode psychosis. *Journal of Clinical Psychiatry, 68*, 767-774.
Wahlbeck, K., Tuunainen, A., Ahokas, A., & Leucht, S. (2001). Dropout rates in randomized antipsychotic drug trials. *Psychopharmacology, 155*, 230-233.
Waldheter, E.J., Penn, D.L., Perkins, D.O., Mueser, K.T., Owens, L.W., & Cook, E. (2008). The Graduated Recovery Intervention Program for first episode psychosis: treatment development and preliminary data. *Community Mental Health Journal, 44*, 443-455.
Wechsler, D. (1987). *WMS-R Wechsler Memory Scale - Revised Manual*. San Antonio, Texas: The Psychological Corporation Harcourt Brace Jovanovich, Inc.
Weiden, P., Preskorn, S., Fahnestock, P., Carpenter, D., Ross, R., & Docherty, J. (2009). Translating the psychopharmacology of antipsychotics to individualized treatment for severe mental illness: a roadmap. *Current Opinion in Psychiatry, 22*, 374-380.
Weiden, P.J. (2007). Discontinuing and switching antipsychotic medications: understanding the CATIE schizophrenia trial. *Journal of Clinical Psychiatry, 68*(suppl 1), 12-19.
Weintraub, S. (2000). Neuropsychological assessment of mental state. In M. Mesulam (Ed.), *Principles of Behavioral and Cognitive Neurology* (2nd ed., pp. 121-173). New York: Oxford University Press.
Wilkinson, G. (1993). *The Wide Range Achievement Test: Revision 3: Administration Manual*. Wilmington, DE: Jastak Assoc.
Wood, A., White, I., & Thompson, S. (2004). Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. *Clinical Trials, 1*, 368-376.
Woodberry, K.A., Giuliano, A.J., & Seidman, L.J. (2008). Premorbid IQ in schizophrenia: a meta-analytic review. *American Journal of Psychiatry, 165*, 579-587.
Wunderink, A., Nienhuis, F.J., Sytema, S., & Wiersma, D. (2006). Treatment delay and response rate in first episode psychosis. *Acta Psychiatrica Scandinavica, 113*, 332-339.
Wunderink, L., Nienhuis, F., Sytema, S., Slooff, C., Knegtering, R., & Wiersma, D. (2007). Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. *Journal of Clinical Psychiatry, 68*, 654-661.
Wykes, T., Steel, C., Everitt, B., & Tarrier, N. (2008). Cognitive behavior therapy for schizophrenia: effect sizes, clinical models, and methodological rigor.

*Schizophrenia Bulletin, 34*, 523-537.

Yung, A., & McGorry, P. (2007). Prediction of psychosis: setting the stage. *British Journal of Psychiatry, 191*(suppl. 51), s1-s8.

Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I., & Lewis, G. (2002). Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *British Medical Journal, 325*, 1199-1201.

Zygmunt, A., Offson, M., Boyer, C.A., & Mechanic, D. (2002). Interventions to improve medication adherence in schizophrenia. *American Journal of Psychiatry, 159*, 1653-1664.